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Volume of Distribution: A Relevant, Possibly Overlooked Pharmacokinetic Parameter in Drug Development

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Abstract

Volume of distribution (Vd) is an important pharmacokinetic parameter. While conceptually unphysiological, Vd remains a practical indicator for the accessibility of a drug to the tissues as well as a key determinant for the exposure profile. This is particularly true for both central nervous system and oncologic therapeutics because the biological targets are often resided in peripheral body tissues. For instance, antidepressant selective serotonin reuptake inhibitors and anticancer poly (ADP-ribose) polymerase inhibitors, like many effective therapeutic agents, exhibit desirable pharmacokinetic properties, large Vd in particular that is consistent with their intended therapeutic applications.

Physiochemical properties of small-molecule drugs directly impact their disposition in the body, namely absorption, distribution, metabolism, and elimination. Lipophilicity, gauging upon ClogP, and basicity have been shown to be positively associated with Vd, due in part to the roles they play in cell permeation and tissue binding, respectively.

To ensure therapeutic successes in complex drug development, a plethora of aspects and requirements, besides mechanism of action, need to be comprehended and fulfilled. We believe that Vd would be among them, especially if the therapeutic moieties are intended to target the tissues of the central nervous system and solid tumors.

Keywords: Drug development; PARP inhibitor; Physiochemical property; Solid tumor; Volume of distribution;

Abbreviations: AUC: Area Under the Concentration–Time Curve; CL: Clearance; ClogP: Calculated partition coefficient for n-octanol/water; Cmax: Maximum Plasma Concentration; Cmax,ss: Maximum Plasma Concentration at Steady State; Cmin,ss: Minimum Plasma Concentration at Steady State; Cp: Plasma Concentration; D: Dose; F: Bioavailability; fu: Unbound Fraction in Plasma; fut: Unbound Fraction in Tissue(s); K: Binding Affinity; ka: Absorption Rate Constant; ke: Elimination Rate Constant; Kp: Tissue-to-plasma Partition Coefficient; PARPis: Poly(ADP-ribose) Polymerase Inhibitors; pHi: Dissociation Constant of a Drug Under Intracellular pH; pHe: Dissociation Constant of a Drug Under Extracellular pH; PK: Pharmacokinetic; pKa: Ionization Constant; SSRIs: Selective Serotonin Reuptake Inhibitors; $t_{1/2}$: Terminal Elimination Half-life; Tmax: Time After Dose Required to Achieve the Maximum Circulating Concentration; Vd: Volume of Distribution; Vp: Plasma Volume; Vt: Apparent Tissue Volume.

Introduction

Volume of distribution (Vd) is one of the primary pharmacokinetic (PK) parameters and the base for the

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derived secondary parameters, including the exposure metrics (e.g., maximum plasma concentration [Cmax] and area under the concentration–time curve [AUC]). The same is true for the physiological and thus more appreciated parameter of clearance (CL). In terms of physiology, CL depends on hepatic blood flow, plasma protein binding, metabolizing enzyme, active transport, renal function, etc. Hence, any change in these functions and activities may affect CL. On the other hand, Vd is associated with a set of different biochemical and physiological properties, including but not limited to permeability, tissue binding, tissue perfusion, and volume of body fluids. Therefore, CL and Vd are generally independent of each other; one parameter might change in the absence of a change in the other. Nonetheless, CL and Vd in concert are the determinant of the PK profile that guides the intensity and frequency of the administration of therapeutic small molecules.

As a PK parameter, Vd is defined as the volume of body fluid required to dissolve the total amount of a drug (or any xenobiotic) [1], or Vd = D/Cp if bioavailability (F) = 1, where D is dose and Cp is plasma concentration. Vd is hypothetical and unphysiological, assuming the drug is fully dissolved immediately, well-stirred, and thus evenly distributed.

One of the intuitive utilities of Vd is the prediction of the accessibility of a drug to body tissues of interest as:
Vd = Vp + Vt*(fu/fut) (Equation A)
or
Vt = (Vd - Vp)*(fut/fu)

Where Vp is plasma volume, Vt is apparent tissue volume, fu is unbound fraction in plasma, and fut is unbound fraction in tissue(s).

Therefore, if a compound is bound to the tissue with high affinity and thus exhibits a high fu/fut ratio, it is likely to exhibit high Vd, given the limited interindividual variability of Vp (Equation A).

In non-compartmental PK:

$$t_{1/2} = 0.693 * Vd/CL \qquad \text{(Equation B)}$$

Where $t_{1/2}$ is half-life. Therefore, if the CL or apparent CL when given orally (CL/F) is comparable, the larger the Vd, the longer the $t_{1/2}$. Specifically, the compound tends to elicit a long $t_{1/2}$ if it is substantially distributed to peripheral tissues.

As shown in Figure 1 [2], the increase of Vd reshapes AUC on at least 2 aspects: elongation of terminal elimination half-life ($t_{1/2}$) as predicted based on Equation B and attenuation of C_{max} as follows.

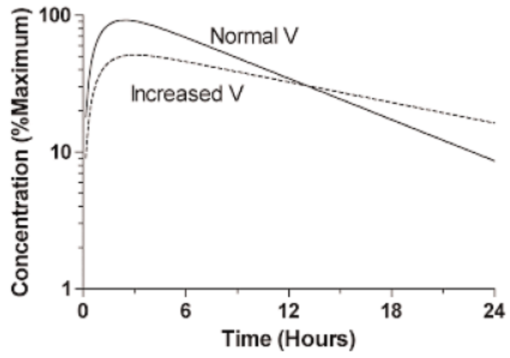


Figure 1: Volume of Distribution on Pharmacokinetic Profile of Small Therapeutic Agents Following Oral Administrations. The pharmacokinetic parameters used for simulation were clearance of 1.16 L/h, volume (V) of 10 L, absorption rate constant of 1 hour^{-1}, and bioavailability of 1 for the "Normal V" scenario. V was increased to 20 L with the others unchanged for the "Increased V" scenario. Adapted from Mehvar R (2004) Am J Pharm Educ 68(2): Article 36. Copyright 2004 by American Association of Colleges of Pharmacy.

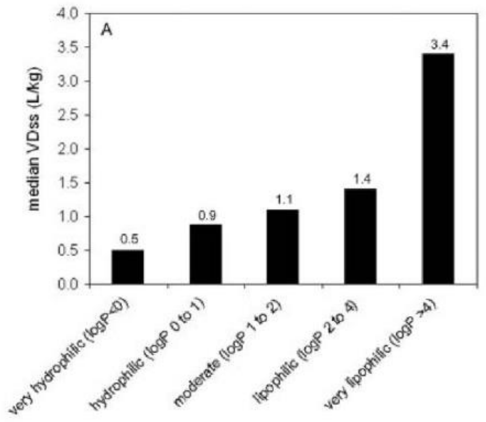


Figure 2: Lipophilicity and Volume of Distribution. VD_{ss}, volume of distribution at steady state. Reprinted from Obach RS, et al. (2008) Drug Metab Dispos 36: 1385-1405. Copyright 1984 by American Society for Pharmacology and Experimental Therapeutics.

Applying the one-compartment model in single oral administration:

$$Cmax = F*D*ka*[\exp(-ke*Tmax)-\exp(-a*Tmax)]/[Vd*(ka-ke)] \qquad \text{(Equation C)}$$

where F is oral bioavailability, D is dose, ka is absorption rate constant, ke is elimination rate constant, and Tmax is the time after dose required to achieve the maximum circulating concentration. Therefore, based on Equation C, Cmax is the function of 1/Vd, assuming a fixed dose, full oral bioavailability (F=1), constant absorption and elimination rates (ka and ke), and a negligible change if any in Tmax as Tmax = ln(ka/ke)/(ka−ke). Simply, an increase in Vd results in lower Cmax (Figure 1).

More relevantly, in a multiple dose regimen, Vd molds the steady-state exposure, particularly peak (Cmax at steady state [Cmax,ss]) and trough concentrations (minimum plasma concentration at steady state [Cmin,ss]), thus the fluctuation of concentration (Cmax,ss−Cmin,ss). Therefore, Vd could be used to estimate the concentration fluctuation based on Cmax,ss−Cmin,ss = D/Vd. The larger the Vd, the smaller the fluctuation if the dose is fixed. A large Vd is considerably beneficial, especially for the cytotoxic anticancer agents that tend to have a relatively small window for effective yet safe exposure.

Furthermore, Vd is quite practical from a molecular target point of view in that the functional proteins (i.e., enzymes, receptors, etc.), the majority of biologic targets, are often tissue-specifically expressed. Therefore, therapeutic agents, a priori, need to be distributed to the tissues to directly engage with the targets to have an effect. This is particularly crucial in drug development against central nervous system ailments and solid tumors, notably 2 of the largely unmet therapeutic areas.

For example, all selective serotonin reuptake inhibitors (SSRIs) currently on the market (fluoxetine, paroxetine, citalopram, escitalopram, sertraline, and fluvoxamine) exhibit a relatively large Vd, ranging from 3.1 to 45 L/kg (Table 1) [3-9]. Serotonin (or 5-HT) transporters, the biologic target for SSRIs, are abundantly expressed in the central nervous system tissues, especially in the thalamus and striatum of the brain, [10] although they are also detected in some other tissues such as pulmonary endothelial and intestinal epithelial cells [11]. Specifically, when administered orally, SSRIs must penetrate into the brain after crossing the blood–brain barrier to be able to antagonistically bind to serotonin transporters to exert their therapeutic effect.

Species	Vd,ss (L/kg)			
All	Low	Moderate	High	Very High
	<0.6	0.6-5	5-100	>100

Table 1: Classification of Volume of Distribution at Steady State (Vd,ss). Adapted with permission from Smith DA, Beaumont K, Maurer TS, Di L (2015) Volume of distribution in drug design. J Med Chem 58(15): 5691-5698. Copyright 2015 American Chemical Society.

An important determinant for Vd is permeability [12], which is largely associated with the lipophilicity of the molecule. Lipophilic compounds (i.e., those with higher log P, typically ≥2) tend to exhibit high permeability and Vd (Figure 2)[13]. However, permeability is not the sole attribute as Vd is affected by multiple factors, including the ionization class. For instance, alkaline compounds often elicit a larger Vd than acidic compounds (Figure 3 and Table 2).

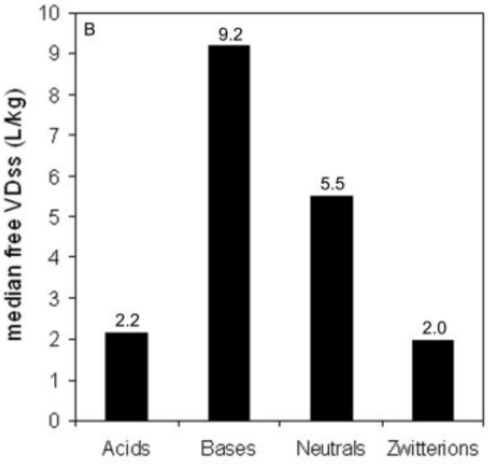


Figure 3: Higher Volume of Distribution of Alkaline Compounds. VDss, volume of distribution at steady state. Reprinted from Obach RS, et al. (2008) Drug Metab Dispos 36: 1385-1405. Copyright 1984 by American Society for Pharmacology and Experimental Therapeutics.

The tissue distribution for alkaline compounds has been further proposed to be dependent on the physiological condition, specifically cellular microenvironment pH-sensitive [12]:

$$Kp = (1+10^{(pKa-pHi)})/(1+10^{(pKa-pHe)}) * fu * (1+K*P*n) \quad \text{(Equation D)}$$

Where Kp is the tissue-to-plasma partition coefficient; pKa is the ionization constant; pHi and pHe are dissociation constants of a drug under intracellular pH and extracellular pH, respectively; and K, P, and n represent the association constant of binding with, the abundance and the number of sites of binding component(s) in tissue, respectively.

Apparently, if the difference between pHi and pHe is either negligible or consistent in the cells including the target cells, the Kp or tissue distribution is controlled by the binding properties of the cells in the peripheral tissues, specifically the binding affinity (K) and total available binding sites (P*n), besides the availability of molecules for the tissue distribution (i.e., the free fraction of circulating drug molecules [fu]).

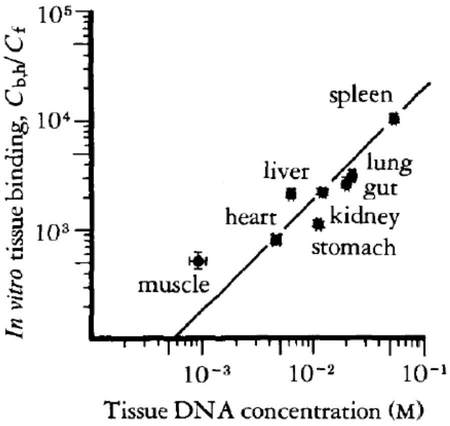
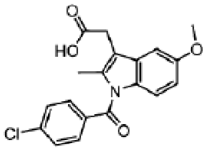
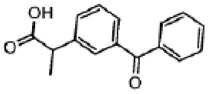


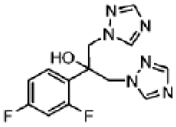
Figure 4: Correlation Between DNA Content and Tissue Binding to Doxorubicin in Tissue Homogenates. $C_{b,h}$ and C_f, the bound and unbound drug concentrations in the tissue homogenates, respectively. Reprinted from Terasaki T, et al. (1984) J Pharm Dyn 7: 269-277. Copyright 1984 by The Pharmaceutical Society of Japan.

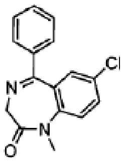
Alkaline compounds are positively charged at a physiological pH (i.e., pH 7.4) and preferentially bind to negatively charged acids [14]. Therefore, 2 of the abundant acidic cellular constituents are critical for Kp or tissue distribution of basic compounds: phospholipids, especially phosphatidylserine [15], and nucleic acids (e.g., DNA) [16,17].

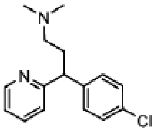
As shown in Figure 4, there appears to be a positive correlation between the tissue binding of the anticancer agent doxorubicin, a weak base (pKa ~8.2), and the amount of DNA in those tissues [17]. Thus, it is likely feasible for alkaline compounds to be distributed to lung tissues such as squamous alveolar cells compared to skeleton muscle, due at least in part to the markedly higher DNA content in the former than the later. More intriguingly, tumor cells often carry extra chromosomes, or so-called polyploidy; this pathophysiological/path morphological property of cancerous cells has been suggested to be a viable advent for anticancer treatment [18]. Indeed; this might have already been exploited in development. The key anticancer activities of doxorubicin, a basic anthracycline exhibiting very high apparent Vd (Vd/F~25 L/kg) is thought to be the direct suppression of DNA processing machinery, via the intercalation of the double-stranded DNA and the formation of DNA adducts, leading to apoptotic cell death [19-21].

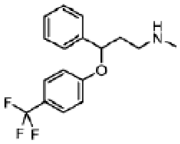

Indomethacin


Ketoprofen


Fluconazole


Diazepam


Chlorpheniramine


Fluoxetine

Drug	Ionization class	pK_a	Log p	Log $D_{7.4}$	PSA	f_u	V_{ss} (L/kg)	$V_{ss,u}$ (L, kg)
Indomethacin	acid	3.9	4.2	0.7	68.5	0.01	0.096	9.6
ketoprofen	acid	4.2	2.9	0.2	54.4	0.008	0.13	16
fluconazole	neutral		0.5	0.5	71.8	0.89	0.75	0.84
diazepam	neutral		2.8	2.8	32.7	0.023	1.0	43
chlorpheniramine	base	9.1	3.4	1.5	16.2	0.056	10	178
fluoxetine	base	10.5	3.9	1.4	21.3	0.06	4.3	71

Table 2: Volume of Distribution Values for Several Acid, Neutral, or Basic Drugs.[a]

[a] All of the depicted molecules exhibit high permeability and can achieve unity in unbound concentration between the blood and tissues despite significant differences in volume of distribution. The volume of distribution values reflects differences in binding to proteins and membranes. Adapted with permission from Smith DA, Beaumont K, Maurer TS, Di L (2015) Volume of distribution in drug design. J Med Chem 58(15): 5691-5698. Copyright 2015 American Chemical Society.

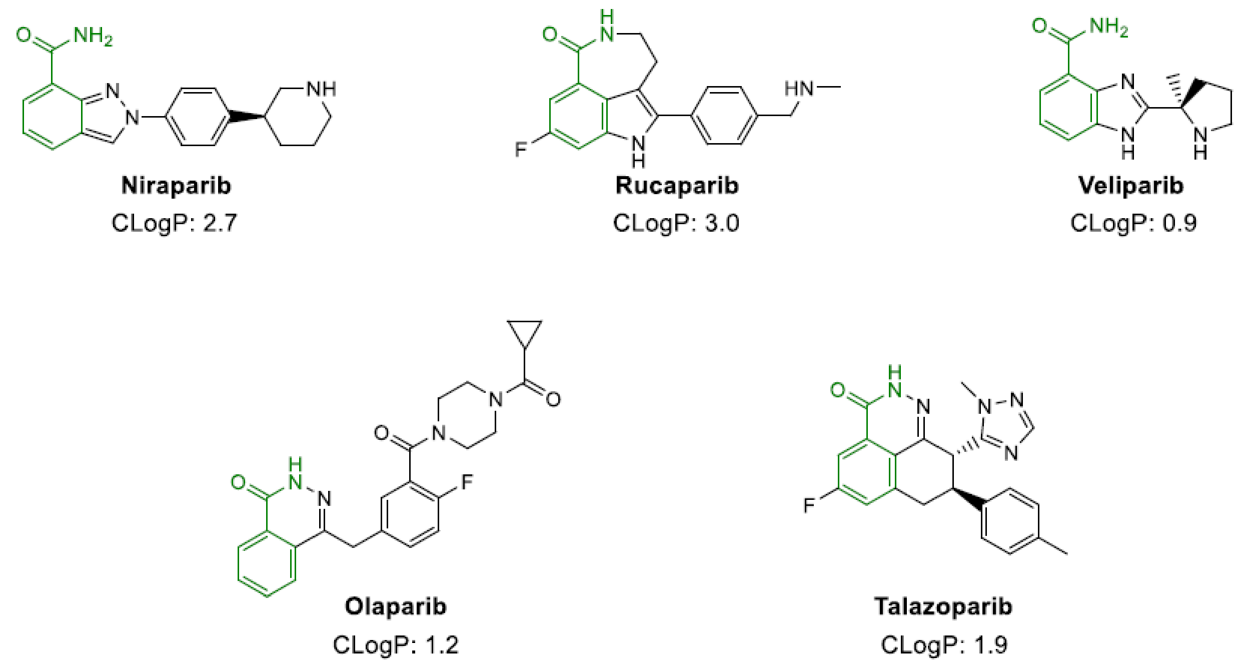


Figure 5: Poly (ADP-Ribose) Polymerase Inhibitors. The poly (ADP-ribose) polymerase inhibitors (PARPis) are either currently prescribed or in the late stage of development. Benzamide moiety, the pharmacophore required for the antagonism against PARPs, is shown in green [22]. Values of ClogP were estimated using ChemBioDraw (Ultra 13.0.2.3021).

As shown in Figure 5, poly (ADP-ribose) polymerase inhibitors (PARPis) are effective anticancer agents being prescribed or continually evaluated to treat an array of solid tumors either as a monotherapeutic agent or in combination [22,23]. These PARPis, albeit with comparable lipophilicity (ClogP ~1–4, except for hydrophilic veliparib with CLogP <1), elicit markedly different Vd estimates in patients with cancer. Specifically, such Vd values (assuming the average body weight of 70 kg) reported for the 5 PARPis on the market or in later development, namely niraparib, olaparib, rucaparib, talazoparib, and veliparib, were approximately 17.4, 2.4, 2.7 (mean of 1.6 and 3.7 determined in 2 clinical studies), 5.9, and 3.1 L/kg, respectively (Figure 6) [24-28]. While the Vd estimates of PARPis are well within the normal range for small therapeutic agents (Table 1) [9,13], the value for niraparib is nearly one-magnitude higher, likely among the top 10% of the therapeutic agents, than the average of the other PARPis. Interestingly, niraparib (pKa of 9.95) appears to be the most alkaline in physiological and/or cellular fluids (pH ~7.4) among the 4 PARPis with comparable lipophilicity (Figure 5) [29]. Of note, while the Vd of niraparib is high (17.4 L/kg), [24] it is far from the extreme for an alkaline compound, with the typical range from 1 to 25 L/kg (Figure 6, Table 2) [9,13]. Meanwhile, Vd estimates of the other PARPis are consistent with neutral compounds, often in the range of approximately 0.7 to 4 L/kg [9].

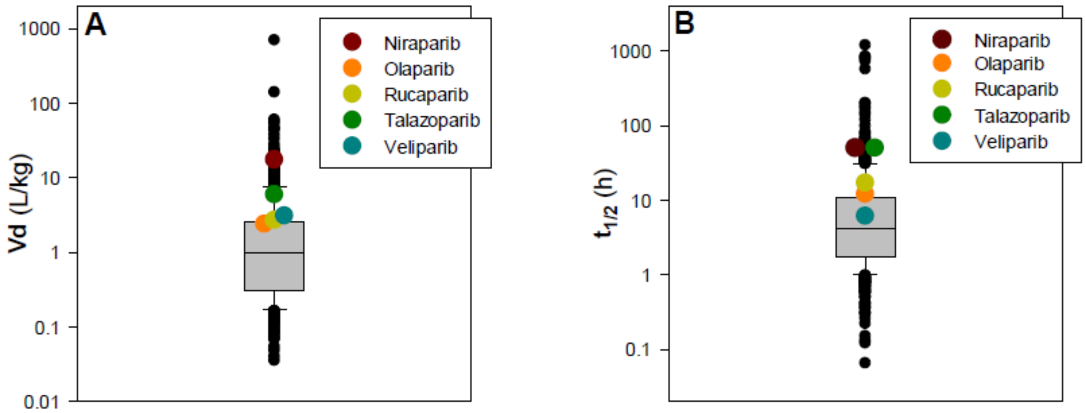


Figure 6: Pharmacokinetic Properties of Therapeutic Small Molecules Including PARPis: Volume of Distribution and Elimination Half-life. The black dots are the subset of 670 small therapeutic agents on the market that showed volume of distribution (V_d) and terminal elimination half-life ($t_{1/2}$) outside of the middle 85%. The estimates of V_d plotted for poly(ADP-ribose) polymerase inhibitors (PARPis) were body weight-normalized, assuming 70 kg/person on average. The data plotted for the 670 agents were adapted from Table 1 in Obach RS, et al. (2008) Drug Metab Dispos 36: 1385-1405.

Hence, besides mechanisms of action or target activities, there appears to be a difference in biopharmaceutical property among these PARPis. This may, in turn, be associated with and differentiate their therapeutic effectiveness, especially in the treatment of neoplasms in deep tissues. Indeed, such a notion has been enlightened in xenograft tumor models. Consistent with the marked difference in Vd, these models showed that tumor exposure was evidently higher and tumor regression more pronounced following oral doses of niraparib than that seen after comparable doses of olaparib [30]. In addition, the distribution of olaparib and rucaparib to the brain was quite poor, in contrast to the feasible brain penetration of niraparib [30-32]. Specifically, the dose-normalized exposure to niraparib was 3-, 16-, or 34-fold higher than that to olaparib in plasma, tumor, or brain, respectively, in BALB/c nude mice subcutaneously implanted with the *BRCAwt* OVC134 ovarian tumor fragment following the doses of niraparib (50 mg/kg qd) and olaparib (67 mg/kg bid) for 2 days [30]. It is also worth noting that the magnitude of difference between the exposure to two PARPis, gauging upon the exposure ratio, appeared to be augmented inversely with the accessibility of the tissues (i.e. brain>xenograft tumor>plasma). Moreover, PARPis are substrates for P-glycoprotein, an efflux transporter highly expressed in the blood–brain barrier and often up-regulated in tumor cells. However, the effect of efflux from P-glycoprotein, which is known to be chemophysical property-dependent [33], varies markedly among those PARPis. Such an effect is quite evident with olaparib and rucaparib, while insubstantial with niraparib, consistent with the large difference in Vd [30-32]. Furthermore, malignant cells are highly proliferating and thus nucleic acid (DNA and RNA)-rich, and, in turn, more feasibly interact with alkaline molecules like niraparib. Notwithstanding, owing to the rather unique and desirable biopharmaceutical properties, it is rational and thereby warranted to further explore niraparib, either as a monotherapeutic agent or in combination, for additional benefits in the treatment of solid tumors beyond the tumor types currently being evaluated (e.g., malignancies in deep or nucleic acid-rich tissues besides lung cancers).

Despite being highly variable (6-50 hours as shown in Figure 6), the $t_{1/2}$ of these PARPis is overall desirable gauging upon the median $t_{1/2}$ of approximately 4 hours for small therapeutic agents [13]. The $t_{1/2}$ estimates of niraparib and talazoparib are longer (~50 hours) than the other PARPis (6–17 hours) [25,27,34-36], concurrent with the larger Vd of niraparib and talazoparib (Eq. B) [24-28]. Therefore, owing to the long $t_{1/2}$, niraparib and talazoparib are administered once daily as compared to twice daily for the other PARPis [25,27,29,35,36]. Specifically, the large Vd would allow for the less frequent dose regimen, a merit for prescription and compliance.

Collectively, this letter provides both theoretical and practical perspectives on Vd, followed by a discussion of chemophysical properties with respect to exposure, and a comparison of such properties in therapeutic small molecules, the anticancer PARPis in particular, to demonstrate the therapeutic relevance of Vd. From a biopharmaceutical standpoint, we hope our thoughts shed some light on the development of effective and safe therapeutic agents, especially among the molecules thought to act on targets with overlapping mechanisms of action.

Acknowledgements

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Conflict of Interest

Zhi-Yi Zhang and Ashley Milton are current employees of TESARO, Inc, the company developed and provides niraparib. Neither of the authors owns any stocks of the companies that are developing and/or commercializing PARPis discussed in the letter.

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