# Role of Clinical Pharmacokinetics Studies in Contemporary Oncology Drug Development

Fatih M. Uckun and Sanjive Qazi

## Contents



**Abstract**

Pharmacokinetics (PK) studies enable drug developers to elucidate the relationship of dose to blood concentrations of drugs in various patient populations and determining the need for dose adjustment based on PK differences among demographic subgroups or subgroups with impaired elimination. PK studies also provide the basis for therapeutic drug monitoring in rare patient populations or when effective drugs with very narrow safe therapeutic windows must be used. Population PK studies are aimed at optimizing the dose and schedule by identifying the factors that alter the dose-concentration relationship and determining if such alterations change the therapeutic index using a data-driven approach and integrated sources of information. The clinical importance of identifying and implementing optimum dosing strategies has led to increased application of the population PK strategies in early oncology clinical trials. Multi-scale mechanistic PK models have been developed in an attempt to better predict the clinical performance of the oncology drug candidates.

F. M. Uckun (✉)
AresMIT Biomedical Computational Strategies (ABCS), Minneapolis, MN, USA

Ares Pharmaceuticals, St. Paul, MN, USA
e-mail: fatih.uckun@att.net; fatih.uckun@aresmit.com

S. Qazi
AresMIT Biomedical Computational Strategies (ABCS), Minneapolis, MN, USA

Ares Pharmaceuticals, St. Paul, MN, USA

Bioinformatics Program, Gustavus Adolphus College, St. Peter, MN, USA
e-mail: sqazi@gustavus.edu



F. J. Hock, M. R. Gralinski (eds.), *Drug Discovery and Evaluation: Methods in Clinical Pharmacology*,
https://doi.org/10.1007/978-3-319-56637-5_24-1

Over the last two decades PK studies have increasingly become an integral part of early clinical development of promising oncology drugs entering the clinical space. Of the total of 4,481 interventional clinical oncology trials with integrated PK studies registered in the clinicaltrials.gov data repository that were initiated within the 24-year time interval between 1994 and 2018, ~60% of the clinical PK studies were initiated within the last 8 years.

## Introduction

Pharmacokinetics (PK) is the study of the drug concentrations in the body during a period of time, and it includes the processes by which the drug is absorbed, distributed, metabolized, and excreted (ADME). An ideal drug should have high absolute bioavailability with low variability and exhibit linear PK over therapeutic dose range without significant modulation of the PK by concomitant food or pH-altering medications. An ideal drug should also reach the target site(s) of action promptly at effective/nontoxic concentrations, should not accumulate in nontarget organs, and should not have a narrow therapeutic index. Furthermore, it should not be extensively metabolized by a liver enzyme so that its clearance would not be significantly affected by hepatic dysfunction or by concomitant use of other drugs that affect one or more metabolizing enzymes. However, the PK profiles of most drugs are influenced by their physicochemical properties, product/formulation, administration route, patient's intrinsic and extrinsic factors (e.g., organ dysfunction, diseases, concomitant medications, food). PK studies enable drug developers to elucidate the relationship of dose to blood concentrations of drugs in various patient populations and determining the need for dose adjustment based on PK differences among demographic subgroups or subgroups with impaired elimination (e.g., hepatic or renal disease). Defining the optimum dosing strategy for a population, subgroup, or individual patient requires resolution of the interindividual, kinetic, as well as random variability (Turner et al. 2015; Undevia et al. 2005). Population PK studies are aimed at optimizing the dose and schedule by identifying the factors that alter the dose-concentration relationship and determining if such alterations change the therapeutic index using a data-driven approach and integrated sources of information, as detailed in a 1999 FDA Guidance for Industry that was prepared by the Population Pharmacokinetic Working Group of the Clinical Pharmacology Section of the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the FDA (1999). In 2003, the FDA Exposure-Response Working Group under the Medical Policy Coordinating Committee, Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER) at the FDA issued another guidance for industry regarding study design, data analysis, and regulatory applications related to exposure-response relationships (FDA 2003a; Overgaard et al. 2015).

The clinical importance of identifying and implementing optimum dosing strategies has led to increased application of the population PK strategies in early oncology clinical trials. Population PK studies provide actionable safety, efficacy, and dosage optimization information for the drug label because of their early integration with clinical oncology trials. The purpose of this chapter is to review and discuss the increasing role of PK studies in the oncology drug development process.

## Contribution of Pharmacokinetics to Clinical Development of Oncology Drugs

Over the last two decades, PK studies have increasingly become an integral part of early clinical development of promising oncology drugs entering the clinical space (Chen et al. 1999; Uckun et al. 1995, 2013, 2015; Ursino et al. 2017; Waller et al. 2018; Wicki et al. 2018). As shown in Fig. 1, a pronounced and continued increase in the use of integrated PK analyses was

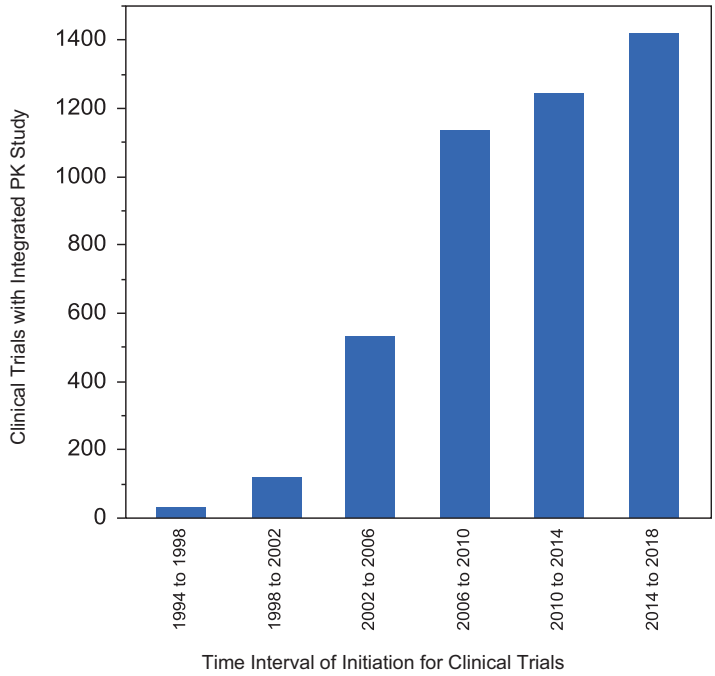


**Fig. 1** Clinical trials with integrated PK studies in oncology. We interrogated the clinicaltrials.gov data repository (https://clinicaltrials.gov/) to determine the number of interventional clinical trials that employed PK studies from 1994 to 2018 in 4 year increments. All Interventional trials that were started over the 4-year period were included in the totals. There were a total of 4481 trials counted from 1994 to 2018. A pronounced increase in the use of PK studies was observed after the year 2002. Search terms to identify the trials were "pharmacokinetics," "interventional studies," and "cancer"

observed in clinical trials that started after the year of 1998. Of the total of 4481 interventional clinical oncology trials with integrated PK studies registered in the clinicaltrials.gov data repository that were initiated within the 24-year time interval between August 1994 and July 2018, only 30 (0.7%) were started between August 1994 and July 1998, 121 (2.7%; 3.8-fold increase from previous 4 years) between August 1998 and July 2002, 532 (11.9%; 4.4-fold increase from previous 4 years) between August 2002 and July 2006, 1135 (25.3%; 2.1-fold increase from previous 4-years) between August 2006 and July 2010, 1244 (27.8%; 9.6% increase from previous 4 years) between August 2010 and July 2014, and 1420 (31.7%; 14.1% increase from previous 4 years) between August 2014 and July 2018. Notably, ~60% of the clinical PK studies were initiated within the last 8 years. Hence, PK studies are playing an increasingly important role in the clinical development path of oncology drugs.

PK studies often combined with integrated pharmacodynamics (PD) components play a pivotal role in clinical comparisons of different formulations, prodrugs and dosing schedules aimed at identifying the best way of using a promising new drug at a nontoxic dose level. For example, DTS-201 is a doxorubicin (Dox) prodrug that shows encouraging data in experimental models in terms of both efficacy and safety compared with conventional Dox. Notably, a high equivalent dose of Dox could be delivered without severe drug-related cardiac events. DTS-201 was administered at four dose levels ranging from 80 to 400 mg/m$^2$, which is equivalent to 45–225 mg/m$^2$ of conventional Dox (Schöffski et al. 2017). The recommended phase II dose (RP2D) was 400 mg/m$^2$.

PK modeling and model-informed precision dosing (MIPD) have been explored as tools to optimize treatment outcomes in oncology by maximizing patient safety via overdose protection and

by avoiding treatment failures caused by suboptimal drug exposures (Barbolosi et al. 2015). NCT02732275 is a first-in-human phase I study of the epigenetic modulator DS-3201b, a dual inhibitor of enhancer of zeste homolog 1 (EZH1) and EZH2 in patients with relapsed/refractory lymphomas. Recently, a population PK model was developed using the integrated PK data from the study to define the dose-exposure relationships and reported that a 2-compartment PK model with first-order elimination and absorption lag-time best characterized the plasma concentration-time profile of DS-3201a (Atsumi et al. 2017).

Physiologically based pharmacokinetic (PBPK) modeling is a potential tool which can be effectively applied throughout all phases of oncology drug development and allows a more granular prediction of tissue drug exposures (Schwenger et al. 2018; Schultze-Mosgau et al. 2018; Cheeti et al. 2013; Ferl et al. 2016; Saeheng et al. 2018; Rowland 2013; Sager et al. 2015). The number of experimental animals and human participants enrolled in the studies can be reduced using PBPK modeling and PBPK-population-PK modeling. For example, Tsukamoto et al. studied the kinetics of capecitabine and its metabolites. Their PBPK model integrated tissue-specific information about metabolic enzyme activity between tumor and normal cells from in vitro data and enabled the prediction of the therapeutic index in terms of exposure in target organs and toxicity in off-target organs (i.e., gastrointestinal tract toxicity) (Tsukamoto et al. 2001).

Besides the systemic exposure levels of the parent compound and/or its metabolites, several baseline characteristics, including but not limited to age, gender, and race as well as comorbidities of the host also affect the risk of severe side effects and tolerability as well as efficacy of drugs at optimized dose levels (Owonikoko et al. 2018). Therefore, it is very important to identify biomarkers that (i) allow the rational assignment of individual patients to those treatments that are most likely to benefit them and ensure maximized patient safety as well as best survival outcome and likewise and (ii) enroll into a particular study a biomarker-enriched population that is most likely to benefit from the treatment program (Jamal et al. 2017). For example, inhibition of Janus-kinase 1/2 (JAK1/2) is an innovative strategy to treat myeloproliferative neoplasms, but recently this exciting new treatment approach has been shown to be associated with a 15-fold higher risk of development of aggressive B-cell lymphomas. Lymphomas occurring during JAK1/2 inhibitor treatment were preceded by a preexisting B-cell clone in all patients tested. Therefore, detection of a preexisting B-cell clone may identify individuals at risk (Porpaczy et al. 2018).

Unlike small molecules which bind to their molecular targets without significantly affecting the systemic exposure levels, biotherapeutic agents, such as monoclonal antibodies (e.g., the anti-PD1 monoclonal antibody pembrolizumab), bind to their targets with much higher affinity and display a nonlinear "target-mediated drug disposition" (TMDD). The disposition of the drug-target molecular complexes can influence the systemic exposure levels (Ahamadi et al. 2017; Moreau et al. 2012). In addition, the lack of a relationship of pembrolizumab PK and overall survival (OS) in patients with advanced melanoma and non-small cell carcinoma (NSCLC) demonstrates the challenges in determining the RP2D and optimal dosing for monoclonal antibodies and immune-oncology drugs (Turner et al. 2018; Freshwater et al. 2017; Chatterjee et al. 2016; Turan et al. 2018). It is also important to take into consideration the circadian fluctuations of the ADME of oncology drugs (Vérennoneau-Veilleux and Bélair 2017).

Importantly, PK studies provide the basis for therapeutic drug monitoring in rare patient populations or when effective drugs with very narrow safe therapeutic windows must be used (Thomas et al. 2018a). Therapeutic drug monitoring is particularly important for optimized clinical use for certain therapeutics, such as oral antihormonal drugs are essential in the treatment of breast and prostate cancer, that display a high interpatient PK variability, when the treatments employ fixed doses, which has the associated risks of underdosing as well as overdosing (Groenland et al. 2018; Paci et al. 2014).

When there is compelling evidence from nonclinical studies for an association between systemic exposure levels of a drug or its metabolite and the desired treatment outcomes, PK-guided dose escalation studies utilizing real-time PK measurements to determine the dose cohorts based on the systemic exposure levels could provide the opportunity to determine the maximum tolerated systemic exposure (MTSE) levels and how they compare to the systemic exposure levels proven effective in nonclinical studies.

## The Impact of Hepatic and/or Renal Impairment on PK of Oncology Drugs and Patient-Tailored Dosing Schedules

The Cancer Therapy Evaluation Program (CTEP) at the NCI prioritized study of special patient populations with hepatic dysfunction phase I clinical trials (HDCT) to determine safe administration parameters of oncology drugs for subjects with varying degrees of liver dysfunction. HDCT sponsored by CTEP and others have provided clinically useful information on the optimal dosing of oncology drugs in subjects with different degrees of liver test abnormalities that have provided administration guidance in the labels for patients with abnormal organ function. Hepatic dysfunction phase I clinical trials (HDCT) provide safe administration parameters of oncology drugs for subjects with varying degrees of liver dysfunction (Mansfield et al. 2016).

The elimination of several oncology drugs, such as the proteasome inhibitor bortezomib, occurs through metabolism by liver enzymes (Tan et al. 2018). The change in liver function may potentially change the inhibitory and/or inducing potential of the liver metabolizing enzymes, thus the PK and PD in patients with hepatic impairment may differ from patients with normal hepatic function. As cancer patients often have alterations in their liver function due to disease-related reasons (e.g., liver metastases), hepatotoxic treatments (chemotherapy, radiation therapy, treatment with immuno-oncology drugs), and/or other comorbidities they may have, it is important to determine the effects of hepatic impairment on the PK and safety of drugs metabolized by liver enzymes and also, if possible, determine whether dose modification would be necessary in such patients. Patients in these studies are typically assigned to different groups according to their liver function as per NCI and FDA guidance (FDA 2003b). The primary objective of such studies is to evaluate the effect of hepatic impairment on the steady state PK of the respective therapeutic agents in advanced cancer patients. The secondary objectives are to evaluate the effect of hepatic impairment on the safety and antitumor activity of the respective therapeutic agent in advanced cancer patients.

Some of the ongoing studies evaluating the effects of hepatic impairment on the PK and safety of targeted therapeutics include among others NCT01767623 (A Study of The Impact of Severe Hepatic Impairment on the Pharmacokinetics and Safety of Vemurafenib – a BRAF kinase inhibitor – in BRAF V600 Mutation-Positive Cancer Participants), NCT02894385 (Effect of Hepatic and Renal Impairment on the Pharmacokinetics, Safety and Tolerability of BAY1841788/daralutamide – a nonsteroidal antiandrogen), NCT03092999 (Effect of Hepatic Impairment on the Pharmacokinetics, Safety and Tolerability of BAY1002670/Vilaprisan – a steroidal selective progesterone receptor modulator/SPRM), NCT03359850 (Pharmacokinetic and Safety Study of Niraparib – a PARP inhibitor – With Normal or Moderate Hepatic Impairment Patients), NCT03282513 (A Study of AG-120 (Ivosidenib) – an IDH1 inhibitor in Subjects With Mild or Moderate Hepatic Impairment or Normal Hepatic Function), and NCT01429337 (Pharmacokinetics and Safety of Midostaurin – FLT3 inhibitor – in Subjects With Impaired Hepatic Function and Subjects With Normal Hepatic Function).

In a recent Pfizer study (NCT01576406), the effect of hepatic impairment was evaluated on the pharmacokinetics and safety of the ALK-inhibitor crizotinib in patients with advanced cancer. No adjustment to the approved 250 mg twice daily (BID) dose of crizotinib was recommended for patients with mild hepatic impairment. The recommended dose was 200 mg BID for patients

with moderate hepatic impairment, and the dose was recommended not to exceed 250 mg daily for patients with severe hepatic impairment. Adverse events appeared consistent among the hepatic impairment groups (El-Khoueiry et al. 2018). Sonidegib is a potent, selective, and orally bioavailable inhibitor of the Hedgehog signaling pathway, primarily metabolized by the liver. Horsmans et al. assessed the PK and safety of sonidegib in subjects with varying degrees of hepatic function. Sonidegib exposures were similar or decreased in the hepatic impairment groups compared with the normal group, and sonidegib was generally well-tolerated in all subjects. Dose adjustment was not considered necessary for subjects with mild, moderate, or severe hepatic impairment (Horsmans et al. 2018). By comparison, the analysis of the impact of hepatic impairment on the PK and PD of the alkylating agent Trabectedin, that is metabolized by the liver and has been associated with liver toxicities, including including hepatic failure, revealed that Trabectedin treatment of patients with hepatic impairment results in higher plasma exposures but hepatotoxicity in patients with normal liver function can be effectively addressed through dose reductions and delays (Calvo et al. 2018).

It is generally known that renal impairment can affect not only the disposition of drugs that are cleared primarily through the kidney but also other drugs with minimal renal elimination because of the effects of kidney disease on drug-metabolizing enzymes, transporters, and drug-binding proteins. Some drugs such as Udenafil, a phosphodiesterase-5 inhibitor, used to treat erectile dysfunction, are not predominantly eliminated by the kidney but renal impairment can alter its secretion/transport pathways. Significant correlations were observed among the creatinine clearance, oral clearance, and maximum concentration of Udenafil and a dose adjustment of Udenafil would seem warranted in subjects with moderate or severe renal impairment (Cho et al. 2018). Drug PK and safety of oncology drugs must therefore be assessed in subjects with a renal impairment. PK studies in combination with model-based strategies, including population PK and physiologically based PK (PBPK) modeling, have been used to evaluate the impact of renal impairment on dose-exposure relationships and optimize dosing for patients with various degrees of renal impairment (Xiao et al. 2017; Beumer et al. 2016; Tortorici et al. 2012). The insights gained from these studies are used for dose selection/dose adjustment in patient populations with renal impairment to improve the therapeutic index of anti-cancer treatments (EMA 2015; FDA 2010).

## Importance of PK in the Changing Regulatory Landscape Regarding Access of Pediatric and Young Adult Patient Populations to New Treatment Platforms

The clinical trial landscape in oncology has traditionally been associated with significant delays in the evaluation of promising new therapies in poor prognosis pediatric cancer patients who are in urgent need for therapeutic innovations (FDA 2018; Freyer et al. 2013; Bleyer et al. 2018; Burke et al. 2007; Uckun and Kenny 2018; Vassal et al. 2015; Veal et al. 2010; Beaver et al. 2017; Thomas et al. 2018b; Chuk et al. 2017; Fern and Taylor 2018). There is growing consensus among pediatric hematologists-oncologists, US Food and Drug Administration (FDA), European Medicines Agency (EMA), coalitions of subject matter experts, support groups, and other stakeholders that these delays have contributed to the unsatisfactory progress in improving the survival outcomes of adolescents with cancer (Kim et al. 2017; FDA 2018; Gaspar et al. 2018; Stark et al. 2016). Both FDA and EMA launched new regulatory initiatives aimed at improving the access of pediatric cancer patients to novel therapies developed for adults with cancer. The European Pediatric Medicine Regulation [(EC)-No1901/2006)] mandated the establishment of the EMA's Pediatric Committee to provide guidance to pharmaceutical companies regarding their Pediatric Investigation Plans (PIPs) for their drugs in pipeline (EC 2006). The multistakeholder platform ACCELERATE (http://www.accelerate-platform.eu) presented a consensus expert opinion in support of early drug access for adolescents with

cancer indicating that enrollment of adolescents of 12 years and over in adult early-phase clinical drug trials would represent a safe and efficient strategy in drug development (Gaspar et al. 2018). Several changes were proposed by ACCELERATE to facilitate that adolescents have access to early drug development programs, including that (i) there should be no set upper or lower age limit criteria for phase II and phase III trials for cancers that are present in both pediatric and adult populations with similar biology and (ii) adolescents over 12 years of age should be included from the onset of the cancer drug development process in adults (Gaspar et al. 2018). In June 2018, FDA issued a draft guidance entitled "Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials" (FDA 2018) emphasizing that pediatric oncology drug development should be coordinated with oncology drug development for adults as part of an overall drug development plan and detailing a series of recommendations regarding inclusion of pediatric patients in adult oncology trials in the USA which was based on a previous FDA publication (Chuk et al. 2017) and can be viewed as a strong endorsement of the recent ACCELERATE proposal (Gaspar et al. 2018) in Europe. The new FDA recommendations would certainly expand the options available for adolescent cancer patients who have relapsed after or are refractory to standard therapeutic strategies with no curative options, or for whom no standard therapies with curative intent exist. The draft guidance suggesting that adolescent patients may be enrolled in first-in-human clinical trials after initial adult PK and toxicity data are obtained is aimed at providing significant risk mitigation for adolescents (FDA 2018). Furthermore, the important provisions of the Race for Children Act, which is incorporated as Title V of the FDA Reauthorization Act (FDARA) that was enacted on August 18, 2017 (FD&C Act Sec. 505B (a)(3), 21 USC 355c (a)(3), Public Law 115-52), has created a mechanism to expedite the evaluation of novel medicines with the potential to address the unmet need in the pediatric population by requiring pediatric investigation of appropriate new drugs intended for adults with cancer (Reaman 2018). Specifically, Title V requires evaluation of new molecularly targeted drugs and biologics "intended for the treatment of adult cancers and directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer" in molecularly targeted pediatric cancer investigation to generate clinically meaningful study data, "using appropriate formulations, regarding dosing, safety and preliminary efficacy to inform potential pediatric labeling" by designing and executing earlier rational dose finding and signal seeking trials (Reaman 2018). The Alliance for Childhood Cancer, representing more than 30 national patient advocacy groups and professional medical and scientific organizations invested in advancing the interests of children with cancer, applauded the inclusion of the RACE for Children Act in the FDA Reauthorization Act of 2017 (FDARA) legislation, passed in the Senate and in the House in July of 2017. These new regulatory initiatives by EMA and FDA combined with umbrella clinical trial initiatives aimed at allowing children and adolescents with relapsed or refractory pediatric cancers early access to promising targeted precision medicines have the potential to significantly alter the therapeutic landscape for difficult-to-treat pediatric/adolescent cancers for the benefit of current and future pediatric cancer patients (Uckun and Kenny 2018).

The FDA recommendations in the draft guidance are based in part on the observed similarities in disposition and PK of drugs in adolescents and adults (Thai et al. 2015; Fern and Taylor 2018; Smith et al. 2016; Freyer et al. 2013; FDA 2018; Gaspar et al. 2018; Fouladi et al. 2010; Forrest et al. 2018; Paoletti et al. 2013). Sometimes, the adult PK exposure can be used as target for dose finding in pediatrics. For example, the pediatric sunitinib PK data were adequately predicted from adult data with a mean prediction error of 1.80% (Janssen et al. 2017).

It should be noted, however, that the cited similarities were based on single agent studies with the inherent limitation that a careful consideration of the PK and PD features of the major metabolites were not included in relationship to other cancer drugs that are typically used in

combination trials or comorbidities of patients. The single agent trials have traditionally not included pharmacometabolomics, pharmacogenetics, and pharmacogenomics studies for the parent drug or its metabolites. Modifications of critical proteins through reactive metabolites are thought to be responsible for a number of adverse drug reactions (Krauss et al. 2012; Niu et al. 2017; Kalgutkar and Dalvie 2015; Reis-Mendes et al. 2015; Han et al. 2017; van Andel et al. 2018; Chavan et al. 2018; Sun et al. 2018). Therefore, besides the levels of drug exposure, the generation of chemically reactive metabolites also contributes to drug side effects. The metabolism of some of the anticancer drugs is highly complex due to the engagement of multiple enzymes and transporters and is therefore prone to unintended drug-drug interactions. For example, the standard anticancer drug Irinotecan serves as the prodrug for the 2–3 logs more potent topoisomerase I inhibitor SN-38 that is responsible for the dose-limiting toxicities (DLTs) associated with irinotecan. Single nucleotide polymorphisms in several drug metabolizing enzymes (e.g., uridine diphosphate glucuronosyltransferase [UGT] 1A1, UGT1A7, UGT1A9) and drug transporters (e.g., ATP-binding cassette [ABC] B1, ABCC1) are associated with irinotecan toxicity (de Man et al. 2018). Fluoroacetate is considered one of the major metabolites of 5-fluorouracil responsible for its cardiotoxicity (Reis-Mendes et al. 2015). Several therapeutic and toxic effects of cyclophosphamide are the result of the actions of its active metabolites formed by the hepatic microsomal cytochrome P450 mixed function oxidase system: The active cyclophosphamide metabolites hydroxycyclophosphamide and acrolein are shown to be more cardiotoxic than the parent drug. In human autopsy cardiac tissues of previously doxorubicin (Dox)-treated patients, the cardiac levels of the metabolite doxorubicinol were almost double of the parent compound doxorubicin (Reis-Mendes et al. 2015). Although Paclitaxel cardiotoxicity is usually low and does not seem to be related with the formation of reactive metabolites, its concomitant use with Dox results in significantly increased cardiotoxicity because the pharmacokinetic interactions between paclitaxel and DOX and also because paclitaxel stimulates the NADPH-dependent reduction of Dox into doxorubicinol. The schedule paclitaxel followed by Dox is more cardiotoxic with an incidence of 18–20% of congestive heart failure than in patients with breast cancer given Dox followed by paclitaxel at standard dose levels (Reis-Mendes et al. 2015). Ponatinib is an orally available pan-BCR-ABL tyrosine kinase inhibitor that has been approved for treatment of resistant chronic myeloid leukemia (CML) and Philadelphia chromosome-positive ALL. However, it can cause severe side effects including cardiovascular toxicity with both arterial and venous thromboembolism and severe systemic hypertension, vascular occlusions as well as pancreatitis, and liver toxicity. Although the initial work had suggested CYP3A4 as a major pathway of ponatinib disposition, Lin et al. recently reported that CYP1A1, a highly inducible enzyme that unlike many other P450s can be expressed in most tissues such as lung and lung tumors, is highly active toward this compound and metabolism by CYP1A1 results in the formation of reactive epoxides from ponatinib that likely contribute to the side effects associated with its clinical use (Lin et al. 2017). Epoxides are chemically reactive and can react covalently with both DNA and proteins to cause mutations and toxicity. CYP1A1 levels are constitutively very low but are highly inducible on activation of the aryl hydrocarbon receptor by compounds including polycyclic aromatic hydrocarbons found in cigarette smoke. Notably, hypertension or vaso-occlusive disease observed in ponatinib-treated patients has been associated with smoking. Therefore, it is of vital importance that hybrid adolescent-adult studies incorporate detailed analyses aimed at characterizing the drug-drug interaction at the level of the parent compounds as well as their metabolites both in adolescents and adult populations. Risk mitigation measures aimed at maximizing the safety of adolescent patients enrolled on the hybrid studies should take the data from such analyses into consideration. In view of these regulatory changes, we anticipate a growing emphasis on PK studies in future clinical trials of oncology drugs with a major focus on the PK profiles of precision medicines in the

pediatric/adolescent and young adult patient populations.

## Multiscale Mechanistic PK Modelling Platforms

The majority of oncology drug candidates fail in early oncology clinical trials due to excessive toxicity and/or disappointing efficacy (Krauss et al. 2012; Turner et al. 2015; Gadkar et al. 2016). Multiscale mechanistic PK models have been developed in an attempt to better predict the clinical performance of the oncology drug candidates (Rousseau and Marquet 2012; Smith et al. 2017; Darwich et al. 2017; Barbolosi et al. 2015; Bizzotto et al. 2017a, b; Wilkins et al. 2017; Yankeelov et al. 2016). These models take into consideration the complexity of the host response, flux of the drug through different compartments of the host body, nonlinear treatment-emergent responses through drug-induced pertubation of a complex system and account for patient-to-patient differences in regard to drug metabolism and transportation.

Systems level consideration of drug responses in these models attempt to better characterize the hierarchical, nonlinear, dynamic responses at the network level of drug action that may affect both efficacy and toxicity in clinical settings. Systems PK also aims to explain the variations in drug uptake and metabolism by considering (i) drug-specific factors such as physiochemical properties and drug regimens, (ii) patient-specific factors that account for individual differences in the quality (e.g., affinity, catalytic activity of transporters and metabolic enzymes) and quantity of interactions (e.g., synthesis and degradation of drugs entering the body), (iii) epigenetic factors that regulate expression of transporters and metabolism of drug, (iv) tissue organ variabilities in anatomy, size of parenchymal cell numbers, and fluid volumes; and (v) environmental factors that modify the PK via food uptake and nutrition. The software platforms available as analytical tools for these models have also evolved to evaluate a large number of variables, perform clinical simulations along with databases allowing the integration of different knowledge environments. An example of a modelling platform includes "The Drug Disease Model Resources" (DDMoRe; http://www.ddmore.eu/) consortium that aims to improve the accessibility and cost effectiveness of model-informed drug discovery and development (Wilkins et al. 2017) by providing a curated model repository and an interoperability framework to integrate infrastructure for efficient exchange and integration of models across modelling languages (e.g., PFIM, Onolix, Simulx, R, NONMEM7, PsN, WinBUGS, MATLAB, SimCYP). In this contemporary modeling environment, the user is able to interact with the "Interoperability Framework" (IIF) via a graphical front-end interface (MDL-IDE; Bizzotto et al. 2017b; Smith et al. 2017) to enable editing of models written in HTML exchange formats such as PharmML (Swat et al. 2015; Bizzotto et al. 2017a). The advantage of the MDL-IDE workflows is realized by use of scripting in the R statistical computing language which enables full access to thousands of statistical and simulation packages. The IIF can be fully customized for speed, consistency, and fit-for-purpose modeling to better predict the toxicity and efficacy of the drug candidates.

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