Review

Clinical Cancer Research

Clinically Relevant Concentrations of Anticancer Drugs: A Guide for Nonclinical Studies

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Abstract

Approved and marketed drugs are frequently studied in nonclinical models to evaluate the potential application to additional disease indications or to gain insight about molecular mechanisms of action. A survey of the literature reveals that nonclinical experimental designs (*in vitro* or *in vivo*) often include evaluation of drug concentrations or doses that are much higher than what can be achieved in patients (i.e., above the maximally tolerated dose or much higher than the clinically relevant exposures). The results obtained with these high concentrations may be particularly helpful in elucidating off-target effects and toxicities, but it is critical to have a dose–response curve that includes the minimally effective or clinically effective concentration for comparison. We have reviewed the clinical literature and drug product labels for all small molecules and biological agents approved by the FDA for use in oncology to identify and compile the available pharmacokinetic parameters. The data summarized here can serve as a guide for selection of *in vitro* concentrations and *in vivo* plasma exposures for evaluation of drug effects in nonclinical studies. Inclusion of drug concentrations or exposures that are relevant to those observed in clinical practice can improve translation of nonclinical mechanism of action findings into potentially relevant clinical effects. *Clin Cancer Res; 23(14); 3489–98. ©2017 AACR.*

Introduction

Nonclinical studies are important foundations for modern drug discovery. Beyond initial discovery, nonclinical investigations with approved drugs are frequently conducted to explore possibilities for expanded use and additional disease indications. In this situation, nonclinical experiments can take advantage of existing pharmacokinetic and toxicity findings, along with related exposure data, to design studies to test drugs at concentrations *in vitro* or *in vivo* that are relevant to observed clinical exposures. In doing so, concentrations known to be achievable and efficacious in patients can be included in the design of novel nonclinical studies. In a recent commentary, Smith and Houghton (1) cited several examples of reported activities of anticancer agents that were derived from *in vitro* studies that used concentrations far greater than those that could be realistically achieved in a clinical setting. In some cases, these drug concentrations were several orders of magnitude greater than concentrations needed to inhibit the desired targets of the drug. The use of such high concentrations increases the possibility that the effects observed are due to off-target activities that are not relevant when the drug is provided at therapeutic concentrations in clinical practice, and efforts to translate conclusions drawn from these studies may be unsuccessful. Therefore, awareness of the relationship between concentrations tested nonclinically and what is achievable in a clinical context can greatly assist the interpretation and translation of such studies.

As an aid to guide dose and concentration selection, we provide herein a comprehensive compilation of human plasma exposures for drugs approved by the FDA for use in oncology. We sought to identify the maximum plasma concentration at the highest single dose recommended in the drug product label to be used as a guide to derive a range of drug concentrations to include in nonclinical studies. We have focused on therapies that have direct effects on tumor growth or cancer cell viability. Adjunct or strictly palliative therapies such as analgesics and antiemetics were excluded, although these are widely used for supportive care during cancer treatment. We also excluded diagnostics, imaging agents, and radiologic therapies. Several drugs that are not approved specifically for use in cancer but are increasingly being reported in experimental settings (e.g., metformin and celecoxib) have been included where possible.

Methods

A comprehensive list of agents approved for use as anticancer therapies in the United States was assembled from several sources. The National Cancer Institute (NCI) maintains a list of approved drugs with drug information summaries (2); this list includes most individual agents plus many commonly used drug combinations in oncology. A list of single agents derived from this source was cross-checked against lists of oncology therapies compiled by MediLexicon (3) and Centerwatch (4), two databases that allow searching of FDA-approved drugs by therapeutic area (oncology). The resulting combined list was triaged to remove strictly palliative agents, such as analgesics and antiemetics. Combination drug therapies were removed

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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from the list, as each component within the combinations was included as the individual drug. Biological agents were parsed into a separate list. Within biological agents, vaccines were not included. All compounds on the final list were verified for approval status at www.fda.gov, and drug product labels were downloaded from FDA (5) or DailyMed (6), a service provided by the National Library of Medicine.

Human pharmacokinetic data were identified by examination of the drug product label, the original literature, or conference abstracts, with priority given to the clinical pharmacology section within the drug product label. The intent was to determine the exposure defined by maximum plasma concentration (C_{max}) and the integrated area under the plasma concentration–time curve (AUC) associated with the highest recommended dose of the drug. If the information in the label was not sufficiently explicit or detailed to derive exposures associated with discrete dosing levels, the original publications describing the pharmacokinetic data were identified using Thompson-Reuters Integrity (7) and PubMed. These sources were reviewed, and a single reference was selected for each compound based on (i) the use of a dose equivalent to the highest dose recommended in the label and (ii) the availability of the key parameters of C_{max} and AUC, typically calculated from time zero to infinity. Whenever possible, studies reporting C_{max} and AUC following a single administration at the highest dose recommended in the product label were chosen for review. When these data were not found, the study reporting a dose as close as possible to the highest recommended dose was selected.

Results

Our survey identified 145 unique small-molecule drugs approved to treat cancer, 10 of which are prodrugs. Table 1 provides a summary of the human pharmacokinetic parameters for all 135 unique small-molecule drugs and five alternative formulations approved for use in oncology indications in the United States, excluding prodrugs. Table 2 includes all 10 drugs delivered as prodrugs, where the chief pharmacologic activity is provided by an active metabolite. The 40 unique biological agents that have been approved for oncology are summarized in Table 3. We noted 16 additional drugs that are not currently approved for cancer indications but have been reported in clinical trials for various cancers; these have been included in Table 4.

Each table is sorted alphabetically by the unique generic name. Also provided is one proprietary (brand) name; some drugs are sold under multiple brands, particularly outside of the United States market. The dose and route of administration from which the pharmacokinetic data are derived are shown, which are typically the highest dose recommended in the label. For drugs administered intravenously, the duration of injection is included. The maximum plasma concentration (C_{max}) is usually reported as ng/mL, from which we calculated micromolar concentration units. Also collected are the time of maximum plasma concentration (T_{max}) and the plasma half-life ($T_{1/2}$). The AUC is shown, following conversion to a consistent unit of ng•hr/mL. The raw values and units for C_{max} and AUC, as reported in the cited reference, are included in the Supplementary Tables. The fraction bound to plasma protein is also included, as this is an important parameter to consider when translating from *in vivo* settings to *in vitro* systems with varied protein composition.

A few agents included in Table 1 have been discontinued, and some older agents are no longer listed in the FDA "Orange Book" (8). Although these agents are no longer marketed in the United States, they may be used experimentally, particularly in drug combination studies, so the pharmacokinetic data for these drugs have been included.

Several agents are intentionally administered as a prodrug that is converted *in vivo* into the active drug; these are summarized in Table 2. In these cases, the metabolite carries the predominant pharmacologic activity, so the levels of these metabolites following recommended doses of the parent have been reported. For abiraterone acetate, fludarabine phosphate, and lomustine, the levels of the parent prodrug were below the limit of quantitation *in vivo*, so only the levels of the active metabolite are shown. Three drugs are precursors of the cytotoxic pyrimidine, 5-fluorouracil (5-FU): floxuridine, capecitabine, and tegafur. Each of these is converted to 5-FU in the liver and other tissues. Because plasma 5-FU levels following floxuridine may be as high as the parent, it was considered a prodrug and included in Table 2. Two compounds (dacarbazine and temozolomide) are precursors of the same active species, N-demethyldacarbazine (MTIC). Dacarbazine is converted intracellularly to MTIC through cytochrome P450 oxidation (9), with little accumulation of the active metabolite in plasma, so only exposure of the parent is shown in Table 1. However, temozolomide is rapidly converted nonenzymatically to MTIC at physiologic pH, resulting in readily detectable plasma exposure of the active metabolite, so MTIC levels following temozolomide administration are included in Table 2. In one instance, mechlorethamine, the parent molecule undergoes such rapid chemical transformation that plasma levels of the parent drug were difficult to measure reliably, and a C_{max} could not be determined.

Table 3 presents a summary of the human pharmacokinetic parameters reported for all 40 biological therapeutics approved for cancer indications in the United States, excluding vaccines and radiologicals. The table is sorted alphabetically by unique generic name, followed by proprietary brand name. As in Table 1, the dose and route of administration are given, followed by the C_{max} provided as micromoles/liter and the integrated AUC. T_{max} and $T_{1/2}$ are also shown, where reported, as well as the duration of injection for drugs administered intravenously.

The 16 drugs included in Table 4 are approved for other indications but are not specifically approved for use in cancer, although finasteride, dutasteride, and alfuzosin have been approved to treat benign prostatic hyperplasia. All of these agents are currently undergoing clinical trials for cancer indications, thus the pharmacokinetic data will be useful to researchers and have been included.

An expanded table is available for download in the Supplemental Materials, which combines all small molecules in Tables 1, 2, and 4 into a single, sortable spreadsheet (Supplementary Table S1). A separate file containing the biological agents from Table 3 is also provided (Supplementary Table S2). These are Excel files that include full references for the primary sources of the pharmacokinetic values and the official drug product labels. Annotations of the molecular target (if known), the C_{max} and AUC in raw units as reported in the reference, the plasma clearance (Cl) and volume of distribution (V_d) are included as available. The year of initial approval in the United

Table 1. Key human pharmacokinetic parameters for small-molecule drugs approved for oncology indications

Generic name	Brand name	Dose	Dose unit	Route	Infusion	C_{max} (μmol/L)	C_{max} (ng/mL)	AUC (ng·hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Protein binding
Abarelix	Plenaxis	100	mg	IM	—	0.031	43.4	12,000	72	316.8	96%–99%
Afatinib	Gilotrif	40	mg	PO	—	0.052	25	324	4.0	26.9	95%
Alectinib	Alecensa	600	mg	PO	—	1.38	665	7,430	4.0	33	>99%
Alfuzosin	UroXatral	10	mg	PO	—	0.035	14	194	8.0	10	82%–90%
Allopurinol	Zyloprim	300	mg	PO	—	14.3	1,940	4,814	1.4	1.4	Negligible
Altretamine	Hexalen	200	mg	PO	—	3.76	790	—	0.5–3	4.7–10.2	94%
Amifostine	Ethyol	200	mg/m^2	IV	7.5 min	105	22,472	4,238	—	0.26	Negligible
Aminoglutethimide	Cytadren	500	mg	PO	—	25.4	5,900	—	1.5	12.5	21%–25%
Aminolevulinic acid	Levulan Kerastick	100	mg	IV*	1 min	129	16,900	13,700	—	0.83	—
Anastrozole	Arimidex	1	mg	PO	—	0.035	10	536	—	41.3	40%
Arsenic trioxide	Trisenox	0.1	mg/kg	IV	2 h	0.910	180	*	—	—	75%
Axitinib	Inlyta	5	mg	PO	—	0.163	63	466	1.8	3.1	>99%
Azacitidine	Vidaza	75	mg/m^2	SC	—	3.07	750	960	0.50	0.68	—
Azacitidine	Vidaza	75	mg/m^2	IV	10–40 min	11.3	2,750	1,044	—	0.36	—
Belinostat	Beleodaq	1,000	mg/m^2	IV	30 min	134	42,657	29,005	—	1	94%
Bendamustine	Treanda	120	mg/m^2	IV	60 min	16.3	5,840	13,635	—	0.7	94%–96%
Bexarotene	Targretin	300	mg/m^2	PO	—	3.39	1,180	5,980	2.5	3.4	>99%
Bicalutamide	Casodex	50	mg	PO	—	1.78	768	230,838	31	139	96%
Bleomycin	Blenoxane	15	mg/m^2	IV	Bolus	706	1,000,000	4.99E+06	—	4	1%
Bortezomib	Velcade	1.3	mg/m^2	IV	Bolus	0.312	120	196	0.08	48.7	83%
Bosutinib	Bosulif	500	mg	PO	—	0.377	200	3,650	4–6	22.5	96%
Busulfan	Busulflex	0.8	mg/kg	IV	2 h	4.96	1,222	4,790	—	—	32%
Cabazitaxel	Jevtana	25	mg/m^2	IV	1 h	0.270	226	991	1.0	95	89%–92%
Cabozantinib	Cometriq	140	mg	PO	—	4.61	2,310	41,600	2–5	55	99.7%
Capecitabine	Xeloda	1,250	mg/m^2	PO	—	21.1	7,570	8,450	0.82	0.43	Approx 35%
Carboplatin	Paraplatin	400	mg/m^2	IV	30 min	135	50,000	83,333	0.50	3	0%
Carfilzomib	Kyprolis	27	mg/m^2	IV	5 min	5.88	4,232	379	—	<1	97%
Carmustine	BiCNU	600	mg/m^2	IV	2 h	19.4	4,150	—	—	—	80%
Ceritinib	Zykadia	750	mg	PO	—	1.21	674	14,000	5.0	41	97%
Chlorambucil	Leukeran	0.2	mg/kg	PO	—	1.62	492	883	0.83	1.3	99%
Cisplatin	Platinol	80	mg/m^2	IV	1 h	14.4	4,321	42,921	—	0.44	n/a*
Cladribine	Leustatin	0.09	mg/kg/day	IV	24 h	0.020	5.7	—	—	—	20%
Cladribine	Leustatin	0.12	mg/kg	IV	2 h	0.168	48	—	—	5.4	20%
Clofarabine	Clolar	40	mg/m^2	IV	2 h	0.744	226	931	—	4.9	47%
Cobimetinib	Cotellic	60	mg	PO	—	0.514	273	4,340	2.4	44	95%
Crizotinib	Xalkori	250	mg	PO	—	0.913	411	3,880	4.0	34.9	91%
Cyclophosphamide	Cytoxan	600	mg/m^2	IV	Bolus	128	33,408	226,082	—	3–12	20%
Cytarabine	Cytosar-U	3,000	mg/m^2	IV	3 h	54.4	13,219	38,928	—	3.82	13%
Dabrafenib	Tafinlar	150	mg	PO	—	4.86	2,527	10,751	2.0	4.8	99.7%
Dacarbazine	DTIC-Dome	200	mg/m^2	IV	30 min	34.4	6,270	4,860	—	5	<5%
Dactinomycin	Cosmegen	0.70–1.50	mg/m^2	IV	Bolus	0.020	25	44.5	0.25	14–43	5%
Dasatinib	Sprycel	100	mg	PO	—	0.264	129	478	2.0	6.2	96%
Daunorubicin	Daunoxome	50	mg/m^2	IV	1 h	0.310	175	575	—	11	97%
Decitabine	Dacogen	15	mg/m^2	IV	3 h	0.323	74	163	2.5	0.62	<1%
Degarelix	Firmagon	240	mg	SC	—	0.016	26	25,296	48	—	90%
Dexrazoxane	Zinecard	500	mg/m^2	IV	15 min	136	36,500	—	—	2.5	<2%
Docetaxel	Taxotere	100	mg/m^2	IV	1 h	5.47	4,420	5,900	—	41	97%
Doxorubicin	Adriamycin	60	mg/m^2	IV	5 min	6.73	3,660	1,850	—	14.2	75%
Doxorubicin (liposomal)	Doxil	20	mg/m^2	IV	30 min	15.34	8,340	590,000	—	55	70%
Enzalutamide	Xtandi	160	mg	PO	—	35.7	16,600	—	1.0	5.8	98%
Epirubicin	Ellence	120	mg/m^2	IV	10 min	16.6	9,000	3,400	—	33.7	77%
Eribulin mesylate	Halaven	1.4	mg/m^2	IV	2–5 min	0.508	371	757	0.17	40.4	49%–65%
Erlotinib	Tarceva	150	mg	PO	—	3.15	1,238	18.6	5.5	24.4	93%
Etoposide	VePesid	100	mg/m^2	IV	60 min	33.4	19,660	29,800	—	3.62	97%
Everolimus	Afinitor	10	mg	PO	—	0.064	61	514	1.0	—	74%
Exemestane	Aromasin	25	mg	PO	—	0.027	7.9	52	1.2–2.9	24	90%
Fluorouracil (5-FU)	Adrucil	400	mg/m^2	IV	Push	426	55,400	11,590	—	—	10%
Flutamide	Eulexin	250	mg	PO	—	0.409	113	—	1.3	7.8	94%–96%
Fulvestrant	Faslodex	500	mg	IM	—	0.041	25	11,400	—	960	99%
Gefitinib	Iressa	250	mg	PO	—	0.356	159	5,115	3.0	50.5	90%
Gemcitabine	Gemzar	1,250	mg/m^2	IV	30 min	89.3	23,500	12,500	—	0.23	Negligible
Goserelin acetate	Zoladex	10.8	mg	SC	—	0.007	8.9	—	1.8	—	27%
Hydroxyurea	Droxia	2,000	mg	PO	—	795	60,441	299,181	1.2	3.32	—
Ibrutinib	Imbruvica	560	mg	PO	—	0.277	122	1,263	2.0	9.2	98%

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Table 1. Key human pharmacokinetic parameters for small-molecule drugs approved for oncology indications (Cont'd)

Generic name	Brand name	Dose	Dose unit	Route	Infusion	C_{max} (μmol/L)	C_{max} (ng/mL)	AUC (ng•hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Protein binding
Idarubicin	Idamycin	15	mg/m^2	IV	5 min	0.123	61	173	—	21.8	97%
Idelalisib	Zydelig	150	mg	PO	—	5.18	2,152	9,599	1.8	5.75	84%
Ifosfamide	Ifex	3,000	mg/m^2	IV	3 h	431	112,534	2,448,857	—	4.1	Negligible
Imatinib	Gleevec	600	mg	PO	—	7.50	3,700	48,800	—	17	95%
Imiquimod	Aldara	75	mg	Topical	—	0.0056	1.4	0.0291	—	—	90%–95%
Ingenol	Picato	0.5	mg	Topical	—	BLOQ	BLOQ	—	—	—	>99%
Ixabepilone	Ixempra	40	mg/m^2	IV	3 h	0.497	252	2,143	—	35	67%–77%
Ixazomib	Ninlaro	4	mg	PO	—	0.118	61	1,160	1.0	228	99%
Lanreotide	Somatuline Depot	120	mg	SC	—	0.007	7.7	—	—	—	—
Lapatinib	Tykerb	1,250	mg	PO	—	4.18	2,430	36,200	4.0	14.2	>99%
Lenalidomide	Revlimid	25	mg	PO	—	1.74	451	3,820	1.5	5.3	30%
Lenvatinib	Lenvima	24	mg	PO	—	0.761	325	3,010	2.0	28	98%–99%
Letrozole	Femara	2.5	mg	PO	—	0.406	116	2,246	1.5	—	60%
Leuprolide acetate	Eligard	30	mg	SC	—	0.124	150	—	3.3	—	43%–49%
Mechlorethamine	Mustargen	0.4	mg/kg	IV	Bolus	BLOQ	BLOQ	—	—	—	—
Megestrol acetate	Megace	800	mg	PO	—	1.96	753	10,476	5.0	—	—
Melphalan	Alkeran	20	mg/m^2	IV	15–20 min	9.17	2,800	—	—	1.25	60%–90%
Mercaptopurine	Purinethol	75	mg/m^2	PO	—	0.590	90	274	—	1.3	19%
Mercaptopurine	Purixan	50	mg	PO	—	0.625	95	136	—	2	19%
Methotrexate	Abitrexate	30	mg	PO	—	1.31	594	2,466	1.2	2.9	50%
Methoxsalen	Uvadex; 8-MOP	40	mg	PO	—	0.624	135	440	2.0	2	90%
Mitomycin C	Mitozytrex	15	mg/m^2	IV	30 min	2.18	729	691	—	0.81	24%
Mitoxantrone	Novantrone	12	mg/m^2	IV	30 min	0.715	318	298	—	17	78%
Nab-paclitaxel	Abraxane	260	mg/m^2	IV	30 min	21.9	18,740	20,324	—	27	89–98%
Nilotinib	Tasigna	400	mg	PO	—	0.840	445	11,900	4.0	13	98%
Nilutamide	Nilandron	150	mg	PO	—	2.84	900	39,000	2.8	56	80%–84%
Octreotide	Sandostatin	0.1	mg	SC	—	0.0038	4.0	12.4	0.64	2.25	65%
Olaparib	Lynparza	400	mg	PO	—	13.1	5,700	58,000	1.3	11.9	82%
Omacetaxine	Synribo	1.25	mg/m^2	SC	—	0.046	25	136	0.55	7	50%
Osimertinib	Tagrisso	80	mg	PO	–	0.126	63	3,132	6.0	64	99%
Oxaliplatin	Eloxatin	110	mg/m^2	IV	2 h	4.96	1,970	4,990	—	1.86	>90%
Paclitaxel	Taxol	175	mg/m^2	IV	3 h	4.27	3,650	15,007	—	20.2	89%–98%
Palbociclib	Ibrance	125	mg	PO	—	0.101	45	1,427	6.0	22.2	85%
Pamidronate	Aredia	90	mg	IV	4 h	11.1	2,610	17,120	4.0	—	—
Panobinostat	Farydak	20	mg	PO	—	0.082	29	280	1.0	15.5	90%
Pazopanib	Votrient	800	mg	PO	—	133	58,100	1,037,000	2–4	30.9	>99%
Pemetrexed	Alimta	500	mg/m^2	IV	10 min	306	131,000	188,000	—	4.4	81%
Pentostatin	Nipent	4	mg/m^2	IV	15 min	1.82	489	1,232	—	5.3	4%
Plerixafor	Mozobil	0.24	mg/kg	SC	—	1.84	926	4,741	0.50	5.1	58%
Pomalidomide	Pomalyst	4	mg	PO	—	0.274	75	400	2–3	9.5	12%–44%
Ponatinib	Iclusig	45	mg	PO	—	0.137	73	1,253	—	24	>99%
Porfimer	Photofrin	2	mg/kg	IV	3–5 min	33.9	40,000	2,400,000	—	415	90%
Pralatrexate	Folotyn	40	mg/m^2	IV	5 min	10.3	4,900	4,900	—	1.8	67%
Prednisone	Deltasone	50	mg	PO	—	0.145	52	—	—	—	Extensive
Procarbazine	Matulane	300	mg	PO	—	3.13	692	217	0.21	0.154	—
Raloxifene	Evista	60	mg	PO	—	0.0011	0.5	27.2 (ng•hr/mL)/(mg/kg)	—	27.7	95%
Regorafenib	Stivarga	160	mg	PO	—	8.08	3,900	58,300	4.0	28	99.5%
Romidepsin	Istodax	14	mg/m^2	IV	4 h	0.697	377	1,549	—	3	92%–94%
Rucaparib	Rubraca	600	mg	PO		6.000	1,940	16,900	1.9	17	70%
Ruxolitinib	Jakafi	25	mg	PO	—	1.09	335	979	0.63	2.3	97%
Sonidegib	Odomzo	200	mg	PO	—	2.12	1,030	22,000	2–4	672	>97%
Sorafenib	Nexavar	400	mg	PO	—	20.1	9,350	107,000	2.5	23.8	99.5%
Streptozocin	Zanosar	1,500	mg/m^2	IV	Push	1,438	381,400	72,150	—	0.22	—
Sunitinib malate	Sutent	50	mg	PO	—	0.181	72	1,296	8.5	41–86	95%
Tamoxifen citrate	Nolvadex	20	mg	PO	—	0.108	40	—	5.0	120–168	>99%
Tegafur	Utefos	50	mg/m^2	PO	—	19.0	3,803	26,480	1.0	7.88	—
Temsirolimus	Torisel	25	mg	IV	30–60 min	0.568	585	1,627	—	17	87%
Teniposide	Vumon	300–750	mg/m^2	IV	72 h	23.1	15,200	—	—	—	>99%
Thalidomide	Thalomid	200	mg	PO	—	8.91	2,300	23,300	5.8	4.12	55% (+)-(R); 66% (-)-(S)
Thioguanine	Tabloid	40	mg/m^2	PO	—	0.313	52	0.0979	1.5	—	—

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Table 1. Key human pharmacokinetic parameters for small-molecule drugs approved for oncology indications (Cont'd)

Generic name	Brand name	Dose	Dose unit	Route	Infusion	C_{max} (μmol/L)	C_{max} (ng/mL)	AUC (ng·hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Protein binding
Topotecan	Hycamtin	2.3	mg/m^2	PO	—	0.015	6.3	22.7	—	3.49	35%
Toremifene	Fareston	120	mg	PO	—	4.56	1,850	115,100	2.9	56.5	>99.5%
Trabectedin	Yondelis	1.5	mg/m^2	IV	24 hr	0.0024	1.8	56.8	—	175	97%
Trametinib	Mekinist	2	mg	PO	—	0.021	13	69.7	2.0	3.9–4.8	97%
Tretinoin	Vesanoid	45	mg/m^2	PO	—	1.15	347	682	2.2	—	>95%
Triptorelin	Trelstar Depot	22.5	mg	IM	—	0.034	44	—	1–3	—	0%
Valrubicin	Valstar	800	mg	Intra-cisternal	—	0.011	8	56.4	2–6	—	>99%
Vandetanib	Caprelsa	300	mg	PO	—	2.16	1,025	20,460	5	456	90%
Vemurafenib	Zelboraf	960	mg	PO	—	127	62,000	601,000	3.0	57	>99%
Venetoclax	Venclexta	400	mg	PO	—	4.48	21,000	32,800	5–8	26	>99%
Vinblastine	Velban	1**	mg/m^2	IV	Bolus	0.035	28	45	0.12	26.20	98%–99%
Vincristine	Vincasar PFS	1	mg/m^2	IV	Bolus	0.007	5.4	—	—	—	75%
Vincristine (liposomal)	Marqibo	2.25	mg/m^2	IV	60 min	1.479	1,220	14,566	—	7.66	75%
Vinorelbine	Navelbine	25	mg/m^2	IV	20 min	0.811	632	585	—	21.40	89%
Vismodegib	Erivedge	150	mg	PO	—	33.9	14,282	2,283,446	—	96	>99%
Vorinostat	Zolinza	400	mg	PO	—	1.20	317	1,110	1.5	2	71%
Zoledronic acid	Zometa	4	mg	IV	15 min	0.971	264	420	—	146	33%–40%

NOTE: A single (*) or double (**) asterisk refers readers to notes in Supplementary Table S1.

Abbreviations: Approx, approximately; BLOQ, below the limit of quantitation; hr, hours; IM, intramuscular; IV, intravenous; min, minute(s); n/a, not applicable; PO, *per os*; SC, subcutaneous; T_{max}: time post-dose of maximum plasma concentration; $T_{1/2}$: plasma half-life.

States is shown, along with the indication approved for use in the United States.

The C_{max} values reported here represent the peak exposures observed at the highest clinically recommended doses delivered as a single administration (except where noted). In the clinic, most agents are typically given by repeated administration that may lead to accumulation, so some agents may achieve higher exposures at steady state. With intravenous administration, the C_{max} is typically reported at the end of the infusion but is sometimes reported as C_0, a calculated concentration extrapolated from the plasma concentration–time curve to time zero. The C_{max} following intravenous administration is highly dependent on the duration of the injection, so the recommended injection duration is provided in the tables for reference. The C_{max} and AUC

Table 2. Key human pharmacokinetic parameters for small-molecule prodrugs and their active metabolites approved for oncology indications

Generic name	Brand name	Dose	Dose unit	Route	Infusion	C_{max} (μmol/L)	C_{max} (ng/mL)	AUC (ng·hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Protein binding
Abiraterone acetate	Zytiga	1,000	mg	PO	—	BLOQ	BLOQ	—	—	—	—
Abiraterone[a]	(Zytiga)	As above		PO	—	0.647	226	1,173	—	12	>99%
Estramustine phosphate	Emcyt	2,000	mg/m^2	IV	60 min	797	414,700	889,884	—	2.5	—
Estramustine[a]	(Emcyt)	As above		IV	—	10.4	4,420	37,605	—	99	—
Estramustrone[a]	(Emcyt)	As above		IV	—	15.6	6,620	211,351	—	129	—
Floxuridine	FUDR	30	mg/kg	IV	8 h	1.05	259	1,365	—	0.22	—
5-FU[a]	(FUDR)	As above			—	0.88	115	—	—	—	—
Fludarabine phosphate	Fludara	25	mg/m^2	IV	30 min	BLOQ	BLOQ	—	—	—	19%–29%
2-F-araA[a]	(Fludara)	As above		IV	—	3.00	808	3,285	—	11.3	—
Irinotecan	Camptosar	340	mg/m^2	IV	90 min	5.78	3,392	20,604	—	11.7	30%–68%
SN-38[a]	(Camptosar)	As above		IV	—	0.143	56	474	—	21	95%
Irinotecan (liposomal)	Onivyde	70	mg/m^2	IV	90 min	63.4	37,200	1,364,000	—	25.8	<0.44%
SN-38 (liposomal)[a]	(Onivyde)	As above		IV	—	0.014	5.4	620	—	67.8	95%
Lomustine (CCNU)	Gleostine	130	mg/m^2	PO	—	BLOQ	BLOQ	—	—	—	50%
cis+trans 4-OH-CCNU[a]	(Gleostine)	As above		PO	—	3.39	847	3,400	2–4	1.8	—
Nelarabine	Arranon	1,500	mg/m^2	IV	2 h	16.8	5,000	4,400	—	0.3	<25%
Ara-G[a]	(Arranon)	As above		IV	—	111	31,400	162,000	—	3.2	<25%
Temozolomide	Temodar	150	mg/m^2	IV	90 min	37.6	7,300	24,600	1.0	1.8	15%
MTIC[a]	(Temodar)	As above		IV	—	1.64	276	891	—	—	—
Testosterone enanthate	Delatestryl	200	mg	IM	—	n.d.	n.d.	—	—	—	—
Testosterone[a]	(Delatestryl)	As above		IM	—	0.051	15	—	55	—	98%
Thiotepa	Thioplex	80	mg	IV	Push	9.66	1,828	4,127	—	2.3	10%
TEPA[a]	(Thioplex)	As above		IV	—	2.04	353	7,452	—	15.7	—

Abbreviations: BLOQ, below the limit of quantitation; hr, hours; IM, intramuscular; IV, intravenous; min, minutes; n.d., not determined; PO, *per os*; T_{max}: time post-dose of maximum plasma concentration; $T_{1/2}$: plasma half-life.

[a]Key human pharmacokinetic parameters for active metabolites (of small-molecule prodrugs) approved for oncology indications.

Table 3. Key human pharmacokinetic parameters for biological drugs approved for oncology indications

Generic name	Brand name	Dose	Dose unit	Route	Infusion	C_{max} (μmol/L)	AUC (μg•hr/mL)	T_{max}	$T_{1/2}$ (days)
Ado-trastuzumab emtansine	Kadcyla	3.6	mg/kg	IV	90 min	0.572	19.8	End of infusion	4.2
Free DM1	(Kadcyla)	—	—	—	—	0.006	—	—	—
Aldesleukin	Proleukin	1.1	mg	SC	—	0.00159	0.0157	2.5 h	0.071
Alemtuzumab	Campath	30	mg	IV	2 h	0.07356	—	—	6
Asparaginase (*Escherichia coli*)	Elspar	5,000	U/m2	IV	30 min	0.51684	307	—	0.771
Asparaginase (*Erwinia chrysanthemi*)	Erwinaze	30,000	IU/m^2	IV	3 h	20 IU/mL	—	—	0.267
Atezolizumab	Tecentriq	1,200	mg	IV	60 min	2.79000	—	—	27
Bevacizumab	Avastin	10	mg/kg	IV	30 min	1.90604	—	—	21
Blinatumomab	Blincyto	28	μg	IV	24 h	0.000011	—	—	0.0875
Brentuximab vedotin	Adcetris	1.8	mg/kg	IV	30 min	0.20915	3.19	0.089 d	4.43
Free MMAE	(Adcetris)	—	—	—	—	0.00696	0.0015	2.09 d	3.6
Cetuximab	Erbitux	400	mg/m^2	IV	2 h	1.40622	19,000	3 h	3.13
Daratumumab	Darzalex	16	mg/kg	IV	6.5 h	6.18243	—	—	18
Denileukin diftitox	Ontak	19	μg/kg	IV	60 min	1,309 U/mL	33,482 U•min/mL	—	0.056
Denosumab	Prolia	60	mg	SC	—	0.04592	13.2	10 d	25.4
Denosumab	Xgeva	180	mg	SC	—	0.21156	55	10 d	29.1
Dinutuximab	Unituxin	17.5	mg/m^2	IV	10–20 h	0.07667	—	—	10
Elotuzumab	Empliciti	10	mg/kg	IV	15–60 min	2.27819	40,701	4.1 h	0.197
Filgrastim	Neupogen	5	μg/kg	IV	15–30 min	0.01004	0.638	—	0.463
Gemtuzumab ozogamicin	Mylotarg	9	mg/m^2	IV	2 h	0.01869	123	—	3.02
Free calichaemicin	(Mylotarg)	—	—	—	—	0.00365	0.22	—	4.21
Interferon alfa-2b	Intron A	20×10^6	IU	IV	20 min	0.00031	0.00950	—	—
Ipilimumab	Yervoy	3	mg/kg	IV	90 min	0.54730	—	—	—
Necitumumab	Portrazza	800	mg	IV	60 min	3.51519	67,821	—	5.21
Nivolumab	Opdivo	3	mg/kg	IV	60 min	0.41034	15,813	3.1 h	17
Obinutuzumab	Gazyva	1,000	mg	IV	See label	3.75770	366	—	28.4
Ofatumumab	Arzerra	2,000	mg	IV	See label	10.14374	674,463	—	15.8
Olaratumab	Lartruvo	15	mg/kg	IV	60 min	3.09700	42,400	2.53 h	7.21
Oprelvekin	Neumega	50	μg/kg	SC	—	0.00100	0.242	2.7 h	0.3375
Palifermin	Kepivance	90	μg/kg	IV	Bolus	0.12228	0.232	—	0.196
Panitumumab	Vectibix	6	mg/kg	IV	60 min	1.44898	54.4	7.5 d	—
Pegaspargase	Oncaspar	2,500	IU/m^2	IV	1–2 hr	0.35740	—	—	7
Pegfilgrastim	Neulasta	100	μg/kg	SC	—	0.00587	29.3	48 h	0.883
Peginterferon alfa-2b	PEG-Intron	6	μg/kg	SC	—	0.00014	0.43	—	2.125
Pembrolizumab	Keytruda	2	mg/kg	IV	30 min	0.44090	58.7	0.17 d	26
Pertuzumab	Perjeta	420	mg	IV	30–60 min	1.01351	2,762	—	19.1
Ramucirumab	Cyramza	8	mg/kg	IV	60 min	1.16327	18,300	—	7.54
Rasburicase	Elitek	0.2	mg/kg	IV	30 min	0.11375	45.2	—	0.879
Rituximab	Rituxan	375	mg/m^2	IV	See label	3.22397	—	—	—
Romiplostim	Nplate	1	μg/kg	IV	Bolus	0.00022	0.0267	—	0.1
Siltuximab	Sylvant	11	mg/kg	IV	60 min	2.28966	—	—	20.6
Thyrotropin alfa	Thyrogen	0.9	mg	IM	—	0.00122	—	10 h	1.04
Trastuzumab	Herceptin	6	mg/kg	IV	90 min	1.48422	—	—	12
Ziv-aflibercept	Zaltrap	4	mg/kg	IV	1 h	1.00516	12.2	—	5.5

Abbreviations: BLOQ, below the limit of quantitation; d, days; hr, hour(s); IM, intramuscular; IV, intravenous; min, minutes; PO, *per os*; SC, subcutaneous; T_{max}: time post-dose of maximum plasma concentration; $T_{1/2}$: plasma half-life.

values are presented as total plasma exposure (bound and unbound) of the parent molecule only, without consideration of the presence of active metabolites. It is important to note that the C_{max} and AUC values presented here are average values, and interindividual variability can be quite large due to genetic polymorphisms in clearance and other factors (e.g., mercaptopurine).

A few alternative formulations of equivalent active ingredients have been included in this compilation. For example, the nanoparticle formulation of paclitaxel (nab-paclitaxel; Abraxane) has recently been approved, and allows shorter infusion times and higher doses to be delivered compared with paclitaxel (Taxol). A suspension formulation of mercaptopurine (Purixan), which offers greater dosing flexibility than the original tablet, was approved in 2014. Liposomal formulations of doxorubicin (Doxil), irinotecan (Onivyde), and vincristine sulfate (Marqibo) have been approved. These formulations have distinct pharmacokinetic properties compared with the original dosage forms, so they have been included in Table 1.

Three biological agents are available both as the native compound and as polyethylene glycol (PEG) conjugates: asparaginase (pegaspargase; Oncaspar), filgrastim (pegfilgrastim; Neulasta), and interferon alpha-2b (peginterferon; Sylantron, PEGintron). Pegylation retains the biological activity but alters the molecular form of the drug; it is not processed *in vivo* to release the parent biological agent, so these are not prodrugs. Hence, these were regarded as independent species distinct from the parent compound and have been included separately in Table 3. Three biological agents are antibody–drug conjugates (ADC), with cytotoxic agents covalently bound to an antibody (ado-tratuzumab emtansine, bretuximab vedotin, gemtuzumab ozogamicin). In these cases, the plasma levels of the free cytotoxic agents are also included in Table 3.

Table 4. Key human pharmacokinetic parameters for selected small-molecule drugs NOT approved for oncology indications

Generic name	Brand name	Dose	Dose unit	Route	Infusion	C_{max} (μmol/L)	C_{max} (ng/mL)	AUC (ng·hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	Protein binding
Alfuzosin	UroXatral	10	mg	PO	—	0.035	14	194	8.0	10	82%–90%
Aminoglutethimide	Cytadren	500	mg	PO	—	25.4	5,900	—	1.5	12.5	21%–25%
Celecoxib	Celebrex	400	mg	PO	—	4.60	1,752	13,049	—	8.8	97%
Chloroquine	Aralen	750	mg	PO	—	0.725	232	8,385	3.7	—	55%
Dutasteride	Avodart	0.5	mg	PO	—	0.076	40	—	2–3	840	99%
Finasteride	Proscar	5	mg	PO	—	0.124	46	389	1.8	6	90%
Histrelin acetate	Supprelin	0.0567	mg/day	SC		0.00083	1.1	2,318	12	—	70%
Hydroxychloroquine	Plaquenil	200	mg	PO	—	0.35000	117.4	12,015	3.8	564	45%
Ibandronate	Boniva	6	mg	IV	30 min	1.02	327	942	0.63	12	86%
Medroxyprogesterone acetate	Provera	20	mg	PO	—	0.0026	1.0	6.95	2.7	12.1	90%
Metformin	Glucophage	1,500	mg	PO	—	24.0	3,100	18,400	1.5	5.98	Negligible
Quinacrine	Acrichine	100	mg	PO	—	0.300	120	—	—	—	80%–90%
Sildenafil	Viagra	100	mg	PO	—	0.794	377	1,295	1.0	2.76	96%
Sirolimus (rapamycin)	Rapamune	2	mg	PO	—	0.016	15	230	3.5	62	92%
Tacrolimus	Prograf	5	mg	PO	—	0.037	30	243	1.6	34.8	99%
Zalcitabine (dideoxycytidine)	Hivid	1.5	mg	PO	—	0.119	25	72	0.80	—	<4%

Abbreviations: min, minutes; PO, *per os*; SC, subcutaneous; T_{max}: time post-dose of maximum plasma concentration; $T_{1/2}$: plasma half-life.

The plasma C_{max} and AUC were considered to be the key pharmacokinetic parameters to enable translation of clinical drug exposure to a nonclinical study application. The C_{max} data were found for all but two of the 145 unique small-molecule drugs or their active metabolites listed in Tables 1 and 2; the AUC was not found for 21 of these. Two agents (ingenol and mechlorethamine) were reported as below the limit of quantitation (BLOQ). Additional pharmacokinetic parameters (including half-life, T_{max}, clearance, and volume of distribution) were included when available, but not all of these parameters were reported for every agent. For the biological agents, C_{max} was found for all 40 unique drugs listed in Table 3 and AUC was found for 27 of these.

Plasma protein binding of small-molecule drugs varies widely across agents (and occasionally between species) and can have significant impact on plasma-free drug concentrations. This can be an important factor when designing nonclinical studies to examine drug mechanisms, particularly for *in vitro* studies, so plasma protein–binding data have been included for all but 14 of the small-molecule drugs in Tables 1, 2, and 4. Protein binding of biological agents was not considered.

Discussion

Translational medicine can be aided greatly by the establishment of pharmacokinetic–pharmacodynamic relationships in nonclinical models (10–13). A fundamental aspect of translational studies is the determination of the concentrations of drug that are likely to be observed in clinical use. Attempts to translate doses or plasma exposures from nonclinical models to humans most often utilize allometric scaling (14, 15), *in vivo* pharmacokinetics (16, 17), or pharmacokinetics/pharmacodynamics and physiologically based pharmacokinetic models to bridge doses from animal studies to humans (13, 18, 19). Very few studies have incorporated a "reverse translation" of clinical exposure data to aid design of studies in nonclinical oncology models. When testing approved oncology drugs in nonclinical studies to explore expanded cancer indications, awareness of clinically achievable exposure can facilitate study design. Similarly, when attempting to repurpose approved agents from their original indications to use in oncology (e.g., metformin, celecoxib, and sirolimus), it is valuable to have an appreciation of clinically relevant exposures to assist translation to nonclinical models. For *in vivo* studies, these human exposures can be used to help determine the appropriate doses to use in model species, either by allometric scaling or empirical measurement. Allometric scaling is frequently based on body surface area, although this practice has limitations (20). However, direct comparison of plasma exposure associated with a measured clinical activity in humans (a clinical pharmacodynamic response) to an exposure observed in nonclinical models that used doses and routes of administration that differ from clinical use can assist in the interpretation of pharmacodynamic results in the animal model. In this regard, Spilker and colleagues (21) have recently proposed a rigorous strategy by which human pharmacokinetic parameters can be utilized in conjunction with mouse pharmacokinetic studies to determine the doses and routes of administration that can most closely mimic the clinically relevant exposures in the animal model.

The plasma C_{max} is highly dependent on route of administration, formulation, and physical properties of the drug. It provides an indication of the highest concentration that the subject is exposed to during therapy, and the C_{max} may be considered as an upper limit for drug concentration during *in vitro* studies or the highest plasma exposure for *in vivo* studies to minimize off-target effects. During *in vitro* studies, it is often possible to increase the drug concentration to levels far in excess of what could be achieved *in vivo*. However, testing targeted agents at concentrations 10 or 100 times greater than the IC_{50} or K_i for the molecular target increases the possibility of introducing off-target activities unrelated to the clinical benefit (1), or from on-target activity (enzyme inhibition and receptor occupancy) that is not realistically achievable in the clinic. Either of these situations can lead to a misinterpretation of responses in nonclinical studies. Furthermore, the C_{max} is maintained only transiently for most compounds, and sustained levels well below C_{max} may be sufficient to achieve therapeutic efficacy. In cases where a pharmacodynamic

response is tightly linked to exposure, it may be important to maintain a minimum plasma concentration to sustain inhibition of the target (e.g., receptor occupancy and enzyme inhibition) above a certain threshold. In other cases, particularly when the drug interacts with the target irreversibly (e.g., several alkylating agents; afatinib), the duration of the pharmacodynamic effect (target binding) is uncoupled from the plasma pharmacokinetics and can be much longer than the plasma half-life of the drug (22), so the C_{max} may be more directly related to efficacy than AUC.

Differences in free drug levels due to protein binding can be critical for translation of clinical exposures to nonclinical models, particularly during *in vitro* studies. For small-molecule drugs, plasma drug analysis is typically performed following organic extraction of samples, and the reported values represent total plasma concentration (free + protein bound) rather than free (unbound) drug. As the free (unbound) drug is generally the species that interacts with the molecular target, reduction in free drug levels due to protein binding can dramatically alter the concentration of drug available for interaction with the target during *in vitro* studies (i.e., cell culture or biochemical assays). Discrepancies between free drug concentrations *in vitro* in cell culture media containing 5% to 10% bovine serum and *in vivo* (e.g., human plasma) will be dependent on the degree of protein binding for each drug and the binding capacity of the added protein/serum.

Species differences in plasma protein binding may warrant consideration when designing translational studies, as some drugs show clinically significant species differences in plasma protein binding. For example, at clinically relevant concentrations, vismodegib is primarily bound to α-1-acid glycoprotein (AAG), with a much lower affinity for albumin (23). Quantitative assays of protein binding revealed an approximately 100-fold difference in binding K_d between rat and human AAG, which resulted in significant pharmacokinetic differences between species. In general, any species differences in binding affinity to the target should also be factored into the calculation of the concentrations deemed to be equivalent to human clinical exposure.

Plasma AUC is another key parameter to consider in planning nonclinical studies, particularly when comparing exposures between species or routes of administration. The AUC is the integration of plasma drug exposure over time, and as such takes into account bioavailability, different absorption rates (e.g., intravenous vs. oral) and elimination rates. This provides a more complete picture of drug exposure than C_{max}, which represents exposure at only the T_{max}. Although AUC can be useful to compare exposure following different routes of administration or formulations, it is particularly useful to translate the exposure achieved in humans to that seen in animal models. Modifying the dose or route in animals to mimic more closely the AUC observed in the clinic, using a protocol such as suggested by Spilker and colleagues (21), may provide a more relevant drug exposure in the model and help to avoid high exposures that would not be tolerated in humans or that may lead to off-target activities of the drug.

In cases where active metabolites contribute significantly to efficacy, the concentration of those metabolites in plasma may need to be monitored to capture the exposure responsible for the full pharmacologic activity of the administered product. One example of this is tamoxifen. Through the action of two cytochrome P450 oxidases (CYP2D6 and CYP3A4/5), three metabolites are produced with affinities for the estrogen receptor that are similar to or more potent than the parent molecule (24–27). In patients, these metabolites may be responsible for much of the pharmacodynamic action of the drug (24, 25). It has been shown that mice can produce these metabolites (28), but levels and metabolite profile vary with dose. However, these metabolites may not be produced in all *in vitro* systems under test (e.g., cell culture and biochemical assays), so activity due to parent alone may not reflect the full potential *in vivo* activity of the drug. In addition, polymorphisms in cytochrome P450 enzymes responsible for activation (or degradation) can influence the plasma concentrations of parent and metabolites. Hence, when testing tamoxifen in nonclinical models, levels of parent and these active metabolites should be considered. As can be seen from this example, the interpretation of results is complex in nonclinical models where active metabolites of the parent have the potential to contribute significantly to the pharmacologic action.

Several alkylating agents undergo activation to the reactive species *in vivo*, and this activation should be considered when designing nonclinical studies. Activation of these agents is described in the drug product labels. The platinum-containing drugs (carboplatin, cisplatin, and oxaliplatin) are subject to aquation in water, which will occur in most *in vitro* and *in vivo* systems to generate the active agents. Temozolomide undergoes rapid nonenzymatic hydrolysis to MTIC, which is present at about 3% of parent levels in plasma. Similar to temozolomide, busulfan undergoes nonenzymatic hydrolysis in aqueous media to become activated, releasing methanesulfonate groups. Three alkylating agents are activated by cytochrome P450 enzymes (altretamine, cyclophosphamide, and ifosfamide). For the agents requiring enzymatic activation, evaluation in nonclinical models (*in vitro* and *in vivo*) should ensure that the appropriate P450 enzymes are present within the system to allow full activity to be manifest. Three drugs (aminolevulinic acid, methoxysalen, and porfimir) require photoactivation, which yields free radicals or derivatives that form covalent bonds with nucleic acids and proteins to generate cytoxicity.

The most common routes of administration for oncology drugs in the clinic are oral and intravenous. In animal studies, particularly in rodents, the intraperitoneal route is often preferred. Following intraperitoneal injection, many small-molecule drugs are absorbed by capillaries within the visceral peritoneum, which collect into the mesenteric and omental veins and drain into the hepatic portal vein. Drugs absorbed through this route will be subject to first-pass hepatic metabolism, similar to orally administered drugs (29). For certain high-molecular weight drugs, such as biologics, and some lipophilic small molecules, absorption into the lymphatic drainage predominates, thereby avoiding first-pass hepatic clearance (30). Some biological agents are subject to target-mediated clearance, in addition to the the hepatic and renal clearance mechanisms more typical with small-molecule drugs. The formulation of drugs (vehicle and excipients) can have a significant effect on the rate and extent of absorption following either intraperitoneal or oral delivery. In animal studies, oral drugs are often delivered as suspensions. Although suspensions are generally tolerated for oral administration, drugs delivered intraperitoneally should be fully solubilized. All of these factors can influence C_{max} and AUC, so they should

be considered during the design and interpretation of nonclinical studies.

Our goal in this compilation is to provide a convenient data resource of pharmacokinetic estimates for clinically relevant plasma exposures (C_{max} and AUC) for all single agents marketed for oncology indications in the United States. We chose the highest dose recommended in the label delivered as a single administration (except where noted), the intent being to provide a benchmark for achievable and relevant human exposures. The therapeutic effects of many of the agents are likely due to repeated administration of these doses using a variety of schedules that may lead to accumulation, so some agents may achieve higher exposures at steady state. Consideration of these clinically achievable exposures in conjunction with animal studies to characterize the pharmacokinetics in the model species, such as described by Spilker and colleagues (21) and including dose–response curves, will ultimately improve the translation of pharmacologic activity in the model back to the clinic. We expect the greatest utility of this report will be a source from which an upper boundary on the clinically achievable plasma concentrations of anticancer agents can be readily applied to *in vitro* studies. Admittedly, there are limitations and caveats associated with any attempt to reduce something as complex as efficacy and human pharmacokinetics down to a single approach, and successful application of these clinical exposure values will also require a thorough understanding of the underlying biology of the target and disease processes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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