

# ISSUE BRIEF

Conference on Clinical  
Cancer Research  
November 2013

## Optimizing Dosing of Oncology Drugs

*Richard L. Schilsky*, Chief Medical Officer, American Society of Clinical Oncology

*Oliver Rosen*, Vice President and Head of Global Medical Affairs,

Millennium: The Takeda Oncology Company

*Lori Minasian*, Deputy Director, Division of Cancer Prevention, National Cancer Institute

*Daniel Auclair*, Research Director, Multiple Myeloma Research Foundation

*Atiqur Rahman*, Director, Division of Clinical Pharmacology V, FDA

*Richard Pazdur*, Director, Office of Hematology and Oncology Products, FDA

### Summary

Drug development in oncology presents several challenges unique to this therapeutic area. The purpose of this article is to acknowledge the challenges of optimizing the dosing of oncology drugs and to describe different potential approaches to address these challenges in order to improve dosing and administration guidance for health care professionals. We hope that these approaches will create better opportunities for continued learning during the development of investigational new drugs as it relates to biopharmaceutical properties, the drug target and other sources of variability of drug exposure.

### Introduction

Balancing the benefits and risks of cancer therapies is critical in order to provide longer survival while maintaining or improving quality of life. A key to achieving this balance is identifying the dose at which efficacy is maximized and toxicity is minimized; a dose that is too high can render an otherwise effective drug intolerable, while a dose that is too low can result in the expected therapeutic benefit of a drug not being achieved. Due to the life-threatening nature of cancer, a high degree of drug toxicity is generally considered acceptable, and the need to develop new drugs quickly often takes precedence over the need to find the “right” dose, which, even when defined, is only an estimate for a certain patient population. For any drug dose, a range of beneficial and toxic effects can be anticipated that will vary based on the unique characteristics of each patient receiving the agent. An evaluation of recently approved oncology drugs demonstrates that many of these agents are labeled for use at doses that may be either too high or too low (Table 1), at least for some patients, indicating that our current approach toward dose selection needs improvement. In order for patients to fully benefit from the great strides being made in the fight against cancer, it is important that we devise a comprehensive strategy for drug development that includes dose optimization but does not unnecessarily delay market entry for potentially important new drugs.

In the current oncology paradigm, trials are designed to maximize the chance of obtaining an efficacy signal, and are often performed in advanced disease settings. The objective of phase 1 trials is to determine the highest tolerable dose, based on the *assumption* that higher doses will provide greater efficacy. In these trials, increasing doses of a drug are sequentially evaluated in small cohorts of patients until a pre-specified rate of dose-limiting toxicity (DLT) is reached (1). The dose immediately below that which elicited DLT is considered the maximum-tolerated dose (MTD) and, in most cases, is then used for

phase 2 and subsequent phase 3 trials, which are used to evaluate drug activity and efficacy. It is rare for phase 2 or 3 studies of oncology drugs to evaluate more than one dose, although this approach is common in other therapeutic areas. This paradigm has several limitations. One is that it does not adequately evaluate inter-patient variability in treatment response and toxicity: some patients may require a higher dose to achieve clinical benefit, while other patients may find the “maximum-tolerated” dose to be intolerable. Put in other terms, dose- or exposure-response relationships are rarely well defined for oncology drugs despite their often narrow therapeutic index. The lack of such information often leads to a high rate of dose reductions in cancer clinical trials as well as failure to identify patients who may benefit from a higher dose (leading to a higher exposure). This approach was designed to maximize the dosing of cytotoxic chemotherapy; however, some agents, such as hormonal or targeted therapies, may achieve maximum efficacy at a dose below the MTD. For these agents, the “optimal biologic dose” might be that which results in saturation of a target receptor (2). Pharmacodynamic (PD) endpoints that assess target inhibition may be more relevant for these agents, assuming the drug target is well understood and practical to measure. Finally, the classical oncology drug development program used for cytotoxics does not adequately evaluate long-term cumulative toxicities or changes in tolerability over time. This limitation is especially important as treatments have become more effective and patients stay on therapy far longer than has historically been the case in cancer care. This is further complicated by the fact that decisions around dosing and tolerability are often made in the heavily pre-treated phase 1 population, which typically has a limited life expectancy and risk tolerance compared to the phase 3 or intended use population which may have a very different tolerance for acute and chronic toxicity.

To address these issues, we propose an approach to dose determination for oncology drugs that seeks to optimize dose selection as well as enable a more complete understanding of the relationship between drug exposure and clinical outcomes. Many of the elements of this approach are already included in current oncology drug development; however, a key component of this approach, outlined below, is performance of randomized dose comparison studies, which is not typically done in oncology. We will discuss how this information can be used to improve drug development, inform drug labels and aid in clinical practice, as well as the feasibility of this approach.

### **Proposed Path for Study**

1. Phase 1 trials should include adequate PK sampling to enable a clear determination of the PK properties of the drug and preliminary characterization of dose-exposure relationships. When feasible and appropriate, PD endpoints should be incorporated to determine the drug exposure that results in inhibition of the drug target.
2. Phase 2 trials should go beyond assessment of drug activity and could include adaptive designs and/or randomized exploration of doses. Continued, sparse PK sampling should be included to gain a sense of relationships between exposure and clinical outcomes. If possible, measurements of PD endpoints should be continued.
3. Phase 3 trials should incorporate population PK sampling in order to further evaluate the relationship between covariates influencing exposure and key clinical outcomes.
4. When subjective toxicities are identified in phase 1 trials, patient-reported outcomes (PROs) should be assessed using validated tools if available in phase 2 and phase 3 trials and could be used to guide dose optimization.
5. The PK and PRO dataset collected in phases 1-3 could be used to develop an approach to therapeutic drug monitoring in the post-market setting. This will enable the dose for an individual patient to be adjusted as needed based on observed drug exposure, treatment tolerance and clinical status.

## **What are the needed data elements?**

### ***Exposure data***

The label of an approved drug reflects the dose studied in a defined patient population in clinical trials and the average response of those patients. However, there are many factors that affect the amount of drug that a patient is exposed to, and consequently affect individual patient response. For example, the absorption of some oral drugs may be increased or decreased by taking them with food (3). Drug metabolism is impacted by genetic polymorphisms in drug transporters or drug-metabolizing enzymes (4). Other factors that can affect drug metabolism and/or clearance include, but are not limited to, use of concomitant medications, age, body weight, hepatic and renal function, or the presence of comorbidities. The collection of pharmacokinetic data enables an understanding of the actual drug exposure of each patient in the trial. These data may include plasma peak ( $C_{max}$ ) and trough ( $C_{min}$ ) drug concentrations, which represent the highest and lowest concentrations reached between drug administrations, respectively. Another exposure parameter is the area under the plasma concentration versus time curve (AUC), which represents the overall amount of a drug in the bloodstream over time. The correlation of exposure data with toxicity data and clinical outcomes can improve dose selection for registration trials as well as guide clinical use following approval (5).

The collection of pharmacokinetic and exposure data in oncology phase 2 and 3 clinical trials has increased in recent years. These data can be used to estimate a therapeutic index for a defined patient population. FDA reviewers and drug developers can then perform exposure-safety and exposure-response analyses to assess the contribution of variable drug exposure to the benefit-risk assessment of the drug. The results of these analyses may be used by FDA to determine the need for specific post-marketing studies. Several examples are presented in Table 1. In the case of cabozantinib, which was recently approved for treatment of metastatic medullary thyroid cancer, a high rate of dose modifications due to adverse events was observed in the phase 3 registration trial. Exposure-response analyses indicated that these dose modifications were associated with higher exposures and suggested that lower doses may improve tolerability while maintaining efficacy. This hypothesis is being tested in a randomized dose-comparison trial. In contrast, higher exposures of ado-trastuzumab emtansine, which was recently approved for treatment of HER2+ metastatic breast cancer, were associated with improved efficacy without altering the safety profile of the product. Exposure-response analysis of the ongoing phase 3 trials will be performed to determine whether a post-marketing dose optimization trial is needed. These examples and others in Table 1 illustrate that dose-selection for registration trials is often suboptimal due to insufficient understanding of exposure-response relationships. We propose that randomized dose comparison studies should be included in phase 2 studies and exposure-response analyses should be performed to better inform the selection of dose for phase 3 registration trials.

### ***Patient-Reported Outcomes***

To assess the benefit-risk balance of a new drug, both efficacy and safety must be measured. Toxicities in cancer clinical trials are currently reported and graded by clinicians using the NCI Common Terminology Criteria for Adverse Events (CTCAE), a comprehensive list of adverse events that are common in oncology (6). Although this tool has proven invaluable as a standardized framework for the evaluation of cancer treatment toxicities, research has shown that patient symptoms are systematically under-reported by clinicians (7, 8). In some cases, early patient reports of mild-moderate symptoms have heralded poor long term treatment tolerability or an increased risk of severe adverse events (9). As symptomatic

toxicities have a significant impact on adherence and are a major contributor to treatment discontinuation, it is apparent that patient-reported outcomes (PROs) should also be collected in order to more fully understand the patient experience with a drug. PROs can be informative not only of the side-effects of a drug, but also of any beneficial effects a drug may have on symptoms of the cancer itself.

Although the development of validated PROs for use as endpoints in clinical trials has been hampered in the past by methodological challenges, recent examples show that these challenges can be overcome. The development of ruxolitinib for myelofibrosis utilized a composite PRO measure consisting of six symptoms relevant to that disease, and this PRO served as a key secondary endpoint that, together with the primary endpoint of reduction in spleen volume, ultimately supported approval of ruxolitinib in 2011 (10). In 2012, abiraterone acetate was approved for first-line treatment of metastatic castration-resistant prostate cancer based on the co-primary endpoints of time-to-cytotoxic chemotherapy and time-to-opiate use (11). These examples demonstrate that by identifying symptoms relevant to the course of disease, recruiting the right patient populations into clinical trials, and working closely with the FDA throughout development, PROs can be successfully developed and used to support drug approval and labeling (12). In the future, validated PRO tools may be available and useful for dose optimization. One ongoing initiative is the development of the PRO-CTCAE, a new version of the CTCAE that integrates PROs as well as clinician reports of toxicities into these criteria (13). This is a multi-stakeholder initiative involving clinical researchers from several cancer centers, experts from NCI and FDA, and patient advocates. Through Material Transfer Agreements with partners in both academia and industry, different clinical trial scenarios are being explored that incorporate real-time reporting by patients, integration of that information with clinician grading of toxicity, and analysis of the data in a manner that is used to assess the overall treatment effect. This next phase of its development is intended to evaluate the utility of real time patient reporting of side effects and identify the optimal settings and strategies to apply such reporting. We propose that validated PRO tools be used when medically appropriate and feasible to describe tolerable doses for drugs with symptomatic toxicities.

### **How can these data elements be integrated to improve clinical outcomes?**

Performing dose comparison studies in phase 2 trials could greatly improve the design of phase 3 trials by better informing selection of the dose to be studied in those trials. It could also better enable identification of drugs for which it might be appropriate to prospectively define dose escalation or reduction strategies in phase 3 trials. For example, dose comparison trials might indicate that while anti-tumor responses can be achieved at multiple doses, there is a significant portion of patients that do not respond to the lower dose or do not tolerate the highest dose. Adaptive clinical trial protocols that include provisions for increasing or decreasing the dose under certain conditions (e.g., patient has not responded to initial dose but can tolerate higher doses; patient is responding to the drug but has experienced severe side effects) may enable labeling claims that describe appropriate dose modification strategies, and indeed this has been done for several oncology drugs (Table 2).

For most oncology drugs, however, the label will provide only a starting dose that may need to be modified for each patient based on clinical observation. In the proposed approach, the collection of exposure data and data regarding tolerability across a range of doses could enable the definition of a threshold exposure needed for anti-tumor effect as well as the determination of a peak exposure that correlates with excess toxicity. This could enable therapeutic drug monitoring in clinical practice to ensure that patients are receiving optimal exposure and to make dose adjustments as needed. Drug

monitoring may be most valuable in the setting of chronic treatment. Targeted therapies are often intended to be taken chronically and the tolerability of these agents may be reduced over time. While classical cytotoxic treatments are characterized by acute toxicities that are usually identified shortly after treatment initiation, targeted agents have been characterized by more subjective, cumulative toxicities with later onset (14). Changes in patients' physiology or drug pharmacokinetics over time may also lead to reduced tolerability. For an example of how this approach might change clinical behavior, assume a scenario in which a patient has been on a targeted drug for several months with low-grade toxicity. Eventually the patient reaches a point where the treatment is no longer tolerable, and this could trigger a check of the plasma concentration of the drug. One possibility is that the concentration has increased into a toxic range, perhaps because of some change in how the patient takes the drug or the addition of another drug for an unrelated medical problem that interferes with the clearance of the oncology drug product. This might prompt a dose modification to bring the drug level back into the non-toxic range, enabling the patient to continue taking an effective drug that otherwise might have been discontinued.

Collection of drug exposure and tolerability data, as well as ongoing evaluation of adverse events and dose modifications, from patients in real-world settings may be useful for post-market evidence generation. Such efforts may help aligning regulatory needs with the evolving needs for Health Technology Assessment and will become increasingly possible with the proliferation of routinely collected electronic clinical data. FDA's Sentinel Initiative, for example, is actively demonstrating the value of harnessing electronic health data from claims, hospital administrative records, and electronic health records (EHRs) to monitor the safety of drugs. Sentinel uses a distributed data approach that allows large health insurance plans, hospitals and other data partners to leverage the robust clinical information that they routinely gather without compromising on patient privacy. Tools like the American Society for Oncology's CancerLinQ and independent registries for the collection of clinical data will also help to expand the breadth and depth of real-world data available for continued study of oncology products. Further, the Reagan-Udall Foundation for the FDA's efforts to bolster best practices and methods for post-market evidence generation and analysis through programs such as its Innovation in Medical Evidence Development and Surveillance (IMEDS) will help to ensure an effective, efficient process for gaining real insights from a proliferation of data sources. Taken together, these efforts will contribute to a robust, interconnected data infrastructure that could be used to generate hypotheses regarding whether specific patient characteristics impact drug clearance, exposure, and response. This, in turn, could feed back into clinical decision making based on the characteristics of individual patients.

### **What is the optimal timing of dose comparison studies?**

Ideally, randomized dose comparison studies and exposure-response analyses would be performed in the premarket setting. Such studies could potentially improve the chance of approval success by minimizing the chance that excessive toxicity will be observed because the dose studied is too high, or that inadequate efficacy will be observed because the dose studied is too low. However, performing dose comparison studies in the premarket setting poses significant challenges in that it may slow the development of new cancer drugs or be excessively burdensome when there is uncertainty as to whether a drug will ultimately be approved. It may also be difficult to clearly assess pharmacodynamic endpoints if the drug target is not well understood. While post-marketing trials are being pursued for many recently approved drugs to refine the recommended dose, post-marketing trials also pose significant challenges: patients may not want to participate in a trial of a drug already on the market, drug sponsors may have to perform such trials outside of the US where drug access is more limited, and the FDA has limited enforcement ability to

ensure that these trials are performed in a timely manner. Thus, post-marketing commitments often cannot be met and are rarely completed within the desired timeframe (15-17).

One possible solution to this dilemma may be for sponsors to conduct dose comparison studies in the period of time after the completion of registration-directed trials but prior to marketing approval. This time period presents a window of opportunity. When a new agent has shown significant promise in the registration trial, patients understandably desire access as soon as possible. However, during the FDA review period, drug access is usually not available to patients either through trial participation or the market. A pre-approval window of opportunity protocol examining two different doses of a drug that has already been shown to have activity and is otherwise unavailable would likely accrue patients quickly, particularly when there is no placebo or standard of care control arm and patients can be assured that they will receive the investigational agent. Performing dose comparison studies in this time frame may also be more appealing to drug developers, because there is more confidence that the drug will eventually reach the market as an application for marketing approval is already under review. The primary objective of a dose comparison study at this stage would be to determine whether a lower dose of the agent results in a decrement in an early efficacy endpoint such as response rate, and only minimal data collection would be required. Careful planning and coordinated discussion with the FDA would be essential to ensure that data collected in such a trial could ultimately inform the drug label. We believe that this proposal is in the interest of all stakeholders: drug companies may be able to improve the competitiveness of a drug or extend the length of time that patients can take a drug by identifying more tolerable regimens or dose modification schemes, regulatory authorities will have more information to guide review decisions, clinicians will have more information to guide treatment decisions, and patients will benefit from effective and better tolerated drugs.

**Table 1: Recently Approved Products Evaluating Alternate Doses in Post-marketing Trials**

<b>Products</b>	<b>Approval Date</b>	<b>PMR/PMC*</b>
<p><b>Omacetaxine (Synribo):</b> CML</p> <p>Dose: 1.25 mg/m<sup>2</sup></p>	10/26/2012	<p>Observation: Clearance of Omacetaxine is not related with BSA. Lower body weight patients may be under dosed. Response rates were lower in females compared to males.</p> <p>PMR Trial: Conduct a Phase 1/2 single arm clinical trial to investigate the pharmacokinetic, safety, and preliminary efficacy of omacetaxine following fixed dose administration in patients with chronic phase (CP) or accelerated phase (AP) chronic myeloid leukemia (CML) who has failed two or more TKI therapies. In Cycle 1 evaluate the PK and safety of omacetaxine following a fixed dose administration. Continue treatment, if tolerated, using a fixed dose as long as patients are clinically benefiting from therapy.</p> <p>Observation: Dosing for patients with renal and hepatic impairment is not determined during drug development.</p> <p>PMR Trial: Conduct a mass balance trial in humans to determine the disposition and elimination pathways as well as to characterize the major metabolites of omacetaxine following subcutaneous injection. Depending on the results, hepatic and/or renal impairment trials may be required.</p>
<p><b>Ponatinib (Iclusig):</b> CML</p> <p>Dose: 45 mg</p>	12/14/2012	<p>Observation: Lower dose may be as effective and less toxic. 75% of the patients had their dose reduced in the pivotal trial due to adverse events. 49% required dose reduction to 30 mg from 45 mg and 25% required dose reduction to 15 mg.</p> <p>PMR Trial: Collect sparse PK from ponatinib treated patients in the ongoing trial AP24534-12-301 to characterize exposure-response for Iclusig™ (ponatinib). The exposure-response analysis should be conducted for both efficacy and safety endpoints. Based on the results of these analyses, a trial to evaluate lower dose or an alternate dosing regimen of ponatinib may be necessary.</p>
<p><b>Vandetanib (Caprelsa):</b> Medullary Thyroid Cancer</p> <p>Dose: 300 mg</p>	04/06/2011	<p>Observation: Patients in the highest quartile of exposure had worst PFS among the four quartiles. Dose reduction to 200 mg or 100 mg before or on Day 84 showed comparable PFS with dose of 300 mg. Diarrhea and fatigue (grade 2 or higher) were significantly associated with steady state Day 56 plasma concentration.</p> <p>PMR Trial: Conduct a randomized dose-finding trial in which patients with progressive or symptomatic medullary thyroid cancer will be randomized to vandetanib 300 mg or 150 mg daily. The trial will include analyses of the safety and activity of the 150 mg dose of vandetanib. Safety assessments will include evaluations of vortex keratopathy and corneal stromal changes, with ophthalmology examination every 6 months with corneal photographs of abnormalities. Safety assessments will also include evaluation of heart failure using serial echocardiograms in all patients. A primary endpoint will include overall response rate.</p>

<p><b>Trastuzumab (Herceptin):</b> Breast cancer, Gastric cancer</p> <p>Dose: Initial 8mg/kg Maintenance 6 mg/kg every 3 weeks</p>	<p>09/25/1998</p>	<p>Observation: Low Herceptin trough concentrations that may have resulted in decreased overall survival in 25% of patients treated for gastric cancer.</p> <p>PMR Trial: To evaluate the safety and tolerability of an alternate Herceptin (trastuzumab) dosing regimen that ensures that all patients, inclusive of patients with a Herceptin C<sub>min</sub> of <math>\leq 12</math> mcg/mL on Cycle 1 Day 21 after an initial dose of 8 mg/kg, achieve adequate exposure as reflected by C<sub>min</sub> of at least 12 mcg/mL by Cycle 2 Day 21, and maintain the exposure level throughout the treatment period. This may be achieved either through a specified regimen applied to all patients or through an individualized, pharmacokinetically guided treatment strategy. The pharmacokinetics and tolerability of the alternate Herceptin (trastuzumab) dosing regimen in patients with HER2-overexpressing, metastatic gastric cancer will be determined in a pharmacokinetic trial that enrolls an adequate number of patients to provide an initial assessment of safety.</p>
<p><b>Cabozantinib (Cometriq):</b> Medullary Thyroid Cancer</p> <p>Dose: 140 mg</p>	<p>11/12/2012</p>	<p>Observation: A high proportion (86.4%) of patients in the cabozantinib arm experienced at least one dose modification (e.g., dose interruption, dose reduction, and dose discontinuation) due to adverse events. Exposure-response analyses for efficacy indicated that lower dose intensity may not be associated with reduction of PFS; further exposure-response analyses indicated that early dose modifications due to adverse events are associated with higher exposures, indicating that a lower dose might be effective with improved tolerability.</p> <p>PMR Trial: A randomized dose-comparison trial in patients with progressive metastatic medullary thyroid cancer comparing the safety and activity of oral cabozantinib 140 mg daily to a biologically active and potentially safer lower daily cabozantinib dose. The trial will be designed to test non-inferiority of the lower dose to the approved dose for effect on progression-free survival effect and to assess the comparative safety of the two doses.</p> <p>PMR Trial: A clinical trial designed according to “FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function—Study Design, Data Analysis and Impact on Dosing and Labeling”. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant pharmacokinetic parameters for cabozantinib. A data analysis plan must be included in the protocol. The number of patients enrolled in each of the hepatic function cohorts should be sufficient to reliably detect exposure differences. The trial results should allow for a determination on dosage adjustment recommendations in the label.</p>



<p><b>Radium RA-223 (Xofigo):</b> Castration-resistant prostate cancer</p> <p>Dose: 50 kBq/kg</p>	<p>5/15/2013</p>	<p>Observation: Exploratory analyses suggested that proposed dosing regimen may not be optimal. In the pivotal trial BC1-06, the separation of OS Kaplan-Meier curves stratified by body weight quartiles suggested that higher body weight (i.e., higher dose) may be correlated with better overall survival in the Xofigo arm but not in the placebo control arm. As this was an un-planned, un-stratified analysis and patient numbers in the different weight categories were relatively small, the results have to be interpreted with caution. The incidence of Grade 3 or worse (Grade 3+) adverse events (AEs) is similar across body weight range, with slightly lower incidence of Grade 3+ AEs in Xofigo arm. Furthermore, a trend was observed for ideal body weight (IBW)-normalized dose with a lower OS hazard ratio in the lowest quartile and relatively similar hazard ratios in quartiles 2-4.</p> <p>PMR Trial: Optimize the dosing regimen of Xofigo by conducting a randomized Phase 2 clinical trial to evaluate the efficacy and safety of Xofigo at a dose higher than 50 kBq/kg in patients with castration-resistant prostate cancer with bone metastases. Depending on the results of the Phase 2 trial, a randomized Phase 3 trial may be needed to further confirm the appropriateness of the dosing regimen determined in the Phase 2 trial.</p>
<p><b>Ado-trastuzumab emtansine (Kadcyla):</b> Breast Cancer</p> <p>Dose: 3.6 mg/kg</p>	<p>2/22/2013</p>	<p>Observation: After accounting for baseline risk factors, the exposure-response analysis demonstrated that increases in T-DM1 exposures are related with better efficacy (OS, PFS, and objective response rate (ORR)).</p> <p>PMC Trial: Conduct ado-trastuzumab emtansine exposure-response analyses for progression-free survival, final overall survival, and safety utilizing data from trial BO25734/TDM4997 (TH3RESA). The result of the exposure-response analyses from both TH3RESA and BO21977/TDM4370g (EMILIA) will be used to determine whether a postmarketing trial is needed to optimize the dose in patients with metastatic breast cancer who have lower exposure to ado-trastuzumab emtansine conjugate at the approved dose (3.6 mg/kg q3w). Submit a final report of the exposure-response analyses based on TH3RESA and EMILIA.</p>

\*PMC- Post-marketing commitment, PMR- Post-marketing requirement

**Table 2: Dose Escalation in Oncology/Hematology Drug Labels**

<b>Drug</b>	<b>Indication</b>	<b>Dosing Recommendation</b>
<b>Dasatinib (Sprycel)</b>	CML, ALL	The recommended dosage of Sprycel is 140 mg/day administered orally in two divided doses (70 mg twice daily [BID]), one in the morning and one in the evening with or without a meal. Dose increase or reduction of 20-mg increments per dose is recommended based on individual safety and tolerability. In clinical studies of adult CML and Ph+ ALL patients, dose escalation to 90 mg BID (chronic phase CML) or 100 mg BID (advanced phase CML and Ph+ ALL) was allowed in patients who did not achieve a hematologic or cytogenetic response at the recommended dosage.
<b>Axitinib (Inlyta)</b>	RCC	The recommended starting oral dose of Inlyta is 5 mg twice daily. Dose increase or reduction is recommended based on individual safety and tolerability. Over the course of treatment, patients who tolerate Inlyta for at least two consecutive weeks with no adverse reactions >Grade 2 (according to the CTCAE), are normotensive, and are not receiving anti-hypertension medication, may have their dose increased. When a dose increase from 5 mg twice daily is recommended, the Inlyta dose may be increased to 7 mg twice daily, and further to 10 mg twice daily using the same criteria.
<b>Ruxolitinib (Jakafi)</b>	Myelofibrosis	The recommended starting dose of Jakafi is based on platelet count. If the response is insufficient and platelet and neutrophil counts are adequate, doses may be increased in 5 mg twice daily increments to a maximum of 25 mg twice daily. Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks. Consider dose increases in patients who meet all of the following conditions: a. Failure to achieve a reduction from pretreatment baseline in either palpable spleen length of 50% or a 35% reduction in spleen volume as measured by CT or MRI; b. Platelet count greater than $125 \times 10^9/L$ at 4 weeks and platelet count never below $100 \times 10^9/L$ ; c. ANC Levels greater than $0.75 \times 10^9/L$ .
<b>Mitotane (Lysodren)</b>	Adrenal Cortical Carcinoma	The recommended treatment schedule is to start the patient at 2 g to 6 g of Lysodren per day in divided doses, either 3 or 4 times a day. Doses are usually increased incrementally to 9 g to 10 g per day. If severe side effects appear, the dose should be reduced until the maximum tolerated dose is achieved. If the patient can tolerate higher doses and improved clinical response appears possible, the dose should be increased until adverse reactions interfere. Experience has shown that the maximum tolerated dose will vary from 2 g to 16 g per day, but has usually been 9 g to 10 g per day. The highest doses used in the studies to date were 18 g to 19 g per day.

This table describes the dose escalation provision in some oncology/hematology indications. The recommendations are based on the original NDA review or data obtained from efficacy supplements.

## **References**

1. Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. *Journal of the National Cancer Institute*. 2009;101:708-20.
2. Marshall JL. Maximum-tolerated dose, optimum biologic dose, or optimum clinical value: dosing determination of cancer therapies. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012;30:2815-6.
3. Singh BN, Malhotra BK. Effects of food on the clinical pharmacokinetics of anticancer agents: underlying mechanisms and implications for oral chemotherapy. *Clinical pharmacokinetics*. 2004;43:1127-56.
4. Bosch TM. Pharmacogenomics of drug-metabolizing enzymes and drug transporters in chemotherapy. *Methods in molecular biology*. 2008;448:63-76.
5. FDA. Guidance for Industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications. 2003 [cited; Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>
6. Cancer Therapy Evaluation Program. NCI. Common Terminology Criteria for Adverse Events (CTCAE) v4.0. [cited; Available from: [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm#ctc\\_40](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40)
7. Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. *Journal of the National Cancer Institute*. 2009;101:1624-32.
8. Fromme EK, Eilers KM, Mori M, Hsieh YC, Beer TM. How accurate is clinician reporting of chemotherapy adverse effects? A comparison with patient-reported symptoms from the Quality-of-Life Questionnaire C30. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2004;22:3485-90.
9. Basch E, Bennett A, Pietanza MC. Use of patient-reported outcomes to improve the predictive accuracy of clinician-reported adverse events. *Journal of the National Cancer Institute*. 2011;103:1808-10.
10. Deisseroth A, Kaminskas E, Grillo J, Chen W, Saber H, Lu HL, et al. U.S. Food and Drug Administration approval: ruxolitinib for the treatment of patients with intermediate and high-risk myelofibrosis. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2012;18:3212-7.
11. FDA. Abiraterone supplemental approval: metastatic castration-resistant prostate cancer. 2012 [cited; Available from: <http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm331628.htm>
12. Basch E. Toward patient-centered drug development in oncology. *The New England journal of medicine*. 2013;369:397-400.
13. Cancer Therapy Evaluation Program. NCI. Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). [cited; Available from: <http://outcomes.cancer.gov/tools/pro-ctcae.html>
14. Cleeland CS, Allen JD, Roberts SA, Brell JM, Giralt SA, Khakoo AY, et al. Reducing the toxicity of cancer therapy: recognizing needs, taking action. *Nature reviews Clinical oncology*. 2012;9:471-8.
15. Johnson JR, Ning YM, Farrell A, Justice R, Keegan P, Pazdur R. Accelerated approval of oncology products: the food and drug administration experience. *Journal of the National Cancer Institute*. 2011;103:636-44.
16. Mitka M. Oversight of fast-track drug approval by FDA stuck in low gear, critics say. *JAMA : the journal of the American Medical Association*. 2010;304:1773-5.
17. Fain K, Daubresse M, Alexander GC. The Food and Drug Administration Amendments Act and postmarketing commitments. *JAMA : the journal of the American Medical Association*. 2013;310:202-4.