

## REVIEW

# Toward Optimum Benefit-Risk and Reduced Access Lag For Cancer Drugs in Asia: A Global Development Framework Guided by Clinical Pharmacology Principles

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## INTRODUCTION

Delay in approval (“drug lag”) of new anticancer therapies in Asia has led to increased interest in simultaneous global clinical development inclusive of Asia. Anticancer agents often have a narrow therapeutic window, making characterization of pharmacokinetics (PKs), pharmacodynamics, and safety crucial for maximizing benefit/risk in Asian populations. Herein, we present a global oncology drug development framework informed by quantitative clinical pharmacology, including an exposure-matched dosing strategy when clinically significant PK differences are encountered in Asia.

Cancer is among the leading causes of death worldwide. It has been estimated that > 14 million new cases of cancer and >8 million cancer-related deaths occurred in 2012.<sup>1</sup> Based on predictions of population growth in different regions of the world, the number of new cancer cases may reach more than 20 million annually by 2030.<sup>2</sup> Of note, Asia is estimated to account for half the global burden of cancer.<sup>3</sup> In order to meet the expected need for treatment, drug development strategies should include a global focus to ensure broad worldwide availability and access to new anticancer drugs. Global development strategies inclusive of Asia will be particularly important for malignancies that are more common in Asian regions, such as hepatic, gastric, and esophageal cancer,<sup>1</sup> although a global approach is equally valuable for the development of drugs for other cancers (e.g., colorectal, breast, and lung cancers) that are becoming more prevalent in Asian countries as a consequence of an increasingly Western lifestyle and diet, and changes in smoking patterns.<sup>2</sup>

Drug development and approval in Asian countries often lag behind those of Europe and North America, and there is a significant unmet need to improve access to drugs for patients in Asia. Delays in access arise in part from specific regulatory requirements for local patient data across Asia (e.g., Japan, China, and Taiwan). For example, to receive approval in Japan from the Pharmaceuticals and Medical Devices Agency, clinical safety and efficacy data from Japanese patients must be part of the submission. To help

speed approval by taking advantage of clinical data obtained outside Japan, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued a set of recommendations in 1998.<sup>4</sup> This guidance, known as ICH E5, discusses the potential sources of differential pharmacokinetic (PK), pharmacodynamic (PD), and clinical responses in different ethnic populations, and describes the circumstances under which data from clinical trials outside Japan can be used in concert with Japanese clinical data to support registration in Japan. The development strategy that emerged after publication of ICH E5 is known as a “bridging strategy,” and has been conceptually applied throughout Asia. A notable example of the application of ICH E5 principles to enhance Asian drug development efficiency is the Bridging Study Evaluation review process adopted in Taiwan. The Bridging Study Evaluation considers the ethnic sensitivity of the PK, PD, safety, and efficacy of a drug to intrinsic and extrinsic differences between populations to determine the need for a local bridging study.<sup>5</sup>

Despite the ICH E5 guidance, delays in drug development still exist in Asia. Evaluation of factors contributing to approval lag in Japan has been the subject of many recently published analyses.<sup>6–10</sup> In a recent review of oncology drugs approved between 2001 and 2014 in Japan and also approved in the United States, a steady decline in approval lag over this time period has been reported, with the median approval lag for drugs approved in 2014 (9.4 months;  $N = 10$ ) being still meaningful but substantially lower than that for the overall set of drugs approved during 2001–2014 (29.2 months).<sup>9</sup> However, this review only focused on Japanese oncology drug approvals, and while the data suggest that the lag, although not eliminated, has considerably decreased in recent years, the delays in approval in certain Asian countries (e.g., China) owing to specific local requirements among other factors remain a challenge. For example, regulations in China specify local data from 100 patients/pairs (active:reference) for small molecules and 300 patients/arm for biologics as being required to support registration, although the epidemiology of the disease may

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impact the specific requirements for a given development program.<sup>11,12</sup>

In an effort to reduce lags in development and approval, there is increasing interest in the creation of global drug development strategies.<sup>10</sup> Adoption of a global perspective may be an opportunity to reduce the number of redundant trials, improve overall trial design, and obtain clinical data that can be used to support approval in Asian countries and inform labeling in Asian populations. In analyses of factors associated with the lag in drug approvals in Japan, clinical development strategies that included global/multiregion clinical trials were associated with shorter delays.<sup>7-9</sup> There is also evidence that the use of global clinical trials is steadily increasing,<sup>13</sup> and oncology has the highest proportion of these more inclusive development approaches.<sup>14</sup> However, a global approach to drug development faces a number of key challenges. Available therapies (e.g., standards of care [SOC] that may have been a component of prior treatments received, or may constitute the backbone to which the investigational agent is added as a combination) and disease characteristics may differ among regions. In addition, the worldwide population is heterogeneous, and a number of intrinsic and extrinsic factors impact drug exposure, clinical response, and benefit:risk assessment in different populations.<sup>15,16</sup>

Perhaps one of the greatest challenges facing global drug development is adequate assessment of the PK/PD/safety of new drugs in diverse patient populations. The sources of regional differences in drug exposures, safety, and efficacy are complex and multifactorial and can result in regional differences in drug dosages required to achieve an optimal benefit:risk ratio. Recent reviews of drugs approved in Japan (2001–2009) have revealed that the Western dose was higher than the dose approved in Japan for 32% of drugs across all therapeutic classes, and the Western dose was more than twofold higher than the Japanese dose for 19% of drugs.<sup>17,18</sup> Based on a review of 40 oncology drugs approved in Japan between 2001 and 2013, the approved doses in Japan and the United States/European Union were different for 5 (12.5%) of these 40 drugs.<sup>19</sup> The authors broadly categorized the drugs as cytotoxics or molecularly targeted agents and observed that, although the approved doses were generally conserved for molecularly targeted agents, the approved doses in Japan were lower for 4 of 10 cytotoxic drugs that were approved across the regions.<sup>19</sup> These observations likely reflect differences in therapeutic index of molecularly targeted and cytotoxic agents, and the selected clinical dose in relation to the maximum tolerated dose (MTD). In a recent survey of phase I dose-escalation studies of anticancer agents conducted in Japan, it was observed that 80% of the drugs examined had a similar MTD in Japan and in the Western population. This suggests that the dose-toxicity relationship and observed MTD is different in Japan relative to the West for one of five investigational anticancer agents, and supports the importance of early prospective characterization of safety, PK, and dosing for Asia to facilitate timely globalization of clinical development with an optimum benefit:risk profile for patients in Asia enrolled into global clinical trials.<sup>20</sup>

In the era of targeted anticancer therapies and the evolving balance between benefit and risk for noncytotoxic anticancer treatments, there is increasing advocacy and regulatory expectation for a systematic and objective optimization of dose in clinical development (i.e., optimal biologic dose), such that dosing by default at the MTD is no longer considered acceptable.<sup>21</sup> As uncertainty can be high in the PK/PD relationships for desired anticancer PD effects and in the exposure-safety relationship for long-term safety based on phase I data, a dose-ranging phase II study is recommended to enable optimization of dose and the associated benefit-risk profile.<sup>22</sup> These considerations, by extension, warrant the need to objectively define the optimal dose in global clinical trials across all patient populations (including Asian patients) based on exposure and exposure-response principles.<sup>23</sup> Drug exposure may be different in Western (non-Asian) vs. Asian populations.<sup>24</sup> A key question for clinical pharmacologists in supporting global oncology drug development strategies that are inclusive of Asia is whether a common global dose for clinical trials is appropriate or whether any observed differences in the overall PK/PD/safety profile are sufficiently clinically meaningful to warrant selection of a different dose for this region. Although specific local regulatory expectations for assessment of regional or ethnic sensitivity ahead of globalization of oncology clinical trials may differ, it is important that clinical pharmacologists and drug developers address this question prospectively to ensure that any ethnic differences and implications for dosage for Asian patients are considered in the design of a global clinical development plan. This is especially crucial for small molecule drugs and antibody-drug conjugates that contain small molecule cytotoxic payloads, in which drug disposition can be different between Asian and Western populations. However, the risks for ethnic sensitivity in PK and differences in dosage between Asian and Western patient populations are lower for antibody therapeutics.<sup>25</sup>

In this review, we discuss the importance of prospective integration of quantitative clinical pharmacology considerations in characterizing dosage of anticancer drugs in Asian patient populations to enable globalization of development to include Asia. This review discusses this topic from the perspective of the common scenario of initiation of clinical development in the West rather than in Asia. In some cases, depending on the epidemiology of the specific cancer type (e.g., gastric cancer, which is more common in Asia) or other considerations, it is possible for Asia to lead initiation of clinical development. In such cases, the concepts and development strategies discussed here should be translatable in principle (albeit in the reverse direction from Asia to the West) in order to efficiently globalize clinical development to include the West and minimize global access lag.

The concepts illustrated in this review are in the context of single agent development. However, it should be noted that combinations of new molecular entities with established SOC as well as new molecular entity-new molecular entity novel-novel combinations represent important components of oncology drug development. Although not explicitly discussed here, the fundamental principles discussed in this review are foundational in the context of combination

development, in which the potential for differences in PK/PD properties and dose requirements for the multiple combination partners will need to be considered in addition to other clinical pharmacology considerations, such as the assessment of the potential for mutual drug-drug interactions between the combination partners. In addition, for combinations of the investigational agent added onto an SOC backbone regimen, a key question is whether the dose and dosing schedule of the SOC regimen is conserved in Asia vs. Western regions, as this will be an important consideration in defining the overall global clinical development strategy.

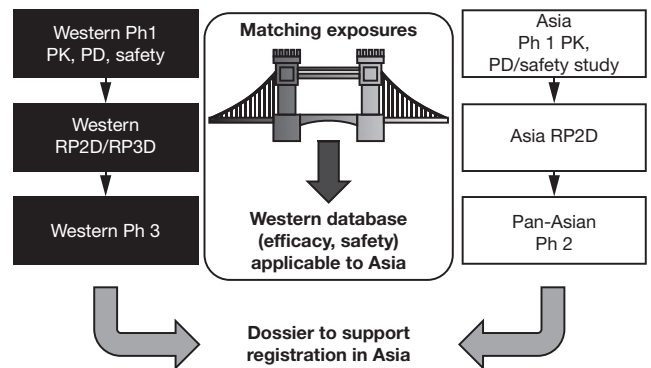
Asia is a diverse continent. Information on race/ethnicity is self-reported by patients enrolled in clinical studies with variable classifications that may be used in data collection tools, thereby impacting the analysis of race/ethnicity data in drug development settings.<sup>16</sup> In the context of these practical realities, the term “Asia,” as used in this review, refers primarily to the East and North Asian region of the continent (i.e., countries comprised primarily of Chinese, Korean, and Japanese ethnic populations). Indian, Indonesian, and Malay populations, for example, are highly heterogeneous with admixed gene pools and pharmacogenetic characteristics<sup>26–28</sup> that cannot be assumed to mirror those of the Chinese, Korean, and Japanese populations that are commonly categorized as collectively belonging to the Asian race in the context of drug disposition evaluations and population PK covariate analyses in drug development.<sup>16,29–31</sup> Accordingly, although the lack of clinically meaningful ethnic sensitivity in the major Asian ethnicities relative to Western populations may permit seamless consideration and integration of the entire continent as a whole in global drug development, the converse may not be true as differences in drug disposition, PK/PD properties, and consequently dosage requirements between Asian (i.e., Chinese, Korean, and Japanese) and Western populations cannot be assumed to directly apply to other highly heterogeneous sections of Asia, such as the Indian subcontinent, Malaysia, or Indonesia.

## GLOBAL DEVELOPMENT AND REGISTRATION STRATEGIES

The two most common approaches to global drug development, inclusive of Asia, are the bridging strategy and the global phase III strategy. Irrespective of the strategy used, a common guiding principle and prerequisite is the need for a comprehensive understanding of PK/PD and safety across populations over the clinically relevant dose range.<sup>4,14</sup> In this section, we will discuss how these two strategies apply to anticancer drugs.

### Bridging strategy

The bridging strategy (**Figure 1**) is a traditional approach that requires conduct of a phase II bridging study in Asia designed according to ICH E5 guidelines. With this approach, phase I and II studies are conducted in Western regions to establish PK/PD, safety, and efficacy profiles. From these results, a phase III registration trial is normally conducted in the West. Although the primary efficacy end point used in the phase III trial depends on the specific indication and associated medical and regulatory considerations, overall survival and/or



**Figure 1** Bridging study approach to oncology drug development and registration in Asia. Ph 1, phase I; Ph 2, phase II; Ph 3, phase III; PD, pharmacodynamic; PK, pharmacokinetic; RP2D, recommended phase II dose range; RP3D, recommended phase III dose range.

progression-free survival are the typical primary clinical efficacy end points. To extend development to Asia, phase I studies that include comprehensive PK characterization are conducted in Asia. If appropriate markers of drug effect are available and were used to define a bioactive dose/exposure range in the Western phase I studies, it is valuable to perform the same PD measurements in the Asian phase I studies. The Asian PK, safety, and PD (where available) data, viewed in the context of the comparable Western data and the exposure-efficacy relationship in the Western phase II study, can be used to define an acceptably tolerated, safe, and clinically active recommended phase II dose (RP2D) for Asian patients. If PK differences are noted in Asian patients requiring a different RP2D for that region compared with the Western phase III dose, the Asian dose although different from the Western dose, can be scientifically rationalized as pharmacologically equivalent for purposes of bridging, based on matching systemic exposures across the populations. The similarity of exposures at the Western and Asian doses based on PK data and supportive PD results (when available) should enable establishment of an appropriate Asian RP2D. After characterization of PK/PD properties and establishment of the Asian RP2D, a phase II bridging study can be conducted in Asia using an acceptable surrogate efficacy end point. If uncertainty in the Asian dose remains (e.g., due to lack of adequate PK/PD understanding to establish a single RP2D for Asia), a dose-ranging design may need to be considered for the Asian phase II bridging study. Results from the phase II bridging study in Asia can then be used to determine whether efficacy and safety profiles in Asian patients are consistent with those observed in the Western phase III trial. Extrapolation of long-term efficacy (e.g., survival benefit) and safety to the Asian population is based on ICH E5 bridging principles and takes into account similarity of exposures across populations and comparable response rates to contribute to the dossier and support approval in Asia.

### Global clinical trial strategy

The global clinical trial strategy for drug development and registration, inclusive of Asia, is becoming increasingly common; a recent review reported that the proportion of global

clinical trials that include both Western and Asian populations is increasing while the proportion of bridging trials is decreasing.<sup>13</sup> The drivers for globalization of oncology clinical development to include not only Japan but also Korea and China have been discussed at multiple recent Asia Cancer Forums,<sup>32,33</sup> with similar ethnic, dietary, and social habits noted as opportunities for joint efforts. In order to address local regulatory requirements in Japan and China efficiently without the need for separate bridging phase II trials, a simultaneous global drug development program comprised of a multiregional clinical trial with a local clinical trial extension phase has been proposed and the associated sample size requirements have been statistically evaluated.<sup>34</sup> Japanese regulatory authorities are encouraging pharmaceutical companies to enroll Japanese patients into global trials and are becoming more flexible in evaluating clinical results from different regions to support simultaneous filing in Asia, provided that an adequate characterization of ethnic and regional sensitivity to intrinsic and extrinsic factors is prospectively gained in clinical development and there is an adequate representation of Japanese patients in the global trials.<sup>13,35</sup> One advantage of the global clinical trial strategy compared with the bridging strategy is less lag time in drug development. A review by Ueno *et al.*<sup>8</sup> reported that, for 183 drugs approved in Japan between 2007 and 2012, the median lag between submission in the West and submission in Japan was ~50 months for drugs developed using a bridging strategy, compared with ~3 months for drugs developed using a global clinical trial strategy.

Inclusion of Asia in pivotal oncology clinical trials can, in some cases, accelerate clinical development by enhancing trial efficiency. This can be especially important in the current era of precision medicine and targeted therapies in which specific molecular signatures predictive of efficacy may be observed at a higher incidence in Asian patient populations. In such cases, Asia may in fact lead the way in facilitating global drug development and constitute a major portion of the global clinical trial population. For example, afatinib, a covalent inhibitor of epidermal growth factor receptor, was approved in the United States for the first-line treatment of patients with metastatic nonsmall cell lung cancer (NSCLC) harboring epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations,<sup>36</sup> as well as in multiple other countries (e.g., European Union, Canada, Taiwan, and Japan), based on data from the “LUX-Lung 3” global pivotal trial. Given that the incidence of somatic *epidermal growth factor receptor* mutations in NSCLC in non-Asian patient populations (15–22% in Europe and North America) is substantially lower than in East Asian populations (47%),<sup>37</sup> and given that patients were selected for inclusion in LUX-Lung 3 by molecular subtype, ~70% of patients enrolled were Asian.<sup>38</sup> This randomized trial of afatinib vs. pemetrexed/cisplatin stratified patients based on Asian vs. non-Asian race and demonstrated that afatinib significantly improved progression-free survival in the overall trial population. In addition, exploratory subgroup analyses of progression-free survival showed consistent results favoring afatinib in both the Asian and non-Asian subgroups,<sup>39</sup> indicating that inclusion of a substantial number of Asian patients did not introduce heterogeneity in terms of progression-free

survival outcomes. In fact, in cases where access to Asian patient populations can facilitate enrollment and trial efficiency, it would be valuable to consider early globalization in a phase II study without waiting for the confirmatory phase of development.

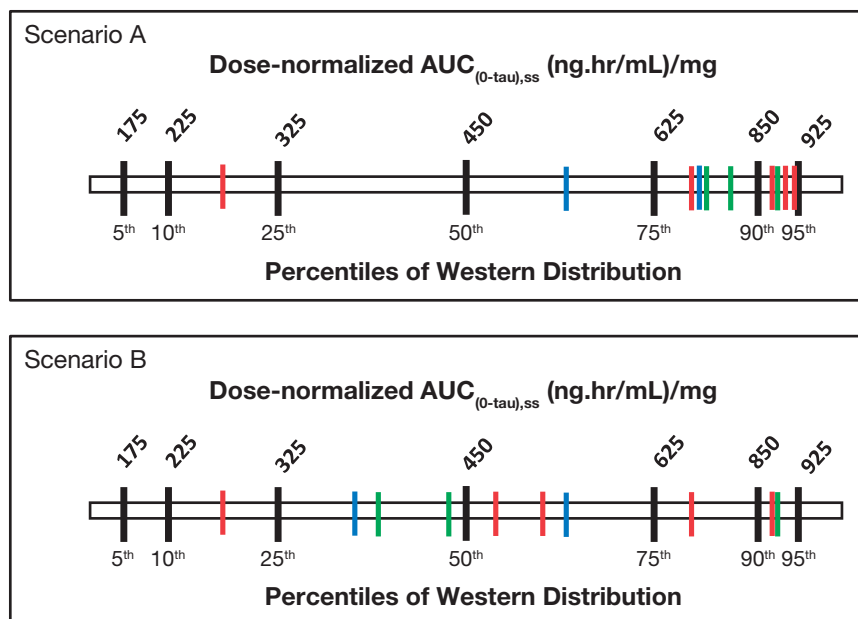
Historically, one limitation of the traditional global clinical trial strategy is that it is typically only feasible when reasonable PK/PD/safety similarity exists across all ethnic groups, which allows for utilization of a common global dose. In the above example of afatinib, there were no statistically significant differences in afatinib PK or exposure between Asian patients (mainly Chinese, Japanese, Korean, South-east Asian, and Taiwanese) and non-Asian patients. The data supported a broad conclusion that race has no clinically meaningful effect on afatinib exposure.<sup>40,41</sup> This finding contributed to a successful global clinical development strategy inclusive of Asia.

When clinically meaningful differences in drug exposure are noted between Asian and non-Asian patient populations, the necessity to vary the dosage for Asian patients can be a challenge when designing global pivotal trials. In the subsequent sections of this review, we offer some perspectives on considerations for dose determination for the Asian region to improve global clinical trial design, and we identify opportunities for quantitative clinical pharmacologists to enable consideration of global trial designs even in the presence of regional differences in drug exposure and consequently dosage requirements.

## PK/PD-INFORMED DOSE SELECTION FOR THE ASIAN REGION

A quantitative clinical pharmacology assessment is critical for dose selection in Asian patients. Recent scientific advances in physiologically based PK (PB-PK) modeling have enabled early prediction of potential differences in PK between Asian and non-Asian populations, based on an understanding of underlying molecular determinants of drug disposition.<sup>42</sup> For example, population PB-PK modeling frameworks have been described for predicting potential differences in systemic exposures between Chinese<sup>43</sup> or Japanese<sup>44</sup> and non-Asian populations for drugs metabolized by cytochrome P-450 (CYP) enzymes. Various factors (not limited to functionally relevant polymorphisms in genes encoding enzymes, such as CYP2C19 that display inter-ethnic differences in allele frequencies) can explain differences in the PK of drugs between Asian and non-Asian patient populations. For example, the intrinsic activity of the hepatic uptake transporter OATP1B1 is lower in Asian populations (estimated to be 40% lower in Japanese) than in non-Asian populations,<sup>45</sup> translating to higher systemic exposures of some of its substrates and, in some cases (e.g., the statin drug rosuvastatin), even a recommendation in the label for a lower starting dose in Asian populations.<sup>46</sup> Predicting PK in Asian populations based on a PB-PK model that is adequately qualified to predict the drug's PK in non-Asians represents a powerful approach to forecast the level of risk for differential drug exposures in Asian patients and to guide design and starting doses for the first Asian phase I study.

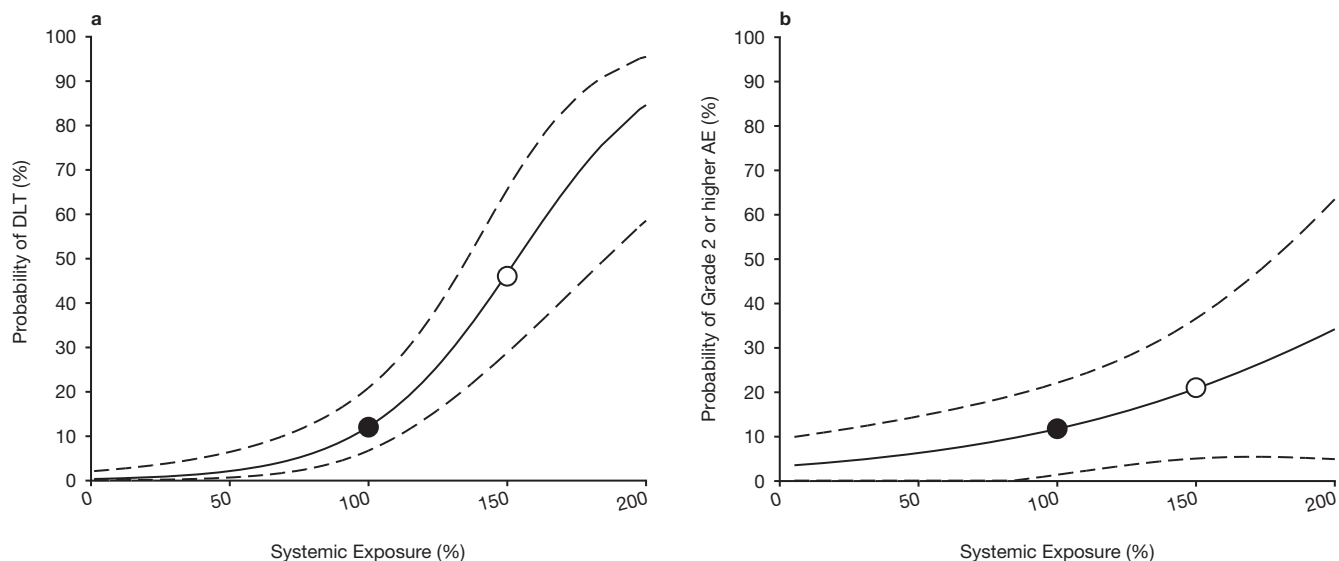




**Figure 2** Application of a population pharmacokinetic (PK) model-based framework to interpret emerging PK data from an ongoing, phase I, dose-escalation study in Asia. The thick black vertical lines mark the percentiles of the Western dose-normalized exposure distribution and dose-normalized exposures in individual patients in the Asia phase I study are shown as the shorter colored vertical lines. In **Scenario A**, the data indicate a higher dose-normalized exposure in Asian patients whereas in **Scenario B**, there are no readily apparent differences between Asian and Western patients, suggesting a low risk for exposure-related differences in dose between Asia and the West.  $AUC_{(0-\tau),ss}$ , area under the plasma concentration-time curve from time zero to time tau at steady state.

Population PK assessment of data from the Western clinical experience can determine sources of variability and identify factors contributing to potential PK differences in Asians. Factors requiring specific consideration may include body size and genetic polymorphisms that lead to changes in the absorption, distribution, metabolism, and excretion (ADME) of drugs in Asian populations. Importantly, the Western population PK model provides a quantitative framework to enable comparison of PK in Asian and non-Asian populations. A simple overlay of observed exposures in an Asian phase I study on the percentiles of the distribution of exposures from a stochastic simulation from the Western population PK model should allow an objective assessment of population differences in systemic exposures of the investigational agent, as illustrated in **Figure 2** using two scenarios A and B for hypothetical investigational agents. The distribution of dose-normalized exposures of the investigational agent in the Western population is characterized based on a population PK analysis, with the vertical solid black reference lines tracking the percentiles of the distribution (indicated in the numbers above the reference lines). Emerging data from PK-evaluable patients in cohorts one to three of an ongoing Asian phase I dose-escalation study are overlaid on the Western distribution (three patients at dose level 1 in green, two patients at dose level 2 in blue, and five patients at dose level 3 in red). In Scenario A, the data clearly reveal a higher exposure in Asian patients, with 8 of 10 patients showing dose-normalized exposures that exceed the 75th percentile of the Western distribution. In contrast, in Scenario B, there are no readily apparent trends suggestive of differences

in dose-normalized exposures between Asian and Western patients when considered in context of overall PK variability, as inferred from an approximately equal distribution of data on either side of the median of the Western distribution, suggesting a low risk for exposure-related differences in dose between Asia and the West. Such a model-based distributional framework for exposure is particularly helpful when reviewing emerging cohort-level PK data from small numbers of patients in Asian phase I dose-escalation studies, as it enables an objective interpretation of these data in relation to the broader Western clinical PK experience. Comparison of PK profiles across regions is crucial for predicting similarities and differences in safety and efficacy and to enable determination of appropriate doses in global clinical trials. Characterization of exposure-safety and exposure-PD (where available) relationships is necessary to assess the potential clinical relevance of observed PK differences in Asian vs. non-Asian populations in relation to compound-specific therapeutic index considerations.<sup>23</sup> This is important because PK differences alone cannot be used in isolation to guide dosing decisions. For example, although steady-state exposure of the anaplastic lymphoma kinase inhibitor crizotinib is clearly 50% higher in Asian vs. non-Asian patient populations,<sup>47</sup> that difference was not considered clinically relevant to warrant dose adjustment for the Asian population based on the safety and efficacy profile,<sup>48,49</sup> enabling clinical development and subsequent approval across Asian and Western countries for anaplastic lymphoma kinase-positive NSCLC at a common global dose when administered according to applicable safety monitoring and toxicity management guidelines.

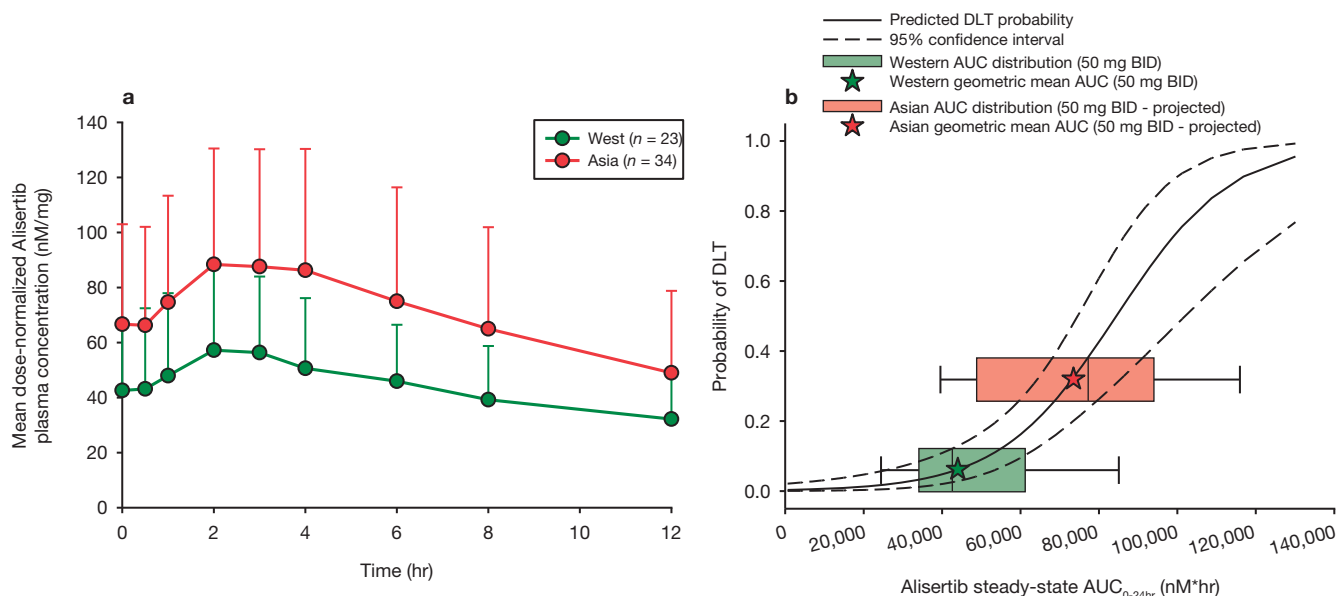


**Figure 3** Application of exposure-safety analysis in interpreting clinical relevance of exposure differences between Asian and Western patient populations to guide determination of dose for Asia. (a) and (b) depict two representative scenarios illustrating the value of quantitatively understanding exposure-toxicity relationships in interpreting the clinical relevance of pharmacokinetic (PK) differences between Asian and Western populations and guiding determination of the dose for Asia. In both panels, systemic exposures on the x-axis are plotted as a percentage of the mean exposure at the Western clinical dose in Western patients. The solid lines are the estimated exposure-toxicity relationships based on logistic regression analyses of Western clinical data, with the dashed lines representing the associated 95% confidence intervals. The solid and open circle symbols are positioned on the exposure-safety relationship at the mean Western and Asian population exposures, respectively. AE, adverse event; DLT, dose-limiting toxicities.

The application of PK/PD principles to guide dose determination for Asian populations is illustrated in **Figure 3** using two representative hypothetical scenarios. Consider two investigational anticancer drugs, A and B, that both display a modestly (50%) higher mean exposure in Asian vs. non-Asian patients based on phase I PK results. Drug A is a cytotoxic agent dosed at its MTD and is associated with risk of febrile neutropenia and severe (grades 3–4) mucositis at doses and exposures above the MTD. In contrast, drug B is a targeted agent administered at an optimized dose (50% of its MTD) demonstrated to be biologically active and tolerable. The principal adverse events associated with drug B are grade 1–2 rash and fatigue, and the overall safety profile indicated a <15% incidence of grade 2 toxicities across phase I/II studies at the selected clinical dose, permitting long-term, daily, oral dosing. **Figure 3a, b** show the respective exposure-toxicity relationships for drugs A and B developed from logistic regression analyses of clinical PK and safety data from their respective Western development programs. Based on the steepness of the exposure-toxicity relationships for A and B, it is clear that drug A has a narrow therapeutic range, such that the 50% higher exposure in Asian populations can be expected to translate to an unacceptably high (nearly 50%) incidence of dose-limiting toxicities (DLTs). In contrast, although the same relative increase in exposure to drug B is expected in the Asian population, that translates to a more modest increase in adverse event burden (21% vs. 12% incidence of grade  $\geq 2$  toxicity), which should be manageable with appropriate dose reductions, as needed, in individual patients. A global drug development strategy with a

common dose would not be advisable for drug A, and PK/PD considerations support evaluation of a reduced dose (e.g., two-thirds of the Western clinical dose) for Asian patients. Although the dose for Asia needs to be reduced for drug A to avoid exposures exceeding the MTD and to maintain a favorable safety profile, it is important to appreciate that this does not put efficacy at greater risk for patients in Asia relative to the West, as the systemic exposures at the reduced dose in Asia will match those observed in Western patients receiving the full Western dose. In contrast, a global phase III trial at a common dose across regions should be feasible for drug B.

We will now discuss a recent example of the case of an investigational Aurora A kinase inhibitor, alisertib, which is similar to the scenario illustrated in **Figure 3a**. Alisertib is a cytotoxic agent that is under development for hematologic and nonhematologic malignancies. In the single-agent setting, phase I studies conducted in the United States<sup>50,51</sup> and Europe<sup>52</sup> determined an MTD/RP2D of 50 mg b.i.d. administered for 7 days in 21-day treatment cycles. Population PK, exposure-PD, and exposure-safety analyses were performed on data collected across the Western clinical development program.<sup>53</sup> These quantitative clinical pharmacology analyses supported achievement of bioactive exposures associated with robust PD effects of decreased chromosome alignment and spindle bipolarity in tumor mitotic cells indicative of target inhibition while providing acceptable tolerability (<10% estimated population incidence of DLTs). In order to enable future globalization of clinical development of alisertib to include Asia, a dose-escalation phase I PK and safety study was conducted in patients with cancer of Korean and



**Figure 4** Rationale for lower Asian recommended dose of the investigational anticancer agent alisertib relative to the Western patient population. (a) Shows the steady-state, dose-normalized plasma concentration-time profiles (mean + SD) in patients with advanced cancers in Asia ( $n = 34$ ; red symbols and lines)<sup>54</sup> in comparison to corresponding data in Western patients ( $n = 23$ ; green symbols and lines).<sup>51</sup> (b) Shows the estimated relationship between steady-state area under the concentration-time curve (AUC) and probability of dose-limiting toxicity (DLT) for alisertib (with 95% confidence intervals) in Western patients.<sup>53</sup> Overlaid are the AUC distributions at the Western recommended phase II dose (RP2D; 50 mg b.i.d.; green box plot, with green star at the geometric mean) and the projected distribution at this dose if administered to patients in Asia (red box plot, with red star at the projected geometric mean).

Chinese races enrolled from across clinical sites in South Korea, Taiwan, Hong Kong, and Singapore.<sup>54</sup> This phase I study was designed with a starting dose level of 30 mg b.i.d. (60% of the Western MTD, representing dose level -2 in the West) in the first cohort, and planned escalations to 40 mg b.i.d. and 50 mg b.i.d., as permitted by safety/tolerability according to the rules of a traditional 3+3 design. Whereas no DLTs were observed among the first three evaluable patients enrolled at the starting dose of 30 mg b.i.d., two of five evaluable patients at the 40 mg b.i.d. dose experienced DLTs of grade 3 stomatitis and grade 4 neutropenia lasting for over 1 week, reflecting the antiproliferative/cytotoxic effects of alisertib. PK analyses indicated that dose-normalized steady-state exposures of alisertib were ~70% higher in the Asian population than the corresponding exposures observed in previous Western population studies (Figure 4a). Subsequent expansion of the 30 mg b.i.d. dose level in the Asian phase I study confirmed acceptable tolerability and a PK and safety profile that was consistent with that observed at the 50 mg b.i.d. dose in the Western patient populations. Although the reasons for the observed exposure differences in this case remain to be understood, the differences in dose-toxicity relationships and the 40% lower RP2D established in Asia relative to the West were reconciled very well by the observed differences in systemic exposure. In fact, based on the Western and Asian PK data, the exposure distribution in Asia at 30 mg b.i.d. was nearly identical to that observed at 50 mg b.i.d. in the West, and translated to a low (<10%) DLT incidence when viewed in the context of the exposure-DLT probability relationship. In contrast, a 50 mg b.i.d. dose in

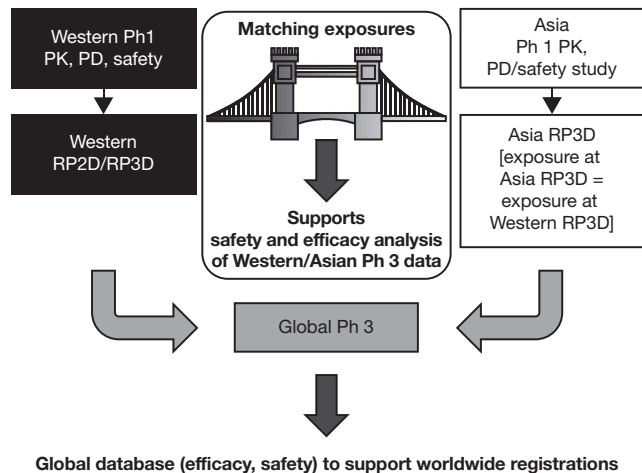
Asia, if advanced into a global clinical trial without phase I characterization in Asia, would be expected to result in exposures translating to a DLT incidence of 32% (Figure 4b). Taken together, this example underscores the importance of systematic PK and safety characterization of investigational anticancer agents in Asian patients to ensure appropriate dose selection, and help establish the preliminary benefit/risk balance ahead of expansion of clinical development to include Asia.

It is also important to prospectively consider potential pharmacogenetic sources of heterogeneity that can influence drug exposure and/or PD and/or antitumor activity.<sup>55</sup> Specifically, collecting relevant pharmacogenetic data in both Western and Asian phase I studies to determine the contribution of purely genetic variation vs. other ethnic and regional factors is important to guide appropriate bridging, trial design, and dosing decisions for subsequent global development. In some cases, there may be genotypes particularly relevant to Asian populations that will require expansion of the pharmacogenetic assay platforms to include their evaluation as part of planning for a clinical protocol in Asia. For example, *UGT1A1\*6* is an important Asian-selective allelic variant that contributes to decreased clearance of *UGT1A1* substrates in addition to other established allelic variants of global cross-population significance, such as *UGT1A1\*28*. Studies with irinotecan (whose active metabolite SN-38 is primarily cleared via *UGT1A1*-mediated glucuronidation) in Asian patients with cancer have consistently demonstrated an association between *UGT1A1\*6*-containing genotypes and severe neutropenic toxicity.<sup>56,57</sup> In

a phase I, dose-escalation study of nanoliposomal irinotecan (PEP02) in Taiwanese patients with advanced solid tumors, treatment-related severe toxicities (grade 4 febrile neutropenia, grade 4 thrombocytopenia with bleeding, and grade 4 diarrhea) led to death in a patient with combined heterozygosity of *UGT1A1\*6/\*28* and increased SN-38 exposure.<sup>58</sup> This example emphasizes the critical importance of carefully considering sources of exposure variability based on available ADME understanding when initiating clinical evaluation in Asian populations. Where appropriate, depending on the ADME properties, safety profile, and therapeutic index of the investigational agent, it may be necessary to consider initial exclusion of potentially “vulnerable” genotypes to ensure patient safety and enable appropriate dose determination; enrollment of those patients could begin when sufficient clinical experience on dose-exposure/toxicity relationships in the nonvariant genotypic population is available.<sup>59</sup>

The importance of drug metabolism enzyme genotype considerations for Asian development is illustrated by the case of the c-Met inhibitor tivantinib, which is metabolized at least in part by CYP2C19, a genetically polymorphic enzyme with a poor metabolizer frequency of only ~2% of white people but ~20% in East Asians.<sup>60</sup> The RP2D of tivantinib was determined to be 360 mg b.i.d. in a phase I, dose-escalation study in Western patients with solid tumors.<sup>61</sup> A Chinese patient treated with 360 mg b.i.d. in this Western phase I study experienced excessive toxicity (grade 4 febrile neutropenia and grade 3 mucositis) with elevated systemic exposures subsequently linked back to a *CYP2C19\*2/\*2* poor metabolizer genotype.<sup>61</sup> This observation together with knowledge of metabolism of tivantinib by CYP2C19 led to a modification of the design of the Japanese phase I study to include stratification by CYP2C19 genotype.<sup>62</sup> The MTD/RP2D was determined separately in Japanese CYP2C19 extensive metabolizer and poor metabolizer patients to be 360 mg b.i.d. and 240 mg b.i.d.; this dosing strategy was supported well by the observed PK data across the patient populations.<sup>62</sup>

Another example is the recent discovery in a multiracial, genome-wide, association study that the nonsynonymous variant rs116855232 in *NUDT15* is an important determinant of decreased dose tolerance of oral mercaptopurine in pediatric patients of Asian ancestry with acute lymphoblastic leukemia.<sup>63</sup> The *NUDT15* genetic variant is most common (~10% allelic frequency) in Asian patients and is rare (~0.2% allelic frequency) in those of European ancestry.<sup>63</sup> *NUDT15*, a nucleoside diphosphatase, has been hypothesized to catalyze enzymatic hydrolysis and inactivation of deoxythioguanosine triphosphate, the active DNA-damaging cytotoxic metabolite of mercaptopurine. Therefore, reduced *NUDT15* enzymatic activity in patients harboring the variant allele may increase toxicity associated with mercaptopurine.<sup>63</sup> Although the implications of these findings for clinical practice remain to be determined, this study and similar subsequent findings from investigations in Taiwanese,<sup>64</sup> Thai,<sup>65</sup> and Japanese<sup>66</sup> pediatric acute lymphoblastic leukemia patient populations provide molecular genomic insights that may explain the decreased tolerance of Asian patients to oral mercaptopurine therapy.



**Figure 5** Exposure-matched global clinical trial strategy to support drug development and registration in Asia in the setting of pharmacokinetic (PK)-related dose differences. The scenario as illustrated here is for a global phase III trial with exposure-matched regional dosing of patients enrolled in Asia. Not shown here but also equally applicable is an alternate scenario of exposure-matched regional dosing in an Asia-inclusive phase II study supported by earlier conduct and availability of the Asia phase I data. Ph 1, phase I; Ph 3, phase III; PD, pharmacodynamic; RP2D, recommended phase II dose range; RP3D, recommended phase III dose range.

### EXPOSURE-MATCHED REGIONAL DOSING: GLOBALIZATION IN THE SETTING OF PK-RELATED DIFFERENCES IN DOSE

Avoiding substantial or clinically meaningful differences in exposure between Asian and non-Asian populations is an important part of risk mitigation in global trial design because differential exposure may adversely affect the benefit:risk balance for patients enrolled in Asia. Additionally, this can compromise the suitability of the data set to support filing not only in Asian regions, but can also potentially increase the heterogeneity in the overall data set and compromise interpretation for Western regulatory review.<sup>67</sup> However, in cases in which Asian vs. non-Asian PK differences are clinically relevant, we propose that such exposure-related variability should not by default lead to a bridging study approach, and that regional differences in dosage because of exposure differences need not limit the conduct of global trials. Novel approaches, such as exposure-matched regional dosing in a global phase II or phase III trial, should be given careful consideration (**Figure 5**). Although exposure-matched dosing is illustrated in **Figure 5** in the context of a global confirmatory phase III trial, this is only intended to be representative. The approach is equally applicable in principle to a phase II study, provided phase I characterization of PK/safety in the Asian population is available before globalization. In an exposure-matched approach to global pivotal development, the drug can be evaluated in a registration trial that includes patients from both the Western and Asian regions, but the Asian dose will be exposure-matched to the Western population as defined by Asian phase I PK and safety results and integrated quantitative population pharmacology analyses.



**Table 1** Pros and cons of two potential development strategies in the setting of regional pharmacokinetic-related dose differences

Strategy	Pros	Cons
Bridging phase II study	<ul style="list-style-type: none"> <li>● Accepted approach</li> <li>● Phase III decoupled from dose-finding in Asia</li> <li>● Phase III avoids risks associated with potential differences in safety/efficacy across populations</li> <li>● Start of bridging phase II study can be gated by phase III efficacy</li> </ul>	<ul style="list-style-type: none"> <li>● Primary end point usually not gold standard (i.e., surrogate) and often under-powered</li> <li>● Phase III enrollment may be reduced by loss of access to patients in Asia</li> <li>● More limited scope of assessments (e.g., HEOR) due to size and cost</li> <li>● Approval in Asia may be delayed</li> <li>● Potential for higher overall program cost</li> </ul>
Global exposure-matched study	<ul style="list-style-type: none"> <li>● Access to larger patient population, especially for rare indications</li> <li>● Primary end point properly powered</li> <li>● Robust global data set</li> <li>● Ancillary end points (e.g., HEOR) to support pricing and reimbursement negotiations</li> <li>● Potential for faster approval in Asia</li> <li>● Potential for lower program cost</li> </ul>	<ul style="list-style-type: none"> <li>● Requires early conduct of Asia phase I</li> <li>● Requires reliable determination of exposure-matching dose</li> <li>● Higher hurdle for regulatory acceptance in a phase III trial (although this may be mitigated if Asia phase I data are available early enough to permit exploratory evaluation of exposure-matched regional dosing in a global phase II study)</li> <li>● Risk for potential dilution of overall treatment effect due to unknown regional differences in benefit:risk profile</li> <li>● Limiting Asian enrollment (e.g., &lt;30%) to mitigate the above risk may compromise local registration (e.g., China, South Korea, and Taiwan)</li> </ul>

HEOR, health economics and outcomes research.

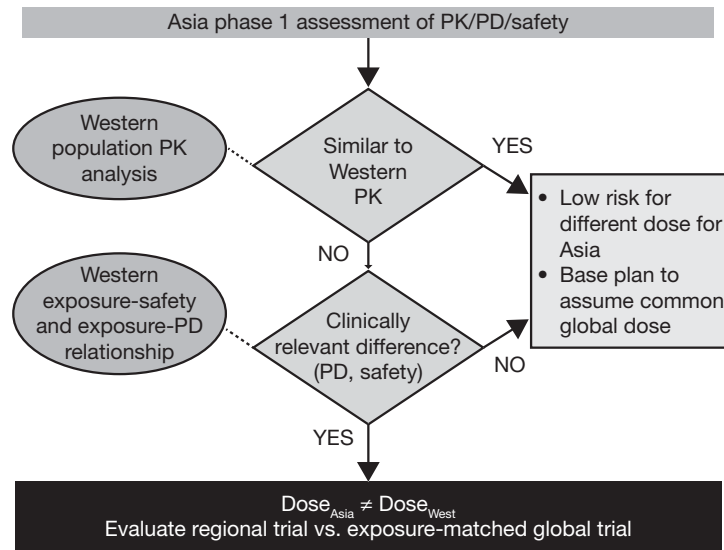
Such an approach represents an extension of the bridging concept and should yield a global database that can support worldwide registration.

The relative advantages and disadvantages of an exposure-matched dosing strategy in a global pivotal trial compared with a traditional phase II bridging strategy are summarized in **Table 1**. The decision regarding which approach to utilize should balance scientific, regulatory, and practical/operational considerations. Although exposure-matched dosing of Asian patients has not been described as an approach to enable globalization of pivotal oncology clinical trials when differential dosing is necessary, it should be noted that there is ample regulatory precedent to support the principle of exposure-based extrapolation of dose for safety and efficacy in other clinical contexts. Such extrapolation is frequently used to recommend dose adjustments for specific populations, such as patients with renal or hepatic insufficiency or genetic polymorphisms associated with impaired drug metabolism, and to account for potential drug-drug interactions. There is also precedent for dose selection in pediatric patients based on exposure-matching considerations when the disease characteristics and response to the treatment are consistent between children and adults. In fact, when appropriate based on these considerations, extrapolation of efficacy from adult to pediatric patients based on bridging principles is acknowledged as a key enabler of efficiency in pediatric drug development.<sup>68</sup>

Finally, it should be noted that exposure-matched differential dosing in Asia relative to the West can be rationalized provided the differences in exposures between the populations are not primarily attributable to other factors associated with Asian race. In the presence of such factors, such as differences in incidence of drug metabolizing enzyme genotypes,<sup>30</sup> an exposure-matched differential dosing strategy guided by genotype rather than race or region would require consideration, as was discussed in the previous section with the example of tivantinib.

Dose determination for Asian patients and an exposure-matched dosing strategy should be based on an adequate sample size from Asian PK studies, be data-driven and well-described, and include an assessment of the clinical significance of PK/PD differences for efficacy and safety outcomes. Although phase I studies are traditionally conducted as separate dose-escalation studies in Japan and other East Asian countries, efficiencies can be gained by conducting Asian phase I development as a multicountry protocol with sites across Japan and other East Asian countries (e.g., Singapore, Taiwan, and South Korea). Such an approach will maximize the ability within a single protocol to collect data on the PK and safety of the investigational agent in multiple, representative Asian races (e.g., Japanese, Chinese, and Korean patients) to support qualification of the dose for expansion of development in Asia. If emerging data reveal differential PK and/or safety parameters in patients from specific countries or races enrolled in such a phase I trial, country-specific or race-specific expansion cohorts can be added to collect additional data and confirm the understanding of PK and safety across the Asian regions and races. Harmonized dosing conditions, PK and safety assessments, and DLT definitions in phase I protocols across regions are an important part of the design of Asian phase I studies to enable unbiased comparison of the Asian and non-Asian data sets.

The appropriateness of an exposure-matched dosing strategy should also take into account disease characteristics across regions, local medical practice, and regional differences in SOC. If clinically meaningful heterogeneity in these factors is expected for the cancer type and/or the mechanism of action of the investigational agent, such that prognosis or response to treatment may be expected to be different in Asian vs. non-Asian populations, globalization of a pivotal trial to include Asia will require careful consideration of the clinical effect of such differences,<sup>69</sup> irrespective of PK considerations or selection of an exposure-matched dosing approach. Examples of such differences in molecular



**Figure 6** Roadmap for prospective integration of pharmacokinetic (PK)/pharmacodynamic (PD) considerations and dose decisions in globalization of oncology drug development inclusive of Asia.  $Dose_{Asia}$ , Dose for Asia;  $Dose_{West}$ , dose for West.

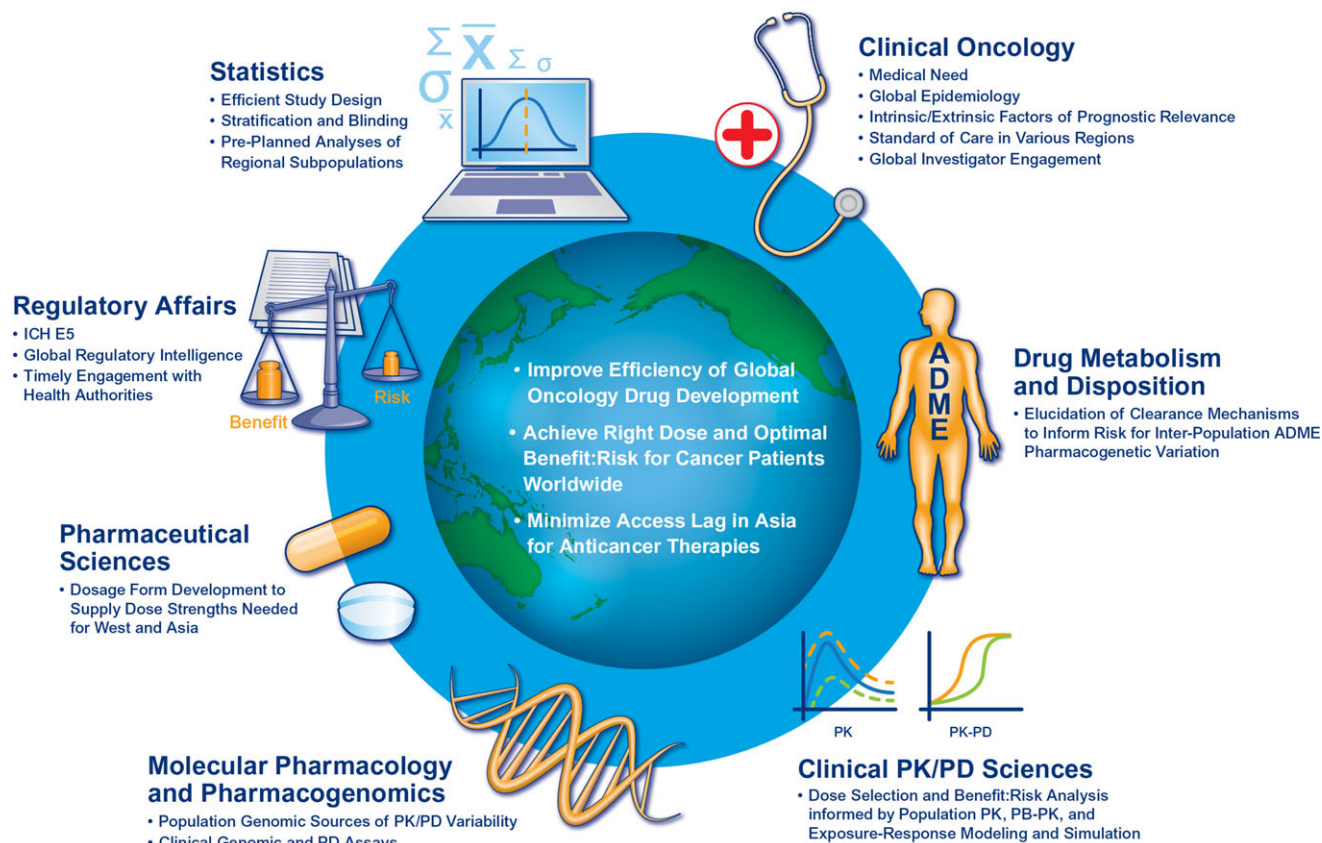
pathophysiology and/or prognosis that are unrelated to PK differences include the higher incidence of *epidermal growth factor receptor* mutations in Asian patient populations with NSCLC<sup>70</sup> and the better survival outcomes for patients with gastric cancer in Asia compared with Western countries that may be related in part to regional differences in gastrectomy surgery.<sup>71</sup> Global registration trials should include informative sparse PK sampling for a global population PK analysis to confirm consistent exposure-safety and exposure-efficacy relationships across regions and races within Asia. A thorough understanding of regional variations will likely be expected by health authorities (e.g., Pharmaceuticals and Medical Devices Agency) in support of global clinical trial designs and benefit:risk extrapolation not only from the West to Asia but also from the broader Asian region to specific countries and races.<sup>13</sup> Emerging lines of evidence from the genetic, biochemical, and clinical PK levels generally support consistency in clinical pharmacologic characteristics across the Asian races.<sup>29-31,72,73</sup> For example, although the steady-state exposures of crizotinib are 50% higher in Asian patients compared with non-Asians,<sup>47</sup> no meaningful differences in exposure or adverse event profile were apparent upon comparison of PK and safety data in Japanese and Korean patients with anaplastic lymphoma kinase-positive NSCLC.<sup>31</sup> Therefore, clinical results from different Asian countries are likely to be broadly useful throughout the region. Finally, when an exposure-matched regional dosing approach is used in a global phase III trial, it is important to seek feedback from regulatory authorities across regions, with the rationale for the proposed approach described and positioned based on the supporting data.

### SUMMARY AND RECOMMENDATIONS

Prospective consideration of potential differences in PK, PD, and safety of investigational oncology drugs in Asian patient

populations is critical to optimizing the benefit:risk profile of these drugs and decreasing access lag through scientifically rationalized global clinical development strategies inclusive of Asia. In general, two clinical approaches have been used to support global development and registration of anticancer agents, inclusive of Asia: the bridging strategy and the global clinical trial strategy. The global clinical trial strategy is becoming increasingly common, especially in oncology, and should be the approach of choice to minimize registration delays in Asian regions and maximize the efficiency of oncology drug development and approval. A global phase III trial that includes a substantial number of Asian patients has traditionally relied on the acceptability of a common dose that adequately balances benefit vs. risk across regions/populations. When exposure differences necessitate differential dosing between Asian and non-Asian populations, a phase II bridging strategy (**Figure 1**) is generally used. In the latter circumstance, when clinically meaningful PK differences between Asian and non-Asian populations are observed and indicate the need for differential dosing, we propose that an exposure-matched regional dosing strategy can be considered within a common global phase II or phase III trial. This approach may provide a way to reduce development delays in Asia for drugs with clinically significant PK differences in Asian vs. Western patients. A number of steps can be taken to expedite and expand oncology drug development in Asia, and a roadmap for prospectively considering PK/PD and dose decisions is offered in **Figure 6**.

The first step will be to ensure timely initiation of dose-finding Asian phase I PK/PD/safety studies. The timing of these studies may be driven by unmet medical need and disease burden in Asia for the primary indication(s) of interest, which will be important considerations in guiding the timing of globalization of clinical development to include Asia. If globalization of a phase III trial is desired, drug development teams should consider starting Asian PK/PD studies no later



**Figure 7** Cross-functional considerations across the pharmaceutical research and development continuum for efficient global oncology drug development to enable timely delivery of anticancer therapies with optimized benefit:risk worldwide inclusive of Asia. ADME, absorption, distribution, metabolism, and excretion; PB-PK, physiologically based pharmacokinetics; PD, pharmacodynamics; PK, pharmacokinetics.

than the Western phase II studies to allow sufficient data to define an optimal dose for Asia ahead of planning for globalization of the Asia-inclusive phase III program. However, if early globalization of a phase II study is desired without waiting until phase III of development, timely initiation, and expedient conduct of the Asia phase I dose-finding study toward the end of the dose escalation phase of the Western first-in-human study is recommended. This suggested timing of the Asia phase I study permits utilization of the results of clinical pharmacology characterization of the investigational agent in the Western patient population (dose-exposure, exposure-safety, and exposure-PD relationships) to guide interpretation of the data from the Asia phase I study in support of dose determination. Such an approach of globalization in phase II would be especially important when considerations of global medical need and expected benefit:risk profile of the investigational agent in the target patient population translate to opportunities for accelerated and adaptive drug development pathways that can support early access to innovative medicines.<sup>74,75</sup>

In the case of antibody therapeutics (i.e., simple unconjugated antibodies without small molecule payloads), the risk for inter-ethnic differences is low and population PK modeling and simulation provides the opportunity to predict poten-

tial differences in PK secondary to body size differences between Asian and Western populations.<sup>25</sup> Therefore, based on the extent of PK nonlinearity related to target-mediated drug disposition, safety profile, and therapeutic index of the antibody in the clinical dose range based on Western experience, the level of risk for inter-ethnic differences in dosage can be estimated. Accordingly, an abbreviated PK and safety characterization (e.g., as a lead-in phase) built into the design of a global phase II study inclusive of Asia, supplemented with global population PK characterization should suffice in lieu of requiring a dedicated phase I dose escalation study.

In addition to prospective planning and timely conduct of the Asia phase I program, it is important to ensure timely conduct of population PK, PK/PD, and PK/safety analyses on Western data for objective interpretation of emerging data from Asia. Collection of relevant PD data, such as biomarkers mechanistically linked to efficacy (when available), in phase I studies can strengthen the rationale for PK and safety-based dose determination.

Second, to better inform potential differences in dose between Asia and Western countries, sources of PK variability should be identified early in drug development, and the reasons for potential PK differences in Asian vs. Western populations must be carefully evaluated after phase I

Asian PK data become available. A robust understanding of ADME properties of the investigational agent should be gained, including *in vitro* identification of molecular determinants of drug clearance and quantification of their relative contributions to overall clearance. A PB-PK model should be developed for the investigational agent. If enzymes or drug transporters with demonstrated inter-ethnic differences in population pharmacogenetics (e.g., CYP2C19, ABCG2) or intrinsic activity (e.g., OATP1B1) are implicated in the disposition of the investigational agent, these data should be incorporated in the development and qualification of PB-PK models. After qualification of the PB-PK model to provide an adequate prediction of PK in the Western population, the model can be used to simulate PK in Asian patient populations.<sup>42</sup> In cases where there is high uncertainty regarding human clearance mechanisms, early conduct of human ADME studies with radiolabeled drugs should be considered to inform PB-PK modeling and to inform covariate analyses in population PK model development, in order to assess ethnic sensitivity of PK. In our experience, based on discussions with global health authorities (the US Food and Drug Administration, the European Medicines Agency Committee for Medicinal Products for Human Use, the China Food and Drug Administration, and the Japanese Pharmaceuticals and Medical Devices Agency), when exposure differences between Asian and non-Asian populations are observed, a systematic evaluation of the factors contributing to such differences is generally expected as part of the sponsor's dose selection for the region. We propose that a comprehensive evaluation of all available data be undertaken, which will permit quantitative *in vitro* and clinical understanding of human ADME mechanisms and PB-PK model development to predict PK in Asian populations. Together with global population PK model-based covariate analyses to quantify the effect on PK of factors, such as metabolic enzyme or transporter genotypes and body size metrics, this approach represents a robust method to explain the sources of any observed PK differences between Asian and non-Asian patient populations. Such scientific inquiry into the underlying reasons for differences in PK in Asian patient populations will be critical to inform dosing recommendations in the context of other covariates and clarify intrinsic vs. extrinsic factor contributions to the observed differences.

Third, the implications of dosage differences in Asia on pharmaceutical dosage form manufacturing and clinical trial supplies in the pivotal trial should be anticipated. If the dose determined for the investigational agent is different for the Asian vs. non-Asian populations, availability of a variety of dosing strengths may be required. For example, if the starting dose of the investigational agent is lower in Asia to match exposures to the non-Asian patient population, the available dosage forms and strengths must permit comparable exposure matching between the populations at not only the starting dose but also at the reduced dose levels for patients requiring dose reductions.

Finally, decisions regarding appropriate options and selection of an optimal strategy should be informed by cross-functional and cross-regional considerations involving all major scientific, clinical development, regulatory, pharma-

ceutical manufacturing, and commercial functions in the global pharmaceutical company setting, with appropriate global regulatory feedback obtained from health authorities before trial initiation. We hope that the points of consideration presented in this review offer a framework for clinical pharmacologists and drug developers to consider and apply as they engage in the multidisciplinary collaborative effort (**Figure 7**) of global oncology drug development to accelerate development and approval of novel anticancer medicines at doses that provide an optimal benefit:risk balance across the globe, inclusive of Asia.

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