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# 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 U.S. Food and Drug Administration (FDA) for use in oncology in order 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.

### Keywords

oncology; pharmacokinetics

## 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*

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*vitro* or *in vivo* that are relevant to observed clinical exposures. In so doing, 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 anti-cancer 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 U.S. 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 anti-emetics were excluded, although these are widely used for supportive care during cancer treatment. We also excluded diagnostics, imaging agents and radiological therapies. Several drugs that are not approved specifically for use in cancer but are increasingly being reported in experimental settings (e.g., metformin, celecoxib) have been included where possible.

## Methods

A comprehensive list of agents approved for use as anticancer therapies in the U.S. 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 which 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 anti-emetics. Combination drug therapies were removed from the list, since 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 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 (PK) 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 PK 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 1) the use of a dose equivalent to the highest dose recommended in the label and 2) 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, of which 10 are prodrugs. Table 1 provides a summary of the human PK parameters for all 135 unique small molecule drugs and 5 alternative formulations approved for use in oncology indications in the U.S, excluding prodrugs. Table 2 includes all 10 drugs delivered as prodrugs, where the chief pharmacological 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 U.S. market. The dose and route of administration from which the PK data are derived is shown, which is typically the highest dose recommended in the label. For drugs administered IV, 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 area under the plasma concentration-time curve (AUC) is shown, following conversion to a consistent unit of ng•hr/ml. The raw values and units for Cmax 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 U.S., they may be used experimentally, particularly in drug combination studies, so the PK 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 pharmacological 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: 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 non-enzymatically to MTIC at physiological 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 PK parameters reported for all 40 biological therapeutics approved for cancer indications in the U.S, 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 area under the plasma concentration-time curve (AUC). The time of maximum plasma concentration ($T_{max}$) and the plasma half-life ($T_{1/2}$) are also shown, where reported, as well as the duration of injection for drugs administered IV.

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 PK 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 merged into a single, sortable spreadsheet (Supplemental Table 1). A separate file containing the biological agents from Table 3 is also provided (Supplemental Table 2). These are Excel files that include full references for the primary sources of the PK 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 U.S. is shown, along with the indication approved for use in the U.S.

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 which may lead to accumulation, so some agents may achieve higher exposures at steady-state. With IV 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 IV 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 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 to 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 PK properties compared to the original dosage forms, so 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.

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 2 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, 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 (PK/PD) 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* PK (16,17) or PK/PD and physiologically-based pharmacokinetic (PBPK) 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, 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 which used doses and routes of administration that differ from clinical use can assist the interpretation of pharmacodynamic results in the animal model. In this regard, Spilker et al. (21) have recently proposed a rigorous strategy by which human PK parameters can be utilized in conjunction with mouse PK 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 ten or one hundred times greater than the IC50 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, 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, 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 PK 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. Since 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 5–10% 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 PK 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., IV vs oral) and elimination rates. This provides a more complete picture of drug exposure than $C_{max}$, which represents exposure at only the $T_{max}$. While 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 et al. (21), may provide a more relevant drug exposure in the model and help to avoid high exposures which 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 pharmacological 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, 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 pharmacological 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 non-enzymatic hydrolysis to MTIC, which is present at about 3% of parent levels in plasma. Similar to temozolomide, busulfan undergoes non-enzymatic hydrolysis in aqueous media to become activated, releasing methanesulfonate groups. Three alkylating agents are activated by cytochrome P450 enzymes (altretamine, cyclophosphamide, 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, in order to generate cytoxicity.

The most common routes of administration for oncology drugs in the clinic are oral and IV. In animal studies, particularly in rodents, the IP route is often preferred. Following IP 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 IP or oral delivery. In animal studies, oral drugs are often delivered as suspensions. While suspensions are generally tolerated for oral administration, drugs delivered IP should be fully solubilized. All of these factors can influence $C_{max}$ and AUC, so should be considered during the design and interpretation of nonclinical studies.

Our goal in this compilation is to provide a convenient data resource of PK estimates for clinically relevant plasma exposures ($C_{max}$ and AUC) for all single agents marketed for oncology indications in the U.S. 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 which 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 PK in the model species, such as described by Spilker et al. (21) and including dose-response curves, will ultimately improve the translation of pharmacological 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 anti-cancer 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

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

| Generic Name | Brand Name | Dose | Dose Unit | Route | infusion | Cmax (uM) | Cmax (ng/ml) | AUC (ng•hr/ml) | Tmax (hr) | $T_{1/2}$ (hr) | Protein binding |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Abarelix | Plenaxis | 100 | mg | IM | - | 0.031 | 43.4 | 12000 | 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 | 7430 | 4.0 | 33 | >99% |
| Allopurinol | Zyloprim | 300 | mg | PO | - | 14.3 | 1940 | 4814 | 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/m2 | IV | 7.5 min | 105 | 22472 | 4238 | - | 0.26 | negligible |
| Aminolevulinic Acid | Levulan Kerastick | 100 | mg | IV* | 1 min | 129 | 16900 | 13700 | - | 0.83 | - |
| Anastrozole | Arimidex | 1 | mg | PO | - | 0.035 | 10 | 536 | - | 41.3 | 40% |
| Arsenic Trioxide | Trisenox | 0.1 | mg/kg | IV | 2h | 0.910 | 180 | *see notes* | - | - | 75% |
| Axitinib | Inlyta | 5 | mg | PO | - | 0.163 | 63 | 466 | 1.8 | 3.1 | >99% |
| Azacitidine | Vidaza | 75 | mg/m2 | SC | - | 3.07 | 750 | 960 | 0.50 | 0.68 | - |
| Azacitidine | Vidaza | 75 | mg/m2 | IV | 10–40 min | 11.3 | 2750 | 1044 | - | 0.36 | - |
| Belinostat | Beleodaq | 1000 | mg/m2 | IV | 30 min | 134 | 42657 | 29005 | - | 1 | 94% |
| Bendamustine | Treanda | 120 | mg/m2 | IV | 60 min | 16.3 | 5840 | 13635 | - | 0.7 | 94–96% |
| Bexarotene | Targretin | 300 | mg/m2 | PO | - | 3.39 | 1180 | 5980 | 2.5 | 3.4 | >99% |
| Bicalutamide | Casodex | 50 | mg | PO | - | 1.78 | 768 | 230838 | 31 | 139 | 96% |
| Bleomycin | Blenoxane | 15 | mg/m2 | IV | bolus | 706 | 1000000 | 4.99E+06 | - | 4 | 1% |
| Bortezomib | Velcade | 1.3 | mg/m2 | IV | bolus | 0.312 | 120 | 196 | 0.08 | 48.7 | 83% |
| Bosutinib | Bosulif | 500 | mg | PO | - | 0.377 | 200 | 3650 | 4–6 | 22.5 | 96% |
| Busulfan | Busulflex | 0.8 | mg/kg | IV | 2h | 4.96 | 1222 | 4790 | - | - | 32% |
| Cabazitaxel | Jevtana | 25 | mg/m2 | IV | 1 h | 0.270 | 226 | 991 | 1.0 | 95 | 89–92% |
| Cabozantinib | Cometriq | 140 | mg | PO | - | 4.61 | 2310 | 41600 | 2–5 | 55 | 99.7% |
| Capecitabine | Xeloda | 1250 | mg/m2 | PO | - | 21.1 | 7570 | 8450 | 0.82 | 0.43 | approx 35% |
| Carboplatin | Paraplatin | 400 | mg/m2 | IV | 30 min | 135 | 50000 | 83333 | 0.50 | 3 | 0% |
| Carfilzomib | Kyorolis | 27 | mq/m2 | IV | 5 min | 5.88 | 4232 | 379 | - | < 1 | 97% |
| Carmustine | BiCNU | 600 | mg/m2 | IV | 2h | 19.4 | 4150 | - | - | - | 80% |

| Generic Name | Brand Name | Dose | Dose Unit | Route | infusion | Cmax (uM) | Cmax (ng/ml) | AUC (ng•hr/ml) | Tmax (hr) | $T_{1/2}$ (hr) | Protein binding |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 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/m2 | IV | 1 h | 14.4 | 4321 | 42921 | - | 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 | 2h | 0.168 | 48 | - | - | 5.4 | 20% |
| Clofarabine | Clolar | 40 | mg/m2 | IV | 2h | 0.744 | 226 | 931 | - | 4.9 | 47% |
| Cobimetinib | Cotellic | 60 | mg | PO | - | 0.514 | 273 | 4340 | 2.4 | 44 | 95% |
| Crizotlnib | Xalkori | 250 | mg | PO | - | 0.913 | 411 | 3880 | 4.0 | 34.9 | 91% |
| Cyclophosphamide | Cytoxan | 600 | mg/m2 | IV | bolus | 128 | 33408 | 226082 | - | 3–12 | 20% |
| Cytarabine | Cytosar-U | 3000 | mg/m2 | IV | 3h | 54.4 | 13219 | 38928 | - | 3.82 | 13% |
| Dabrafenib | Tafinlar | 150 | mg | PO | - | 4.86 | 2527 | 10751 | 2.0 | 4.8 | 99.7% |
| Dacarbazine | DTIC-Dome | 200 | mg/m2 | IV | 30min | 34.4 | 6270 | 4860 | - | 5 | <5% |
| Dactinomycin | Cosmegen | 0.70–150 | mg/m2 | 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/m2 | IV | 1 h | 0.310 | 175 | 575 | - | 11 | 97% |
| Decitabine | Dacogen | 15 | mg/m2 | IV | 3h | 0.323 | 74 | 163 | 2.5 | 0.62 | <1% |
| Degarelix | Firmagon | 240 | mg | SC | - | 0.016 | 26 | 25296 | 48 | - | 90% |
| Dexrazoxane | Zinecard | 500 | mg/m2 | IV | 15 min | 136 | 36500 | - | - | 2.5 | <2% |
| Docetaxel | Taxotere | 100 | mg/m2 | IV | 1 h | 5.47 | 4420 | 5900 | - | 41 | 97% |
| Doxorubicin | Adriamycin | 60 | mg/m2 | IV | 5 min | 6.73 | 3660 | 1850 | - | 14.2 | 75% |
| Doxorubicin (liposomal) | Doxil | 20 | mg/m2 | IV | 30 min | 15.34 | 8340 | 590000 | - | 55 | 70% |
| Enzalutamide | Xtandi | 160 | mg | PO | - | 35.7 | 16600 | - | 1.0 | 5.8 | 98% |
| Epirubicin | Ellence | 120 | mg/m2 | IV | 10 min | 16.6 | 9000 | 3400 | - | 33.7 | 77% |
| Eribulin Mesylate | Halaven | 1.4 | mg/m2 | IV | −5 min | 0.508 | 371 | 757 | 0.17 | 40.4 | 49–65% |
| Erlotinib | Tarceva | 150 | mg | PO | - | 3.15 | 1238 | 18.6 | 5.5 | 24.4 | 93% |
| Etoposide | VePesid | 100 | mg/m2 | IV | 60 min | 33.4 | 19660 | 29800 | - | 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/m2 | IV | push | 426 | 55400 | 11590 | - | - | 10% |

| Generic Name | Brand Name | Dose | Dose Unit | Route | infusion | Cmax (uM) | Cmax (ng/ml) | AUC (ng•hr/ml) | Tmax (hr) | $T_{1/2}$ (hr) | Protein binding |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Flutamide | Eulexin | 250 | mg | PO | - | 0.409 | 113 | - | 1.3 | 7.8 | 94–96% |
| Fulvestrant | Faslodex | 500 | mg | IM | - | 0.041 | 25 | 11400 | - | 960 | 99% |
| Gefitinib | Iressa | 250 | mg | PO | - | 0.356 | 159 | 5115 | 3.0 | 50.5 | 90% |
| Gemcitabine | Gemzar | 1250 | mg/m2 | IV | iO min | 89.3 | 23500 | 12500 | - | 0.23 | negligible |
| Goserelin acetate | Zoladex | 10.8 | mg | SC | - | 0.007 | 8.9 | - | 1.8 | - | 27% |
| Histrelin acetate | Supprelin | 0.057 | mg/day | SC | - | 0.00083 | 1.1 | 2318 | 12 | - | 70% |
| Hydroxyurea | Droxia | 2000 | mg | PO | - | 795 | 60441 | 299181 | 1.2 | 3.32 | - |
| Ibrutinib | Imbruvica | 560 | mg | PO | - | 0.277 | 122 | 1263 | 2.0 | 9.2 | 98% |
| Idarubicin | Idamycin | 15 | mg/m2 | IV | 5 min | 0.123 | 61 | 173 | - | 21.8 | 97% |
| Idelalisib | Zydelig | 150 | mg | PO | - | 5.18 | 2152 | 9599 | 1.8 | 5.75 | 84% |
| Ifosfamide | Ifex | 3000 | mg/m2 | IV | 3h | 431 | 112534 | 2E+06 | - | 4.1 | negligible |
| Imatinib | Gleevec | 600 | mg | PO | - | 7.50 | 3700 | 48800 | - | 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/m2 | IV | 3h | 0.497 | 252 | 2143 | - | 35 | 67–77% |
| Ixazomib | Ninlaro | 4 | mg | PO | - | 0.118 | 61 | 1160 | 1.0 | 228 | 99% |
| Lanreotide | Somatuline Depot | 120 | mg | SC | - | 0.007 | 7.7 | - | - | - | - |
| Lapatinib | Tykerb | 1250 | mg | PO | - | 4.18 | 2430 | 36200 | 4.0 | 14.2 | >99% |
| Lenalidomide | Revlimid | 25 | mg | PO | - | 1.74 | 451 | 3820 | 1.5 | 5.3 | 30% |
| Lenvatinib | Lenvima | 24 | mg | PO | - | 0.761 | 325 | 3010 | 2.0 | 28 | 98–99% |
| Letrozole | Femara | 2.5 | mg | PO | - | 0.406 | 116 | 2246 | 1.5 | - | 60% |
| Leuprolide Acetate | Eligard | 30 | mg | SC | - | 0.124 | 150 | - | 3.3 | - | 43–49% |
| Mechlorethamine (Chlormethine) | Mustargen | 0.4 | mg/kg | IV | bolus | BLOQ | BLOQ | - | - | - | - |
| Megestrol acetate | Megace | 800 | mg | PO |  | 1.96 | 753 | 10476 | 5.0 | - | - |
| Melphalan | Alkeran | 20 | mg/m2 | IV | 15–20 min | 9.17 | 2800 | - | - | 1.25 | 60–90% |
| Mercaptopurine | Purinethol | 75 | mg/m2 | 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 | 2466 | 1.2 | 2.9 | 50% |
| Methoxsalen | Uvadex; 8-MOP | 40 | mg | PO | - | 0.624 | 135 | 440 | 2.0 | 2 | 90% |

| Generic Name | Brand Name | Dose | Dose Unit | Route | infusion | Cmax (uM) | Cmax (ng/ml) | AUC (ng•hr/ml) | Tmax (hr) | $T_{1/2}$ (hr) | Protein binding |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Mitomycin C | Mitozytrex | 15 | mg/m2 | IV | 30min | 2.18 | 729 | 691 | - | 0.81 | 24% |
| Mitotane | Lysodren | 6000 | mg/day | PO | - | 50.9 | 16300 | - | - | 432–3816 | 6% |
| Mitoxantrone | Novantrone | 12 | mg/m2 | IV | 30 min | 0.715 | 318 | 298 | - | 17 | 78% |
| nab-Paclitaxel | Abraxane | 260 | mg/m2 | IV | 30 min | 21.9 | 18740 | 20324 | - | 27 | 89–98% |
| Nilotinib | Tasigna | 400 | mg | PO | - | 0.840 | 445 | 11900 | 4.0 | 13 | 98% |
| Nilutamide | Nilandron | 150 | mg | PO | - | 2.84 | 900 | 39000 | 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 | 5700 | 58000 | 1.3 | 11.9 | 82% |
| Omacetaxine | Synribo | 1.25 | mg/m2 | SC | - | 0.046 | 25 | 136 | 0.55 | 7 | 50% |
| Osimertinib | Tagrisso | 80 | mg | PO | qd | 0.126 | 63 | 3132 | 6.0 | 64 | 99% |
| Oxaliplatin | Eloxatin | 110 | mg/m2 | IV | 2h | 4.96 | 1970 | 4990 | - | 1.86 | >90% |
| Paclitaxel | Taxol | 175 | mg/m2 | IV | 3h | 4.27 | 3650 | 15007 | - | 20.2 | 89–98% |
| Palbociclib | Ibrance | 125 | mg | PO | - | 0.101 | 45 | 1427 | 6.0 | 22.2 | 85% |
| Pamidronate | Aredia | 90 | mg | IV | 4h | 11.1 | 2610 | 17120 | 4.0 | - | - |
| Panobinostat | Farydak | 20 | mg | PO | - | 0.082 | 29 | 280 | 1.0 | 15.5 | 90% |
| Pazopanib | Votrient | 800 | mg | PO | - | 133 | 58100 | 1037000 | 2–4 | 30.9 | >99% |
| Pemetrexed | Alimta | 500 | mg/m2 | IV | 10 min | 306 | 131000 | 188000 | - | 4.4 | 81% |
| Pentostatin | Nipent | 4 | mg/m2 | IV | 15 min | 1.82 | 489 | 1232 | - | 5.3 | 4% |
| Plerixafor | Mozobil | 0.24 | mg/kg | SC | - | 1.84 | 926 | 4741 | 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 | 1253 | - | 24 | >99% |
| Porfimer | Photofrin | 2 | mg/kg | IV | 3–5 min | 33.9 | 40000 | 2400000 | - | 415 | 90% |
| Pralatrexate | Folotyn | 40 | mg/m2 | IV | 5 min | 10.3 | 4900 | 4900 | - | 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 | 272 (nb•hr/ml)/(mg/kg) | - | 27.7 | 95% |
| Regorafenib | Stivarga | 160 | mg | PO | - | 8.08 | 3900 | 58300 | 4.0 | 28 | 99.5% |
| Romidepsin | Istodax | 14 | mg/m2 | IV | 4h | 0.697 | 377 | 1549 | - | 3 | 92–94% |
| Rucaparib | Rubraca | 600 | mg | PO | - | 6.000 | 1940 | 16900 | 1.9 | 17 | 70% |

| Generic Name | Brand Name | Dose | Dose Unit | Route | infusion | Cmax (uM) | Cmax (ng/ml) | AUC (ng•hr/ml) | Tmax (hr) | $T_{1/2}$ (hr) | Protein binding |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ruxolitinib | Jakafi | 25 | mg | PO | - | 1.09 | 335 | 979 | 0.63 | 2.3 | 97% |
| Sonidegib | Odomzo | 200 | mg | PO | - | 2.12 | 1030 | 22000 | 2–4 | 672 | >97% |
| Sorafenib | Nexavar | 400 | mg | PO | - | 20.1 | 9350 | 107000 | 2.5 | 23.8 | 99.5% |
| Streptozocin | Zanosar | 1500 | mg/m2 | IV | push | 1438 | 381400 | 72150 | - | 0.22 | - |
| Sunitinib Malate | Sutent | 50 | mg | PO | - | 0.181 | 72 | 1296 | 8.5 | 41–86 | 95% |
| Tamoxifen Citrate | Nolvadex | 20 | mg | PO | - | 0.108 | 40 | - | 5.0 | 120–168 | >99% |
| Tegafur | Utefos | 50 | mg/m2 | PO | - | 19.0 | 3803 | 26480 | 1.0 | 7.88 | - |
| Temsirolimus | Torisel | 25 | mg | IV | 0–60 min | 0.568 | 585 | 1627 | - | 17 | 87% |
| Teniposide | Vumon | 300–750 | mg/m2 | IV | 72 h | 23.1 | 15200 | - | - | - | >99% |
| Thalidomide | Thalomid | 200 | mg | PO | - | 8.91 | 2300 | 23300 | 5.8 | 4.12 | 55% (+)-(R); 66% |
| Thiolguanine | Tabloid | 40 | mg/m2 | PO | - | 0.313 | 52 | 0.0979 | 1.5 | - | - |
| Topotecan | Hycamtin | 2.3 | mg/m2 | PO | - | 0.015 | 6.3 | 22.7 | | 3.49 | 35% |
| Toremifene | Fareston | 120 | mg | PO | - | 4.56 | 1850 | 115100 | 2.9 | 56.5 | >99.5% |
| Trabectedin | Yondelis | 1.5 | mg/m2 | 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/m2 | 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 Ciste | - | 0.011 | 8 | 56.4 | 2–6 | - | >99% |
| Vandetanib | Caprelsa | 300 | mg | PO | - | 2.16 | 1025 | 20460 | 5 | 456 | 90% |
| Vemurafenib | Zelboraf | 960 | mg | PO | - | 127 | 62000 | 601000 | 3.0 | 57 | >99% |
| Venetoclax | Venclexta | 400 | mg | PO | - | 4.48 | 21000 | 32800 | 5–8 | 26 | >99% |
| Vinblastine | Velban | 1** | mg/m2 | IV | bolus | 0.035 | 28 | 45 | 0.12 | 26.20 | 98–99% |
| Vincristine | Vincasar PFS | 1 | mg/m2 | IV | bolus | 0.007 | 5.4 | - | - | - | 75% |
| Vincristine (liposomal) | Marqibo | 2.25 | mg/m2 | IV | 60 min | 1.479 | 1220 | 14566 | - | 7.66 | 75% |
| Vinorelbine | Navelbine | 25 | mg/m2 | IV | 20 min | 0.811 | 632 | 585 | - | 21.40 | 89% |
| Vismodegib | Erivedge | 150 | mg | PO | - | 33.9 | 14282 | 2283446 | - | 96 | >99% |
| Vorinostat | Zolinza | 400 | mg | PO | - | 1.20 | 317 | 1110 | 1.5 | 2 | 71% |
| Zoledronic Acid | Zometa | 4 | mg | IV | 15 min | 0.971 | 264 | 420 | - | 146 | 33–40% |

Abbreviations: $C_{max}$: maximum plasma concentration; AUC: Area Under the time-plasma Concentration curve; : $T_{max}$: Time post-dose of maximum plasma concentration; : $T_{1/2}$: Plasma half-life

**Table 2**

Key human pharmacokinetic parameters for small-molecule pro-drugs and their *active metabolites approved for oncology indications

| Generic Name | Brand Name | Dose | Dose Unit | Route | infusion | Cmax (uM) | Cmax (ng/ml) | AUC (ng•hr/ml) | Tmax (hr) | $T_{1/2}$ (hr) | Protein binding |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Abiraterone Acetate | Zytiga | 1000 | mg | PO | - | BLOQ | BLOQ | - | - | - | - |
| *Abiraterone | (Zytiga) | as above | | PO | - | 0.647 | 226 | 1173 | - | 12 | >99% |
| Estramustine phosphate | Emcyt | 2000 | mg/m2 | IV | 60min | 797 | 414700 | 889884 | - | 2.5 | - |
| * estramustine | (Emcyt) | as above | | IV | - | 10.4 | 4420 | 37605 | - | 99 | - |
| * estramustrone | (Emcyt) | as above | | IV | - | 15.6 | 6620 | 211351 | - | 129 | - |
| Floxuridine | FUDR | 30 | mg/kg | IV | 8h | 1.05 | 259 | 1365 | - | 0.22 | - |
| * 5-FU | (FUDR) | as above | | | - | 0.88 | 115 | - | - | - | - |
| Fludarabine Phosphate | Fludara | 25 | mg/m2 | IV | 30min | BLOQ | BLOQ | - | - | - | 19–29% |
| * 2-F-araA | (Fludara) | as above | | IV | - | 3.00 | 808 | 3285 | - | 11.3 | - |
| Irinotecan | Camptosar | 340 | mg/m2 | IV | 90min | 5.78 | 3392 | 20604 | - | 11.7 | 30–68% |
| * SN-38 | (Camptosar) | as above | | IV | - | 0.143 | 56 | 474 | - | 21 | 95% |
| Irinotecan (liposomal) | Onivyde | 70 | mg/m2 | IV | 90min | 63.4 | 37200 | 1364000 | - | 25.8 | <0.44% |
| * SN-38 (liposomal) | (Onivyde) | as above | | IV | - | 0.014 | 5.4 | 620 | - | 67.8 | 95% |
| Lomustine (CCNU) | Gleostine | 130 | mg/m2 | PO | - | BLOQ | BLOQ | - | - | - | 50% |
| * cis+trans 4-OH-CCNU | (Gleostine) | as above | | PO | - | 3.39 | 847 | 3400 | 2–4 | 1.8 | - |
| Nelarabine | Arranon | 1500 | mg/m2 | IV | 2h | 16.8 | 5000 | 4400 | - | 0.3 | <25% |
| * ara-G | (Arranon) | as above | | IV | - | 111 | 31400 | 162000 | - | 3.2 | <25% |
| Temozolomide | Temodar | 150 | mg/m2 | IV | 90min | 37.6 | 7300 | 24600 | 1.0 | 1.8 | 15% |
| *MTIC | (Temodar) | as above | | IV | - | 1.64 | 276 | 891 | - | - | - |
| Testosterone enanthate | Delatestryl | 200 | mg | IM | - | n.d. | n.d. | - | - | - | - |
| * Testosterone | (Delatestryl) | as above | | IM | - | 0.051 | 15 | - | 55 | - | 98% |
| Thiotepa | Thioplex | 80 | mg | IV | push | 9.66 | 1828 | 4127 | - | 2.3 | 10% |
| *TEPA | (Thioplex) | as above | | IV | - | 2.04 | 353 | 7452 | - | 15.7 | - |

Abbreviations: $C_{max}$: maximum plasma concentration; AUC: Area Under the time-plasma Concentration curve; : $T_{max}$: Time post-dose of maximum plasma concentration; : $T_{1/2}$: Plasma half-life

**Table 3**

Key human pharmacokinetic parameters for biological drugs approved for oncology indications

| Generic Name | Brand Name | Dose | Dose Unit | Route | infusion | Cmax (uM) | AUC (ug•hr/ml) | Tmax | T1/2 (Days) |
|---|---|---|---|---|---|---|---|---|---|
| Ado-trastuzumab-emtansine | Kadcyla | 3.6 | mg/kg | IV | 90-min | 0.572 | 19.8 | end-of-infusio | 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 |
| Atezolizumab- | Tecentriq | 1200 | mg | IV | 60-min | 2.79000 | - | - | 27 |
| Asparaginase-(E.-coli) | Elspar | 5000 | U/m2 | IV | 30-min | 0.51684 | 307 | - | 0.771 |
| Asparaginase-(Erwinia-chrysanthemi) | Erwinaze | 30,000 | IU/m2 | IV | 3-h | 20-IU/ml | - | - | 0.267 |
| Bevacizumab | Avastin- | 10 | mg/kg | IV | 30-min | 1.90604 | - | - | 21 |
| Blinatumomab | Blincyto | 28 | ug | 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 | |
| Cetuximab | Erbitux- | 400 | mg/m2 | IV | 2-h | 1.40622 | 19000 | 3-h | 3.13 |
| Daratumumab | Darzalex | 16 | mg/kg | IV | 6.5-h | 6.18243 | - | - | 18 |
| Denileukin-Diftitox | Ontak | 19 | ug/kg | IV | 60-min | 1309-U/ml | 33482-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/m2 | IV | 10-20-h | 0.07667 | - | - | 10 |
| Elotuzumab- | Empliciti | 10 | mg/kg | IV | 15-60-min | 2.27819 | 40701 | 4.1-h | 0.197 |
| Filgrastim | Neupogen | 5 | ug/kg | IV | 15-30-min | 0.01004 | 0.638 | - | 0.463 |
| Gemtuzumab-Ozogamicin | Mylotarg- | 9 | mg/m2 | IV | 2-h | 0.01869 | 123 | - | 3.02 |
| free-calichaemicin | (Mylotarg) | - | - | - | - | 0.00365 | 0.22 | - | 4.21 |
| Interferon-alfa-2b | Intron-A | $20\times10^6$ | IU | IV | 20-min | 0.00031 | 0.00950 | - | - |
| Ipilimumab | Yervoy- | 3 | mg/kg | IV | 90-min | 0.54730 | - | - | - |
| Necitumumab | Portrazza | 800 | mg | IV | 60min | 3.51519 | 67821 | - | 5.21 |
| Nivolumab | Opdivo | 3 | mg/kg | IV | 60 min | 0.41034 | 15813 | 3.1 h | 17 |
| Obinutuzumab | Gazyva | 1000 | mg | IV | see label | 3.75770 | 366 | - | 28.4 |
| Ofatumumab | Arzerra | 2000 | mg | IV | see label | 10.14374 | 674463 | - | 15.8 |

| Generic Name | Brand Name | Dose | Dose Unit | Route | infusion | Cmax (uM) | AUC (ug•hr/ml) | Tmax | T1/2 (Days) |
|---|---|---|---|---|---|---|---|---|---|
| Olaratumab | Lartruvo | 15 | mg/kg | IV | 60 min | 3.09700 | 42400 | 2.53 h | 7.21 |
| Oprelvekin | Neumega | 50 | ug/kg | SC | - | 0.00100 | 0.242 | 2.7 h | 0.3375 |
| Palifermin | Kepivance | 90 | ug/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 | 2500 | IU/m2 | IV | 1–2 hr | 0.35740 | - | - | 7 |
| Pegfilgrastim | Neulasta | 100 | ug/kg | SC | - | 0.00587 | 29.3 | 48 h | 0.883 |
| Peginterferon alfa-2b | PEG-lntron | 6 | ug/kg | SC | - | 0.00014 | 0.43 | - | 2.125 |
| Pembrolizumab | Keytruda | 2 | mg/kg | IV | 30 min | 0.44090 | 58.7 | 0.17d | 26 |
| Pertuzumab | Perjeta | 420 | mg | IV | 30–60 min | 1.01351 | 2762 | - | 19.1 |
| Ramucirumab | Cyramza | 8 | mg/kg | IV | 60 min | 1.16327 | 18300 | - | 7.54 |
| Rasburicase | Elitek | 0.2 | mg/kg | IV | 30 min | 0.11375 | 45.2 | - | 0.879 |
| Rituximab | Rituxan | 375 | mg/m2 | IV | see label | 3.22397 | - | - | - |
| Romiplostim | Nplate | 1 | ug/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: $C_{max}$: maximum plasma concentration; AUC: Area Under the time-plasma Concentration curve; : $T_{max}$: Time post-dose of maximum plasma concentration; : $T_{1/2}$: Plasma half-life

**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 | Cmax (uM) | Cmax (ng/ml) | AUC (ng•hr/ml) | Tmax (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 | 5900 | - | 1.5 | 12.5 | 21–25% |
| Celecoxib | Celebrex | 400 | mg | PO | - | 4.60 | 1752 | 13049 | - | 8.8 | 97% |
| Chloroquine | Aralen | 750 | mg | PO | - | 0.725 | 232 | 8385 | 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 | 2318 | 12 | - | 70% |
| Hydroxychloroquine | Plaquenil | 200 | mg | PO | - | 0.35000 | 117.4 | 12015 | 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 | 1500 | mg | PO | - | 24.0 | 3100 | 18400 | 1.5 | 5.98 | negligible |
| Quinacrine | Acrichine | 100 | mg | PO | - | 0.300 | 120 | - | - | - | 80–90% |
| Sildenafil | Viagra | 100 | mg | PO | - | 0.794 | 377 | 1295 | 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: $C_{max}$: maximum plasma concentration; AUC: Area Under the time-plasma Concentration curve; : $T_{max}$: Time post-dose of maximum plasma concentration; : $T_{1/2}$: Plasma half-life