Role of Clinical Pharmacodynamics Studies in the Era of Precision Medicines Against Cancer

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Abstract

Pharmacodynamics (PD) has been integral to the design of rational drug dosing regimens. Detailed PD studies during both the preclinical and clinical stages of the drug development process can also contribute to lead optimization or the selection of the optimal "best-in-class" compound, improve clinical potency estimates and help predict the drug exposure needed to achieve meaningful clinical responses. There has been a substantial and continued increase in the number of clinical oncology trials with integrated PD studies since 2002. Notably, a significant portion of all interventional clinical trials with PD components are initiated for evaluation of oncology drugs. PD studies frequently play a pivotal role in determining the initial dose level for first-in-human clinical studies of immunooncology drugs. The integration of PD data into the dose safety modeling in early oncology studies

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may provide accurate predictions of the dose-effect relationships by advancing the understanding of target engagement as well as exposure response and therefore has the potential to improve the decision making regarding the optimal dose and schedules as well as risk-benefit assessments for later stages in clinical development. PD studies also have the potential to provide early clinical proof of concept when drugs with complementary activity profiles are combined in cancer therapy. In recent years, population pharmacokinetics–pharmacodynamics (PK-PD) modeling has become a key tool towards streamlining and optimizing oncologic drug development through early understanding, identification and quantification of various dose–response relationships in the context of other patient characteristics as well as risk-benefit of different dosing schedules. Finally, a new and exciting strategy known as "Quantitative Systems Pharmacology" is emerging that advances systems level, multiscale models for disease progression and treatment to better characterize the hierarchical, non-linear, dynamic responses at the network level of drug action that may affect both efficacy and toxicity in clinical settings.

Introduction

An improved understanding of the molecular pathology of cancers combined with the development of targeted therapeutics and immuno-oncology drugs that activate the host immunity against cancer cells (Turan et al. 2018; Socinski et al. 2018; Valla et al. 2018) has caused a paradigm-shift in drug development and clinical trial methods by providing the foundation for personalized medicine strategies with specific roadmaps for the patient-tailored rational deployment of specific drugs in biomarker-enriched patient populations (Biankin et al. 2015; Tsimberidou et al. 2017; Phelan et al. 2018; DiNardo et al. 2018; Alsharedi et al. 2018; Drilon et al. 2018; Hidalgo et al. 2018; Mutti et al. 2018; Lu et al. 2016; Torres-Ayuso et al. 2018; Palmirotta et al. 2018; Peck 2015; Jamal et al. 2017; Krebs et al. 2016; Laetsch et al. 2017).

Pharmacodynamics (PD) has been integral to the design of rational drug dosing regimens (FDA 2016). PD is the study of the relationship between drug concentration and its effects at the subcellular, cellular, tissue, organ system, or whole-body level, including all of the pharmacological actions, pathophysiological effects, and therapeutic activities, and adverse side effects of the active drug ingredient, therapeutic moiety, and/or its metabolite(s) (de Man et al. 2018; Derendorf et al. 2000; de Vries et al. 2018). While some PD studies require tissue biopsies, others use surrogate tissues such as blood cells or noninvasive methods such as anatomic or functional imaging. Some drugs result in activation of gene expression which can be leveraged in PD studies. For example, omaveloxolone is a semisynthetic oleanane triterpenoid that potently activates Nrf2 with subsequent antioxidant function. In a recently reported Phase 1 study (NCT02029729), downstream Nrf2 activation was assessed in peripheral blood mononuclear cells by quantification of target gene mRNA expression (Creelan et al. 2017). An increase in select Nrf2 target gene expression was observed during the course of treatment, across multiple dose levels. Mutant IDH1 produces high levels of 2-hydroxyglurate (2HG), thought to initiate oncogenesis through epigenetic modifications of gene expression. Inhibitors of the mutant isocitrate dehydrogenase 1 (IDH1) are being evaluated in patients with brain tumors. Recently, Andronesi et al. described an elegant noninvasive 3D MR spectroscopic neuroimaging method for rapid and easy detection of 2HG to study the PD of IDH305, an orally available, brain penetrant, mutant-selective allosteric high affinity IDH1 inhibitor that acts on both canonical (R132H) and noncanonical (R132C) mutated enzymes (Andronesi et al. 2018). The authors demonstrated the feasibility of image-based 2HG PD serial assessments and demonstrated that the IDH305 treatments of glioma patients during the NCT02381886 Phase 1 clinical study caused a rapid decline of 2HG levels by 70% as expected from an inhibitor of mutant IDH1.

The purpose of this chapter is to discuss the role of PD studies in the drug development process with a focus on the integration of PD studies in contemporary clinical trials of oncology drugs.

Role of PD Studies in Translational Oncology

The drug development strategies should encompass both the nonclinical and clinical stages of the life cycle of a promising new drug candidate. The quality of the nonclinical development, including the identification of robust biomarkers, non-invasive PD assays, well-defined relationships between the PD parameters and pharmacokinetics (PK) parameters, development of laboratory tests for predictive biomarkers, and PD analyses amenable to validation, has a direct and differentiating impact on the success of the early phase clinical development (Brennan et al. 2018). Most drug makers seek earlier decision making about go or no-go plans on the basis of PK and PD characteristics of their promising drug candidates. Detailed PK-PD studies during both the preclinical and clinical stages of the drug development process can also contribute to lead optimization or the selection of the optimal "best-in-class" compound, improve clinical potency estimates and help predict the drug exposure needed to achieve meaningful clinical responses. PD studies frequently play a pivotal role in determining the initial dose level for first-in-human clinical studies of immunostimulatory drugs according to the minimal anticipated biologic effect level (MABEL) approach by integrating all of the available in vitro and in vivo information by PK/PD modeling.

It is also important to note that the insights and lessons learned from nonclinical PD studies often provide the foundation for highly promising combined modality regimens. For example, nonclinical PD studies demonstrated that the FDA-approved 2nd-line anti-chronic lymphocytic leukemia (CLL) drug Venetoclax targeting the anti-apoptotic protein BCL2 potentiated/complemented the activities of and sometimes synergized with the Bruton's tyrosine kinase (BTK) inhibitors Acalabrutinib and Ibrutinib. Tam et al. recently reported the results of a clinical study (NCT02471391) which demonstrated that dual targeting of BTK and BCL2 with Ibrutinib plus Venetoclax as part of an innovative treatment regimen results in significantly improved response rates and treatment outcomes in patients with mantle-cell lymphoma (Tam et al. 2018). The complete response rate at week 16 was 42%, which was markedly higher than the historical result of 9% at this time point with Ibrutinib monotherapy (Tam et al. 2018).

According to the clinicaltrials.gov data repository, a total of 1,930 interventional clinical oncology trials with integrated PD studies were initiated between August 1994 and July 2018. Of these, only 33 (1.7%) were started between August 1994 and July 2002. There has been a substantial and continued increase in the number of clinical oncology trials with integrated PD studies since 2002 (Fig. 1): 224 trials (8.6-fold increase from previous 4 years) were initiated between August 2002 and July 2006, 474 trials (2.1-fold increase from previous 4-years) between August 2006 and July 2010, 564 trials (~19% increase from previous 4 years) between August 2010 and July 2014, and 635 (~13% increase from previous 4 years) between August 2014 and July 2018. Notably, ~62% of the clinical PD studies in oncology were initiated within the last 8 years. Hence, PD studies are playing an increasingly important role in the clinical development path of oncology drugs. Notably, a significant portion of all interventional clinical trials with PD components are initiated for evaluation of oncology drugs. Whereas 635 of the 2,076 clinical PD studies (30.6%) that were initiated between August 2014 and July 2018 were in patients with cancer, only 178 studies (8.6%) were in patients with neurological disorders (Neuro), 177 studies (8.5%) in patients with cardiovascular diseases (CVD), 136 studies (6.6%) in patients with pulmonary disease (PD), 54 studies (2.6%) in patients with allergic disorders (AD), and 129 studies (6.2%) in patients with autoimmune disorders (AI) (Fig. 2). There were more studies in cancer patients (viz.: 635 studies) than in patients with CVD, PD, AD, and AD combined (viz.: 545 studies). Table 1 depicts a select list of actively recruiting clinical

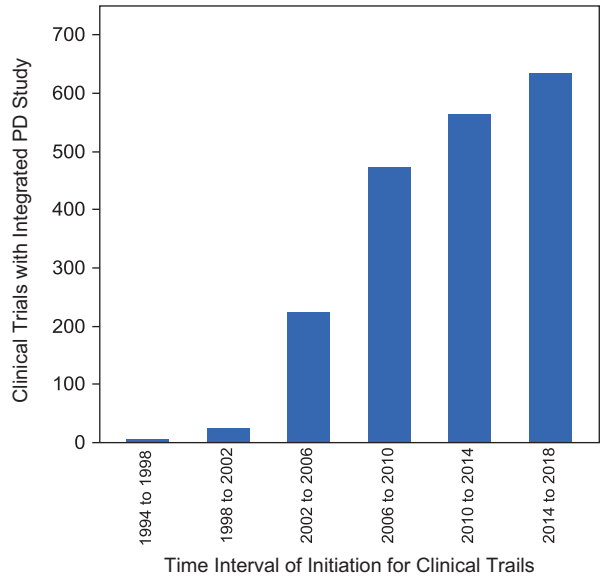

Fig. 1 Clinical trials with integrated PD studies in oncology. We interrogated the clinicaltrials.gov data repository (https://clinicaltrials.gov/) to determine the number of interventional trials that employed pharmacodynamic methods to characterize anti-cancer therapies from 1994 to 2018 in 4 year increments. All Interventional trials that were started over the 4-year period were included in the totals. There was a total of 1,930 trials counted from 1994 to 2018. Search terms to identify the trials were "Pharmacodynamic," "Interventional studies," and "Cancer"

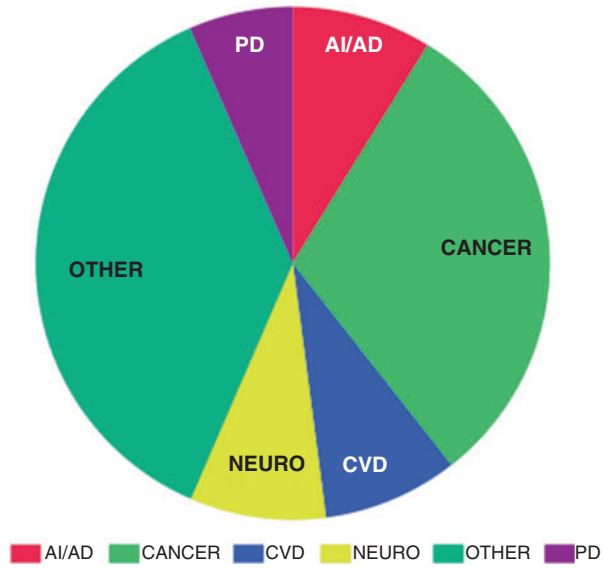

Fig. 2 Patient populations of clinical PD studies initiated between 2014 and 2018. We interrogated the clinicaltrials.gov data repository (https://clinicaltrials.gov/) to determine the number of interventional trials with integrated PD studies that were initiated between August 2014 and July 2018. All Interventional trials that were started over the 4-year period were included in the totals. Search terms to identify the trials were "Pharmacodynamic," "Interventional studies," and either "Cancer," "Cardiovascular Diseases (CVD)," "Pulmonary Disease (PD)," "Autoimmune Diseases (AI)," "Allergic disorders (AD)," or "Neurological Disorder (Neuro)" to stratify the disease types

Table 1 Select list of currently recruiting interventional clinical studies with integrated PD components

NCT study #	Official title	Sponsor	PD/PK study	Patient population
NCT02448589	A Phase I, open-label, nonrandomized, dose-escalating safety, tolerability, pharmacokinetic and pharmacodynamic study of TAS-119 in patients with advanced solid tumors (https://ClinicalTrials.gov/show/NCT02448589)	Taiho Oncology	PD/PK of TAS-119 (Aurora A KI)	Advanced solid tumors
NCT03008018	An open-label ascending dose study evaluating the safety/tolerability, pharmacokinetic and pharmacodynamic effects of KA2507 in patients with solid tumors (https://ClinicalTrials.gov/show/NCT03008018)	Kaxus Therapeutics, Ltd	PD/PK of KA2507 (HDACi)	Advanced solid tumors
NCT03450109	A Randomized and Open-label Study to Assess Pharmacokinetics, Pharmacodynamics and safety of LY01005 versus goserelin comparator (ZOLADEX®) following a single administration in patients with prostate cancer (https://ClinicalTrials.gov/show/NCT03450109)	Luye Pharma Group, Ltd	PD/PK of LY01005 (Goserelin acetate microspheres)	Prostate cancer
NCT02303028	A Phase I and enrichment study of low-dose metronomic Topotecan and Pazopanib in pediatric patients with recurrent or refractory solid tumors including CNS tumors (https://ClinicalTrials.gov/show/NCT02303028)	The Hospital for Sick Children	PD/PK of Pazopanib (TKI)	Pediatric R/R solid tumors and CNS tumors
NCT02619162	Nintedanib plus Letrozole in postmenopausal women with breast cancer: clinical trial phase 0/1 safety and pharmacodynamics (https://ClinicalTrials.gov/show/NCT02619162)	Centro Nacional de Investigaciones Carlos III	PD/PK of Nintedanib (TKI)	Breast cancer
NCT02503709	A Phase 1 trial of the combination of the heat shock protein-90 (HSP90) inhibitor Onalespib (AT13387) and the cyclin-dependent kinase (CDK) inhibitor AT7519M in patients with advanced solid tumors (https://ClinicalTrials.gov/show/NCT02503709)	NCI	PD/PK of Onalespib (Hsp90i) and CDKI AT7519 (CDK1,2,4,6,9 i)	Advanced solid tumors
NCT02679196	An open-label ascending dose study evaluating the safety/tolerability, pharmacokinetic and pharmacodynamic effects of KA2237 In patients with B Cell lymphoma (https://ClinicalTrials.gov/show/NCT02679196)	Karus Therapeutics	PD/PK of KA2237 (PI3Ki)	B-cell lymphoma

(*continued*)

Table 1 (continued)

NCT study #	Official title	Sponsor	PD/PK study	Patient population
NCT02350868	A Phase 1, first-in-human, dose-seeking study evaluating the safety, pharmacokinetics, and pharmacodynamics of orally administered MPT0E028 in subjects with advanced solid malignancies without standard treatment (https://ClinicalTrials.gov/show/NCT02350868)	Taipei Medical University	PD/PK of MPT0E028 (HDACi)	Advanced solid tumors
NCT01977638	Phase 1 study to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of CXD101 given orally (twice-daily dosing for 5 consecutive days in a 21-day period) in patients with advanced malignancies expressing the biomarker HR23B (https://ClinicalTrials.gov/show/NCT01977638)	Oxford University Hospitals	PD/PK of CXD101 (HDACi)	Advanced solid tumors, lymphoma, MM
NCT02514239	An open-label, Phase I, dose escalation study to characterize the safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenous doses of BI 836909 in relapsed and/or refractory multiple myeloma patients (https://ClinicalTrials.gov/show/NCT02514239)	Boehringer Ingelheim	PD/PK of BI-836909 (anti-BCMAxCD3 BiTE)	R/R MM
NCT02605746	A Phase 0/II study of Ceritinib (LDK378) in preoperative glioblastoma multiforme (GBM) and CNS metastasis patients scheduled for resection to evaluate central nervous system (CNS) penetration (https://ClinicalTrials.gov/show/NCT02605746)	St Joseph Hospital Med Center	PD/PK of Ceritinib (ALKi)	GBM/CNS mets
NCT02510001	A sequential Phase I study of MEK1/2 inhibitors PD-0325901 or Binimetinib combined With cMET inhibitor PF-02341066 in patients with RAS mutant and RAS wild type (with aberrant c-MET) colorectal cancer (https://ClinicalTrials.gov/show/NCT02510001)	University Oxford	PD/PK of Binimetinib (MEKi) and Crizotinib (ALKi/ROS-1i)	Colorectal cancer

(*continued*)

Table 1 (continued)

NCT study #	Official title	Sponsor	PD/PK study	Patient population
NCT02501902	An open-label Phase Ib study of Palbociclib (Oral Cdk 4/6 Inhibitor) plus Abraxane (registered) (nab-paclitaxel) in patients with metastatic pancreatic ductal adenocarcinoma (https://ClinicalTrials.gov/show/NCT02501902)	Pfizer	PD/PK of Palbociclib (CDK4/6 i) and Abraxane	Metastatic pancreatic ductal carcinoma
NCT02940132	Phase 1 study to assess the safety, tolerability, pharmacokinetics/pharmacodynamics and preliminary efficacy of SC10914 in patients with advanced solid tumors (https://ClinicalTrials.gov/show/NCT02940132)	Jiangxi Qingfeng Pharmaceutical Co Ltd	PD/PK of SC10914 (PARPi)	Advanced solid tumors

oncology trials with integrated PD components and estimated primary completion dates ranging from 01/01/2017 to 07/31/2018.

Role of PD Studies in Early Oncology Trials

The primary objective of Phase I oncology trials is to determine the optimal dose of an agent or combination of agents that can be used as the recommended phase 2 dose (RP2D) (Cook et al. 2015; Caimi et al. 2017). The RP2D levels of anticancer agents are traditionally determined by dose-limiting toxicities (DLT) and correspond to the maximum tolerated dose (MTD) , which is the highest clinically-safe dose that is derived from DLT data obtained most commonly during the first few treatment cycles. Identification of the MTD is still the most commonly used method to identify the RP2D for oncology drugs. There is a need to reconsider the assessment of MTD for some medicinal products as a need for dose reduction is discovered in a high percentage of patients in Phase III trials, despite the absence of dose-limiting toxicity (DLT) conventionally defined by Grade 3 and 4 events (Lavezzi et al. 2018). A recent workshop demonstrated that many FDA-approved anticancer drugs with molecular targets were subject to dose reductions in late-stage registration trials to improve their tolerability (Jänne et al. 2016). As Phase I trials of molecularly targeted agents often do not use toxicity data beyond the first two cycles of treatment to determine the RP2D, it has been suggested that longitudinal relative dose intensity evaluations may be warranted to obtain more robust RP2D levels (Hirakawa et al. 2018).

The comparisons of the on-target PD profiles of targeted therapeutics may help identify the best in class compounds and contribute to the proof of concept obtained early oncology trials involving in biomarker-enriched patient populations. For example, Acalabrutinib and Ibrutinib exhibited comparable on-target PD in regard to changes in CCL3/CCL4 chemokine production, migration assays, and changes in B-cell receptor signaling pathway proteins, and both are associated with high overall response rates and durable remissions in previously treated CLL (Patel et al. 2018).

There is a growing consensus and enthusiasm among oncologists that a more comprehensive evaluation of the drug activity profile including its PD and PK features should be used to identify the RP2D levels. It has been reported that only one third of the studies used toxicity endpoints alone to determine the RP2D (Hansen et al. 2017). That is in part because new-generation targeted anticancer agents exhibit clinically meaningful activity at levels 25% of the MTD (Jain et al. 2010). The potential advantages of including multiple nontoxicity endpoints such as PD, PK, and

efficacy with or without toxicity to define RP2D as an alternative to toxicity alone include the identification of better tolerable effective dose levels. For example, using an accelerated titration, 3 + 3 dose-escalation, open-label Phase I trial (NCT01940133) of continuous once-daily dosing (OD), Wicki et al. evaluated the safety, pharmacokinetics (PK), and pharmacodynamics of PQR309 in patients with advanced solid tumors. PQR309 is an orally bioavailable, balanced pan-phosphatidylinositol-3-kinase (PI3K), mammalian target of rapamycin (mTOR) C1, and mTORC2 inhibitor (Wicki et al. 2018). The MTD and RP2D of PQR309 was 80 mg of orally OD. PK was dose-proportional and PD showed PI3K pathway phosphoprotein downregulation in paired tumor biopsies (Wicki et al. 2018).

Notably, "nonclassically" defined RP2Ds were associated with a statistically significant five-fold higher rate of FDA drug approval for individual anticancer drugs (Hansen et al. 2017). The commonly used Phase I/II designs with an expansion phase after determination of the MTD during a dose escalation phase allow for early evaluation of clinical activity across multiple MTD-based vs. PD-based RP2D levels. Adaptive trial designs with randomized evaluation of multiple RP2Ds provide the opportunity to select the "best" RP2D.

There is general consensus among stakeholders that the first-in-human Phase I studies should be designed with focus on pharmacometrics tools and PK/PD-based nonsafety endpoints to establish a more rationale dose finding paradigm in oncology drug development. The integration of PK/PD data into the dose safety modeling in early oncology studies may provide accurate predictions of the dose–effect relationships by advancing the understanding of target engagement as well as exposure response and therefore has the potential to improve the decision making regarding the optimal dose and schedules as well as risk-benefit assessments for later stages in clinical development (Grisafi et al. 2018). They may also help optimize the benefit–risk profile of oncology drugs through dose adaptation strategies for individualized dosing.

Role of PD Studies in Defining Optimized Treatments Regimens with a New Therapeutic Intervention

PD studies combined with PK and safety evaluations can provide actionable information regarding the alternative dose and schedule to realize the full clinical potential of a new therapeutic intervention. It was discovered that higher systemic exposures of the histone deacetylase inhibitor vorinostat were required than achieved in pediatric Phase I trials with continuous daily dosing for in vivo increased histone acetylation and cytotoxic activity. Consistent histone acetylation in peripheral blood mononuclear cells (PBMC) was only seen at the highest continuous dose level of vorinostat (300 mg/m^2/dose), a dose determined to be too toxic in combination with isotretinoin in a study performed by the Children's Oncology Group (COG) (NCT00217412) (Fouladi et al. 2010). At the continuous vorinostat MTD (230 mg/m^2/dose), only transient histone acetylation was observed. Consequently, Pinto et al. conducted a Phase I trial in children with relapsed/refractory neuroblastoma to determine the MTD of vorinostat on an interrupted schedule, escalating beyond the previously identified pediatric MTD. The maximum intended dose of vorinostat (430 mg/m^2/day) was tolerable when it was combined with isotretinoin. This dose led to increased vorinostat exposures and increased histone acetylation in surrogate tissues (viz., PBMC) when compared to lower doses of vorinostat (Pinto et al. 2018). Overall, the percent change from baseline in histone acetylation levels at 1 h post treatment was significantly greater in dose level 5 compared to dose levels 1–4 and this difference persisted for 24 h.

The metabolism of drugs and therefore the pharmacogenomics (PG) has a substantial impact on systemic exposure levels of the parent compound as well as its metabolites and the risk/severity of toxicities associated with them. The histone deacetylase inhibitors such as abexinostat, panobinostat, romidepsin, and vorinostat are eliminated through glucuronidation by UGT1A1. PD studies combined with PK and PG have demonstrated that polymorphisms (e.g.,

UGT1A1*28 and UGT1A1*60) that reduce UGT1A1 function cause increased systemic exposure, increased global protein lysine acetylation, and toxicities (e.g., thrombocytopenia) (Goey et al. 2016). Multiparameter modeling combining a population pharmacokinetic (PPK) model and a PD model describing the change in platelet levels in patients with cancer administered belinostat as a 48-h continuous intravenous infusion, along with cisplatin and etoposide, has been employed to optimize the treatment schedule and revealed that a q3week schedule of belinostat allows for sufficient platelet recovery before the next belinostat infusion is optimal (Peer et al. 2018).

Many targeted therapeutics, especially tyrosine kinase inhibitors (TKI), inhibit multiple kinases even if they have been labeled as highly selective inhibitors of one particular tyrosine kinase (Uckun et al. 2002, 2007, 2010; Uckun and Qazi 2010). For example, the BTK inhibitor Ibrutinib has been shown to inhibit other tyrosine kinases, including SRC, LYN, FYN, HCK, LCK, YES1, and FGR at nanomolar concentrations (Uckun and Qazi 2010; Honigberg et al. 2010). Therefore, PD evaluations of such compounds should not be limited to a single target kinase occupancy or inhibition in order to better understand its on-target and off-target effects and design appropriate and data-driven risk mitigation strategies. Ilorasertib (ABT-348) inhibits Aurora and VEGF receptor (VEGFR) kinases. In patients with advanced solid tumors, PD studies indicated that ilorasertib treatment engages both of these intended targets, but with maximum inhibition of VEGFR family kinases occur at lower exposures than typically required for inhibition of Aurora B in tissue. In agreement with the PD data, the DLTs in the NCT01110486 clinical trial were predominantly related to VEGFR inhibition (Maitland et al. 2018).

The combined PK and PD evaluations help determine clinical strategies for effective treatment of target patient populations (Stein et al. 2018; Tan et al. 2018; Tham et al. 2008). For example, for the BTK inhibitor Acalabrutinib that has an elimination half-life of 1 h., a twice daily (BID) dosing is used because it has been shown to maintain plasma concentrations that are associated with >95% target BTK occupancy over the treatment interval and inhibition of BTK phosphorylation and activity in peripheral blood circulating CLL cells (Byrd et al. 2016). Likewise, recent analyses of the quantitative relationship between duration of severe neutropenia (the efficacy endpoint) and area under effect curve of absolute neutrophil counts, the PD endpoint, based on data from filgrastim products, a human granulocyte colony-stimulating factor (G-CSF), have provided useful information regarding the relationship between ANC and duration of severe neutropenia that can be used for dose selection and optimization of clinical trial design for G-CSF (Li et al. 2018).

Pegfilgrastim is a long-acting G-CSF indicated for prevention of febrile neutropenia in patients receiving myelosuppressive chemotherapy by promoting neutrophil recovery. In a Phase I, randomized, double-blind, three-way crossover trial in healthy volunteers, Waller et al. evaluated the PK, PD, safety, and tolerability of the proposed biosimilar, comparing MYL-1401H, reference pegfilgrastim (Neulasta®, Amgen Inc., Thousand Oaks, CA, USA) sourced from the European Union, and reference pegfilgrastim sourced from the USA. The primary PK and PD end points were similar across all groups. MYL-1401H demonstrated similar PK, PD, and safety to reference pegfilgrastim in healthy volunteers and may be an equivalent option for the prevention of febrile neutropenia (Waller et al. 2018). Likewise, combined PK/PD studies are often critical in determining if different administration routes of the same compound are equally effective and safe. For example, PK and PD (viz.: 20S proteasome inhibition) parameters of the proteasome inhibitor bortezomib following subcutaneous versus intravenous administration were very similar and this information together with the similar efficacy of subcutaneous versus intravenous bortezomib supports the approved routes of administration for bortezomib (i.e., intravenous and subcutaneous injection) (Moreau et al. 2012).

That being said, there are multiple challenges in incorporating PK and PD endpoints, including but not limited to increased labor, resource

utilization, and trial complexity; increased burden of multiple blood draws, tumor biopsies, and imaging for the patient populations with advanced cancer; and commonly the absence of validated robust assays that can be used to obtain reliable PD endpoints in clinical settings.

Role of PD for Identification and Development of Combined Treatment Modalities

PD studies have the potential to provide early clinical proof of concept when drugs with complementary activity profiles are combined in cancer therapy (Rocchetti et al. 2009). The addition of the base excision repair inhibitor methoxyamine to fludarabine increases DNA double-strand breaks (Bulgar et al. 2010). Caimi et al. determined the safety, PK, PD, and RP2D of the base excision repair blocker methoxyamine combined with fludarabine in adult patients with relapsed/refractory hematologic malignancies (Caimi et al. 2017). They reported that this drug combination resulted in increased DNA damage measured with the Comet assay, as documented by cumulative increases in comet tail length throughout the first week of the combined methoxyamine + fludarabine therapy, indicating progressive DNA damage. The highly significant correlation between decreases in circulating malignant lymphocytes and comet tail length highlighted the relevance of DNA double-strand break measurements as a surrogate PD marker of the antineoplastic effect of methoxyamine and fludarabine. Notably, methoxyamine combined with fludarabine was safe and well tolerated. Hematologic toxicity was comparable to single agent fludarabine. The PD studies therefore demonstrated the potential of this combination as part of conditioning regimens of stem cell transplant and use of methoxyamine as fludarabine dose-sparing agent.

Sometimes, combined use of multiple anticancer drugs results in excellent treatment outcomes, and the question arises if the therapeutic benefits could be further improved by reducing toxicities with fewer cycles of therapy. Functional/metabolic imaging using PET scans has been frequently applied as a PD measure of the activity of the multiagent regimen. For example, the intensive polychemotherapy regimen eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses) is highly active in patients with advanced-stage Hodgkin's lymphoma, but it is also associated with toxicities. Borchmann et al. investigated in a randomized Phase 3 study whether metabolic tumor response as determined by PET after two cycles of standard regimen eBEACOPP would allow response-directed adjustments of treatment intensity, increasing it for PET-positive patients or reducing it for PET-2-negative patients (NCT00515554) (Borchmann et al. 2018). PET negativity after two cycles allowed reduction to only four cycles of eBEACOPP without loss of tumor control. PET-guided eBEACOPP provided outstanding efficacy for all patients and increased the overall survival by reducing treatment-related risks for patients with excellent PET responses. PET-guided personalized reduced intensity treatment strategies should be considered in patients undergoing treatment with highly active regimens for metabolically active tumors such as non-Hodgkin's lymphoma, Hodgkin's lymphoma, NSCLC, breast cancer.

Based on clinical safety and activity data in the NCT01063816 trial, poly-ADP-ribose polymerase (PARP) inhibitors like Veliparib (Niu et al. 2017) or Rucaparib will likely be used in combination with standard chemotherapy drugs especially for treatment of ovarian cancer (Gray et al. 2018). It will be important to obtain detailed PK and PD data using parent-metabolite PK modeling and PD of these targeted therapeutics to gain insights into drug–drug interactions in order to optimize the administration schedules for the various components of the treatment regimens. It is also important to evaluate the impact of food on the PK and PD of these drugs. For example, Rucaparib can be taken with or without food but has different PK parameters when taken with food (versus fasting) probably due to solubility in the small intestine (Dal Molin et al. 2018).

Tegafur/gimeracil/oteracil (S-1) and irinotecan combination is attractive for breast cancer refractory to anthracyclines and taxanes. A reduction in circulating endothelial cell progenitors (CEPs) used to monitor the PD of S-1 is strongly correlated with antiangiogenic effects. Because vascular endothelial growth factor-A-driven tumor angiogenesis for the formation of a functional vascular bed and the subsequent tumor growth partly depend on the mobilization of CEPs, a change in the CEP level may be a predictive marker for antiangiogenesis therapy. The $CD34^+$ circulating endothelial cell (CEC) level was closely associated with the treatment response to chemotherapy, including S-1. Pharmacokinetics and reductions of $CD34^+$ CECs as pharmacodynamics were also analyzed. There was an association between clinical benefit and reduction in baseline $CD34^+$ CECs (4,6-diamino-2-phenylindole $(DAPI)^+$, $CD45^-$, $CD146^+$, or $CD105^+$ and $CD34^+$) by S-1. These results provided the foundation for combined use of irinotecan and S-1 in advanced GI malignancies (Ishiguro et al. 2017).

PD studies in early oncology trials also provide the first clinical proof of concept for further development of a new clinical strategy for difficult-to-treat cancers. Pelareorep, an oncolytic virus and an isolate of reovirus Type 3 Dearing showed single-agent antitumor activity. A recent PD study in patients with advanced pancreatic cancer demonstrated reovirus replication within pancreatic tumor and associated apoptosis, thereby providing the first proof of concept that the high frequency of RAS mutations in pancreas cancer would promote selective reovirus replication in pancreatic tumors and enhance the anticancer activity of gemcitabine (Mahalingam et al. 2018).

Likewise, it will be very important to emphasize PK/PD analyses in clinical trials involving older adults with cancer, especially those over age 75. The careful analysis of both chronological and functional age and comorbidities on PK/PD of new drugs in relationship to the safety- as well as efficacy-related clinical outcome parameters will help identify subsets of older adults who are likely to benefit from specific therapeutic interventions as well as those who are most vulnerable to morbidity and/or mortality (Nightingale et al. 2018).

Pharmacodynamics Modeling for Development of Oncology Drugs

In recent years, population pharmacokinetics–pharmacodynamics (PK-PD) modelling has become a key tool toward streamlining and optimizing oncologic drug development through early understanding, identification, and quantification of various dose–response relationships in the context of other patient characteristics as well as risk-benefit of different dosing schedules (Garralda et al. 2017; Nightingale et al. 2018; Owonikoko et al. 2018; Sato et al. 2017). The development of nonclinical models that can predict the clinical toxicities of immuno-oncology drugs, including immune checkpoint inhibitors and stimulators, is a focal point of emphasis in contemporary translational cancer research and regulatory science/policy workshops (e.g., FDA-AACR Workshop on nonclinical Models for Safety Assessment of Immuno-oncology Products. September 6th, 2018 Marriott Wardman Park, Washington, DC).

PK/PD modeling is a useful tool throughout all stages of drug development, and applications differ during the preclinical and clinical stage. Modeling strategies can accelerate the clinical development process by (i) providing the foundation for an early analysis of the safety and tolerability profile of drug candidates, (ii) early definition of the risk-benefit ratio and the therapeutic index and (ii) supporting the design of optimal treatment regimens (Meille et al. 2017; Zamboni et al. 2001; Zhou and Gallo 2011). Modeling has been extensively used in anticancer drug development to individualize dosing strategies based on patient characteristics, and design optimal and sometimes personalized dosing regimens (Ait-Oudhia and Mager 2016; Block 2015; Buil-Bruna et al. 2016; Ciccolini et al. 2017; Claret et al. 2009, 2015).

Early understanding of toxicities and PK determination of the oral pan-histone deacetylase inhibitor Abexinostat allowed Fouliard et al. to build a PK/PD model of thrombocytopenia,

which predicted the optimal administration schedule allowing higher doses with minimal thrombocytopenia (Fouliard et al. 2013). This optimized schedule is currently used in the trials in solid tumors with abexinostat. Exposure to anthracycline and trastuzumab was simulated based on available dosing records and by using a kinetic-pharmacodynamics (K-PD) and a fixed PK model from literature, respectively. PD models for troponin T and LVEF were successfully developed, identifying maximum troponin T concentration after anthracycline treatment as a significant determinant for trastuzumab-induced LVEF decline. These models can help identify patients at risk of drug-induced cardiotoxicity and optimize cardiac-monitoring strategies.

One of the contributing factors to the high attrition rate for developmental therapeutics in oncology is the inadequate dose and regimen selection combined with an insufficient understanding of the pharmacology to design an optimal drug development program (Postel-Vinay et al. 2016). The US Food and Drug Administration (FDA), European Medicines Agency (EMA), as well as Japan's PMDA consider quantitative modeling and simulation (M&S), including population PK analyses, population PK and PD model analyses, exposure–response analyses, and physiologically based pharmacokinetic (PBPK) model analyses, as useful tools that can provide actionable insights that inform the decision-making process in early-stage as well as late-stage oncology drug development programs. PK/PD models for anticancer agents have been developed and successfully applied to: (1) provide insights into fundamental mechanisms implicated in tumor growth, (2) assist in dose selection for first-in-human phase I studies (e.g., effective dose, escalating doses, and maximal tolerated doses), (3) design and optimize combination drug regimens, (4) design clinical trials, and (5) establish links between drug efficacy and safety and the concentrations of measured biomarkers (Eigenmann et al. 2017; Garralda et al. 2017; Gallo and Birtwistle 2015). The emergent field of pharmacometrics, defined as "the science of developing and applying mathematical and statistical methods to (a) characterize, understand, and predict a drug's pharmacokinetic and PD behavior, (b) quantify uncertainty of information about that behavior, and (c) rationalize data-driven decision making in drug development process and pharmacotherapy," combines principles from pharmacology (PK and PD), statistics, and computational modeling to support drug development and optimize the use of already marketed drugs. Integrated population PK/PD/disease progression models as part of the pharmacometrics platform provide a powerful tool to predict outcomes so that the right dose can be given to the right patient to maximize drug efficacy and reduce drug toxicity (Buil-Bruna et al. 2016; Musuamba et al. 2017; Manolis et al. 2017).

The importance of PK-PD modeling for the drug development process is best illustrated in the example of pembrolizumab (Turner et al. 2018; Elassaiss-Schaap et al. 2017; Freshwater et al. 2017; Patnaik et al. 2015). Modeling helped identify the FDA-approved 2 mg/kg every 3 weeks dose schedule for nonsmall cell lung cancer therapy by predicting that this dose level which is much lower than the 10 mg/kg dose level studied in patients would have robust clinical activity due to intratumor drug exposure estimations. Notably, pembrolizumab was approved just 4 years after the phase I clinical trial started, through breakthrough designation by the FDA. This timeframe clearly contrasts with the 10 or greater years that former drugs traditionally took to be approved.

Model-informed drug development (MIDD) employs mathematical and statistical models to describe disease progression, PK, and PD to improve the clinical trial design and clinically relevant predictions. Advancing MIDD in oncology and identifying regulatory-acceptable best practices pertaining to MIDD will require close collaboration between drug makers and regulatory agencies as well as multistakeholder workshops, such as the 2014 EMA/European Federation of Pharmaceutical Industries and Associations (EFPIA) Workshop on Dose Finding and the 2018 public FDA-International Society of Pharmacometrics (ISOP) Workshop on Model-Informed Drug Development (https://www.fda.gov/Drugs/NewsEvents/ucm589449.htm)

co-sponsored by the FDA's Center for Drug Evaluation and Research (CDER) and ISOP (Musuamba et al. 2017; Manolis et al. 2017; Schindler et al. 2018). The EMA Modelling and Simulation Working Group (MSWG) in collaboration with the FDA-Office of Clinical Pharmacology (OCP) pharmacometrics group strive to facilitate the much-needed harmonization on good M&S/MIDD practices through dialog and collaboration across all stakeholders. The desired goal is to develop "best practices in integrating PK, PD, efficacy, and safety data into models to best inform oncology drug development, evaluate disease- and mechanism-specific early endpoints to predict long-term efficacy, and discuss potential regulatory implications of model-informed decisions in drug development."

Emerging Role of Quantitative Systems Pharmacology for Model-Informed Drug Discovery and Development

Traditional PD models attempt to determine drug effects by integrating specific and confirmatory similar datasets and then predicting results in related scenarios. In this paradigm, the models are parsimonious, the parameters of the models can be identified, and therefore the models can incorporate population variability and define parameter uncertainties. An emerging new approach is termed "Quantitative Systems Pharmacology" that advances systems level, multiscale models for disease progression and treatment (Iyengar et al. 2012; Lai et al. 2018; Musante et al. 2017; Ribba et al. 2017). 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. These PD models are highly mechanistic and take into consideration the effects of drug actions spanning from the scale of molecular interactions to organ-level responses. Since these interactions are nonlinear at the multiscale levels, the effects of drugs exhibit emergent behaviors relating to pronounced on-target and off-target PD actions of drug treatments. These models strive to integrate data from diverse datasets and hence have required the development of model exchange platforms such as PharmML (Bizzotto et al. 2017) and sophisticated toolboxes to perform multiscale simulations and apply nonlinear statistical analyses (Cheng et al. 2017; Eissing et al. 2011). These types of models prioritize biological detail over parameter identifiability and the simulations enable rich exploration of mechanistic variabilities to better identify on-target and off-target PD effects of drug action. An important aspect of these models relating to precision medicine goals is to explain differences in drug efficacy and toxicity in heterogeneous populations that display genetic or biomarker profile differences.

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