# Lessons Learned: Dose Selection of Small Molecule–Targeted Oncology Drugs

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## Abstract

Evaluation of dose plays a critical role in a successful oncology development program. Typically for oncology agents, the first-in-man phase I dose-escalation trials are conducted to determine a maximum tolerated dose (MTD). This MTD is taken forward into subsequent trials to establish the safety and efficacy of the drug product. Although this approach was appropriate historically for cytotoxics, the application of MTD as the recommend phase II dose has been problematic for the newer small molecule–targeted oncology agents. Promising alternative approaches using dose and exposure exploration, including lessons learned from recent targeted oncology agent development and approvals, are summarized and discussed. *Clin Cancer Res; 22(11); 2630–8. ©2016 AACR.*

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## Introduction

Approximately 50 new molecular entities (NME) were approved in the Office of Hematology and Oncology Products at FDA between 2011 and 2015 (1). More than half of the 30 approved small molecule–targeted anticancer therapies have the maximum tolerated dose (MTD) as the recommended dose in the label (Table 1). The current dose-finding strategy in oncology clinical trials has been driven by the historical experience with cytotoxic therapies and is based on the identification and evaluation of an MTD using the 3 + 3 design. However, an MTD argument for cytostatic or targeted agents is less plausible with the emerging knowledge of the drugs' target (2). In 2004, a review on the theory and practice of dose selection based on toxicity for noncytotoxic agents was conducted by the National Cancer Institute of Canada (3). This report criticized the traditional toxicity endpoints for selection of the recommended phase II dose (RP2D) and instead highlighted pharmacokinetics or measures of molecular drug effects as more appropriate. The limitations of and alternative approaches to the conventional 3 + 3 design are discussed further by Nie and colleagues (4).

Early development programs of noncytotoxic agents were likely misguided by the belief that noncytotoxic mechanisms went hand-in-hand with nontoxicity; however, over 14 years of drug development and research has taught us that these agents are far from toxicity free. Pneumonitis, cardiac toxicity, vascular toxicity, gastrointestinal toxicity, hepatic toxicity, and other toxicities have plagued targeted agents both in development and postapproval. Some of these toxicities are often not predicted by nonclinical testing (5) and may not be observed in the first cycle of treatment, during which the MTD is determined (6). Delayed serious toxicities have limited the use of some of the targeted agents. Due to these concerns, there has been increased interest in alternatives to the MTD approach for targeted agents to optimize effectiveness, minimize toxicity, and promote adherence in patients (7, 8).

On the basis of these observations, from May 18–19, 2015, the FDA and the American Association for Cancer Research (AACR) cosponsored a public workshop in which the group evaluated examples of approved targeted agents that have taken more novel approaches to dose finding. In this article, we distill common themes into what we see as eight key learnings (Box 1) that may be applied to enhance oncology drug development programs to guide dose selection. Details of the approaches for the case examples presented at the workshop are presented below, and discussion and integration of the key learnings from each example will follow.

### Box 1. Lessons learned in small molecule–targeted anticancer therapies

1. Test more than one dose in phase II or III trials.
2. Utilize dose–response and exposure–response modeling approaches integrating all available data.
3. Incorporate biomarkers and data for mechanistic target when mechanism of action is clear.
4. Consider that different doses may be needed in different disease settings.
5. Continually evaluate dosing and dosing regimens throughout drug development.
6. Incorporate long-term safety and tolerability into MTD and dose-limiting toxicity determinations for drugs intended for chronic use.
7. Appropriately address the interaction of food and drug early for oral agents.
8. Consider titration designs.

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**doi:** 10.1158/1078-0432.CCR-15-2646

**Table 1.** FDA-approved small molecule–targeted oncology agents from 2011 to 2015

| Active ingredient | Indication and usage | Comparison of labeled dose to MTD |
|---|---|---|
| Vandetanib | A kinase inhibitor indicated for the treatment of symptomatic or progressive MTC in patients with unresectable locally advanced or metastatic disease | Dose = MTD |
| Abiraterone | A CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration–resistant prostate cancer | Dose < MTD |
| Vemurafenib | A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with *BRAF V600E* mutation as detected by an FDA-approved test | Dose is approximately MTD |
| Crizotinib | A kinase inhibitor indicated for the treatment of patients with metastatic NSCLC whose tumors are *ALK*$^+$ as detected by an FDA-approved test | Dose = MTD |
| Ruxolitinib | A kinase inhibitor indicated for treatment of patients with:<br>• Intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post–essential thrombocythemia myelofibrosis<br>• Polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea | Dose < MTD |
| Axitinib | A kinase inhibitor indicated for the treatment of advanced RCC after the failure of one prior systemic therapy | Starting dose = MTD, but can titrate up or down |
| Vismodegib | A Hedgehog pathway inhibitor indicated for the treatment of adults with metastatic BCC or with locally advanced BCC that has recurred following surgery or who are not candidates for surgery and who are not candidates for radiotherapy | Dose < MTD |
| Carfilzomib | A proteasome inhibitor that is indicated:<br>• In combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy<br>• As a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy | Dose < MTD |
| Enzalutamide | An androgen receptor inhibitor indicated for the treatment of patients with metastatic castration–resistant prostate cancer | Dose < MTD |
| Bosutinib | A kinase inhibitor indicated for the treatment of adult patients with chronic, accelerated, or blast-phase Ph$^+$ CML with resistance or intolerance to prior therapy | Dose = MTD |
| Regorafenib | A kinase inhibitor indicated for the treatment of patients with:<br>• Metastatic CRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *KRAS* wild type, an anti-EGFR therapy<br>• Locally advanced, unresectable, or metastatic GIST who have been previously treated with imatinib mesylate and sunitinib malate | Dose = MTD |
| Cabozantinib | A kinase inhibitor indicated for the treatment of patients with progressive, metastatic MTC | Dose = MTD |
| Ponatinib | A kinase inhibitor indicated for:<br>• Treatment of adult patients with *T315I*-positive CML (chronic phase, accelerated phase, or blast phase) or *T315I*-positive Ph$^+$ ALL<br>• Treatment of adult patients with chronic-phase, accelerated-phase, or blast-phase CML or Ph$^+$ ALL for whom no other TKI therapy is indicated | Dose = MTD |
| Pomalidomide | A thalidomide analogue indicated, in combination with dexamethasone, for patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor, and have shown disease progression on or within 60 days of completion of the last therapy | Dose = MTD |
| Radium RA-223 | An $\alpha$ particle–emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease | Dose < MTD |
| Trametinib | A kinase inhibitor indicated, as a single agent or in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with *BRAF V600E* or *V600K* mutations as detected by an FDA-approved test | Dose < MTD |
| Afatinib | A kinase inhibitor indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have *EGFR* exon 19 deletions or exon 21 (*L858R*) substitution mutations as detected by an FDA-approved test | Dose < MTD |
| Ibrutinib | A kinase inhibitor indicated for the treatment of patients with:<br>• MCL who have received at least one prior therapy<br>• CLL who have received at least one prior therapy<br>• CLL with 17p deletion<br>• WM | Dose < MTD |
| Olaparib | A PARP inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germline *BRCA*-mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy | Dose = MTD |
| Idelalisib | A kinase inhibitor indicated for the treatment of patients with:<br>• Relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities<br>• Relapsed FL in patients who have received at least two prior systemic therapies<br>• Relapsed SLL in patients who have received at least two prior systemic therapies | Dose < MTD |
| Belinostat | A histone deacetylase inhibitor indicated for the treatment of patients with relapsed or refractory PTCL | Dose = MTD |
| Ceritinib | A kinase inhibitor indicated for the treatment of patients with *ALK*$^+$ metastatic NSCLC who have progressed on or are intolerant to crizotinib | Dose = MTD |
| Palbociclib | A kinase inhibitor indicated in combination with letrozole for the treatment of postmenopausal women with ER-positive, *HER2*-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease | Dose = MTD |

*(Continued on the following page)*

**Table 1.** FDA-approved small molecule–targeted oncology agents from 2011 to 2015 (Cont'd)

| Active ingredient | Indication and usage | Comparison of labeled dose to MTD |
|---|---|---|
| Lenvatinib | A kinase inhibitor indicated for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine–refractory differentiated thyroid cancer | Dose = MTD |
| Panobinostat | A histone deacetylase inhibitor, in combination with bortezomib and dexamethasone, indicated for the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent | Dose = MTD |
| Sonidegib | A Hedgehog pathway inhibitor indicated for the treatment of adult patients with locally advanced BCC that has recurred following surgery or radiotherapy, or those who are not candidates for surgery or radiotherapy | Dose < MTD |
| Cobimetinib | A kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with a *BRAF V600E* or *V600K* mutation, in combination with vemurafenib | Dose = MTD |
| Osimertinib | A kinase inhibitor indicated for the treatment of patients with metastatic *EGFR T790M* mutation–positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy | Dose < MTD |
| Ixazomib | A proteasome inhibitor indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy | Dose < MTD |
| Alectinib | A kinase inhibitor indicated for the treatment of patients with $ALK^+$ metastatic NSCLC who have progressed on or are intolerant to crizotinib | Dose = MTD |

Abbreviations: BCC, basal cell carcinoma; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; ER, estrogen receptor; FL, follicular B-cell non-Hodgkin lymphoma; GIST, gastrointestinal stromal tumor; MCL, mantle cell lymphoma; $Ph^+$ ALL, Philadelphia chromosome–positive acute lymphoblastic leukemia; PTCL, peripheral T-cell lymphoma; RCC, renal cell carcinoma; SLL, small lymphocytic lymphoma; TKI, tyrosine kinase inhibitor; WM, Waldenström macroglobulinemia.

## Case Examples

### Nilotinib: leveraging exposure response to refine dose

Nilotinib is a kinase inhibitor indicated for chronic-phase and accelerated-phase Philadelphia chromosome–positive chronic myeloid leukemia (CML). It was approved in the United States in 2007 for adult patients resistant to or intolerant to imatinib at a recommended dose of 400 mg twice daily (9), although in 2010, the first-line indication was approved with a recommended dose of 300 mg twice daily (10).

Initial dose selection for nilotinib was supported by data collected in a phase Ia/II study. Phase Ia of the study evaluated a range of once-daily and twice-daily regimens to determine MTD, and the phase II component consisted of six expansion arms, in which patients received nilotinib at a dose of 400 mg twice daily, with dose escalation to 600 mg if there was no response after 3 months. In the phase Ia portion of the study, the MTD of nilotinib was determined to be 600 mg twice daily. The safety of the 400-mg-twice-daily dose was better than that of the 600-mg twice-daily dose, and there was no increase in systemic exposure when the dose increased from 400 to 600 mg; therefore, a 400-mg dose was chosen for phase II. The available phase II data from this study established an exposure–response relationship for efficacy, which suggested that higher nilotinib exposure was associated with increased response rates (11). In addition, the trough concentrations following a 400-mg-twice-daily dose are in the concentration range (free drug concentration of 36 nmol/L) predicted to inhibit the targets based on nonclinical data ($IC_{50}$ of cellular phosphorylation of Bcr-Abl kinase = 20–60 nmol/L; ref. 12). A risk of QT prolongation and sudden deaths was identified on the basis of the phase Ia/II data and resulted in box warning in the package insert (13). The risk of QT prolongation is exposure dependent (11), with the risk of QT prolongation increasing as nilotinib concentration increased (Fig. 1, from FDA review).

The pharmacokinetics, efficacy, safety, and target inhibition information gathered from the phase Ia/II trial supported the dose selection and overall benefit–risk assessment for nilotinib for the accelerated approval of a 400-mg-twice-daily dose for the second-line indication (14).

When deciding on doses for the confirmatory phase III trial for the first-line CML indication, all available data were considered and two nilotinib doses were tested: 400 and 300 mg twice daily. The 300-mg-twice-daily dose was included with the hope of reasonably maintaining efficacy while improving safety based on the exposure–QT relationship. The results of the phase III study showed that a 300-mg-twice-daily dose had similar efficacy but better safety compared with a 400-mg-twice-daily dose in the first-line setting (15). Therefore, a lower dose of 300 mg twice daily was approved for the first-line indication.

### Ceritinib: importance of exposure response for accelerated timelines

Ceritinib is a kinase inhibitor approved for use in patients with anaplastic lymphoma kinase–positve ($ALK^+$) metastatic non–small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The first-in-human (FIH) trial with ceritinib was a Bayesian dose-escalation and expansion study conducted under fasted conditions (see Fig. 2; ref. 16). The MTD was based on probability of cycle 1 dose-limiting toxicity (DLT) using a Bayesian logistic regression model (BLRM) and clinical assessment. The increasing frequency of grade 1–2 gastrointestinal disturbances, including nausea, vomiting, and diarrhea, precluded escalation above 750 mg even though the BLRM permitted dose escalation to 900 mg (16). Among 114 patients with $ALK^+$ NSCLC who received ≥400 mg of ceritinib per day, the overall response rate (ORR) was 58% (95% CI, 48–67; ref. 17). This early evidence for response was the driver for breakthrough therapy designation and accelerated development of ceritinib 2 years after the first patient was enrolled into the FIH trial (16). The data from the single-arm expansion cohorts in $ALK^+$ NSCLC patients formed the basis for the accelerated approval of the new drug applications (NDA; ref. 18).

Extensive exposure–response analyses were conducted with the data from the FIH study (19). No significant exposure–response relationships were identified for ORR or progression-free survival (PFS); however, higher systemic exposure appeared to be associated with more overall ≥grade 3 adverse events (AE; Fig. 3A, from FDA review). Concentration–QT analyses showed that ceritinib prolonged the QTc

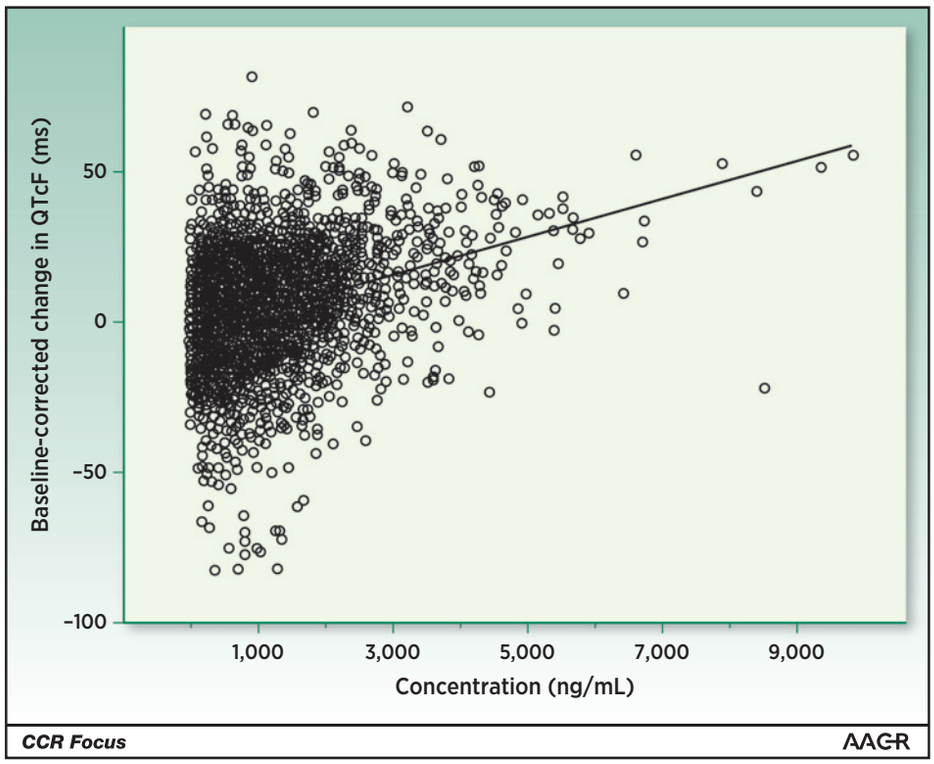


**Figure 1.**
Nilotinib concentration (ng/mL) versus baseline-corrected QTcF (dQTcF). © Novartis Pharmaceuticals. Reprinted with permission of Novartis Pharmaceuticals.

interval in a concentration-dependent manner. Higher systemic exposure also appeared to be associated with earlier and more frequent dose reductions or dose interruption (Fig. 3B, from FDA review). Sixty percent (60%) of patients initiating treatment at 750 mg required at least one dose reduction. Gastrointestinal disorders, including diarrhea, nausea, and vomiting, were reported in 98% of patients and resulted in dose modification in 42% of patients (19).

Nonclinical data indicated that higher ceritinib exposures were needed to maximize efficacy and confer durable responses in the setting of crizotinib resistance (20), and this was confirmed in the FIH study by the high rate of early and durable response following a 750-mg dose. Although safety was manageable via dose modification with a low rate of AEs leading to discontinuation (10%), the high rate of gastrointestinal AEs suggest regimen optimization with food is a viable option to improve tolerability and compliance and keep patients at exposures associated with durable sustained responses. A food effect study was conducted during development, but the results were not available to inform dosing of the FIH expansion cohorts. As the food effect results indicated ceritinib exposure (AUC) increased 60% to 70% under fed conditions, administration of 750 mg of ceritinib with food would increase exposure and thus, due to the positive exposure–safety relationship described above, could increase the rate of overall ≥grade 3 AEs. Therefore, a dose reduction would be necessary if ceritinib was to be given concomitantly with food. For this reason, the FDA requested the sponsor to conduct a study to investigate doses of 450 and 600 mg daily with food compared with the 750-mg dose in the fasted state in terms of systemic exposure and safety (18).

**Axitinib: thinking beyond exposure-mediated dose titration**

Axitinib is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma (RCC) after the failure of one prior systemic therapy. The starting dose of axitinib is 5 mg orally twice daily, with dose modifications ranging from 2 to 10 mg twice daily based on safety and tolerability.

The MTD of 5 mg twice daily was determined from a dose-ranging trial in patients using doses from 5 to 30 mg twice daily. The pharmacodynamics assessment of decrease in tumor blood flow measured by MRI and decrease in soluble VEGFR-2 in plasma supported the MTD of 5 mg twice daily (21).

Although a flat dose of 5 mg twice daily tested in a phase II trial demonstrated a robust 44% response rate, a subset of patients achieved subtherapeutic exposure defined as 12-hour AUC ($AUC_{12}$) below 150 ng·h/mL. Subsequent phase II trials in metastatic RCC patients included upward dose titration to 7 mg and 10 mg twice daily based on individual patient tolerability. Retrospective exploratory analysis of the data showed that most patients achieved therapeutic exposures ($AUC_{12} \geq 150$ ng·h/mL), and the patients who achieved this threshold had a PFS of 12 months compared with 8 months for patients with lower exposure. On the basis of these findings, a dose-escalation and dose-deescalation algorithm was implemented in the phase III trial. Patients were required to meet three criteria for upward dose titration: (i) no adverse reactions >grade 2 Common Toxicity Criteria for Adverse Events for at least 2 consecutive weeks of treatment with 5-mg-twice-daily starting dose, (ii) normotensive; and (iii) not receiving antihypertensive medication. In the trial, 28% of the patients did not require any dose modification, 34% of the patients had dose reduction, and 38% of the patients had dose

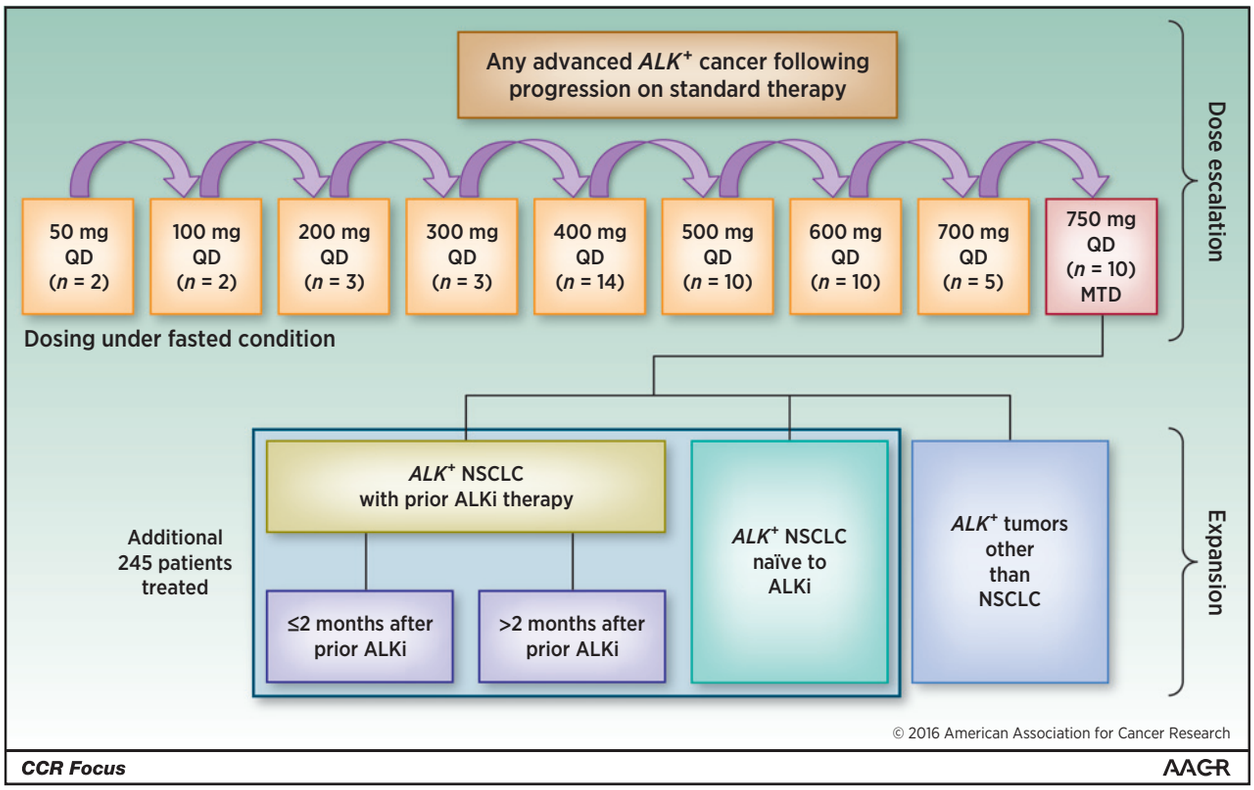


**Figure 2.**
Ceritinib FIH study design. ALKi, ALK inhibitor; QD, daily.

escalation (21). The phase II and III trials confirmed the need for dose titration, and appropriate information was included in the package insert of axitinib (22).

**Vandetanib: exposure response informed postmarketing dose-finding study**

Vandetanib is an oral multikinase inhibitor for the treatment of symptomatic or progressive medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease. It was approved in 2011 at the recommended dose of 300 mg given once daily but with a postmarketing requirement to evaluate and compare the efficacy and safety of a lower daily dose of 150 mg.

Early studies of vandetanib that informed dose included evaluations of the MTD, food effect, and QT prolongation. In the phase I study, oral doses ranging between 50 to 600 mg were tested, with the MTD of vandetanib established at 300 mg once daily. Vandetanib has a large volume of distribution and long terminal half-life of 10 to 20 days, resulting in significant accumulation upon daily dosing such that safety beyond the DLT period is important to consider when determining an RP2D. The dedicated food effect study indicated that vandetanib could be taken with or without food, which informed dosing for the pivotal trial. An exposure–response analysis of a dedicated QT study in healthy volunteers conducted prior to the efficacy studies indicated a concentration-dependent QT prolongation, which increased slowly with time and with the slow accumulation of the drug in plasma (23).

Two separate small phase II studies were also conducted to test the efficacy in MTC at two different daily doses: 100 and 300 mg. Both studies demonstrated efficacy with ORRs of 15% and 20%, respectively. A randomized, double-blind, phase III study was conducted comparing the efficacy of 300 mg versus placebo with a primary endpoint of PFS. Pharmacokinetic measurement was incorporated in the pivotal MTC trial, which allowed for exposure–response analyses for efficacy and safety. The exposure–response analyses revealed that the probability of partial response increased with increasing AUC of vandetanib, and the probability of progressive disease also decreased with increasing AUC of vandetanib at steady state. In addition, the risk of QT prolongation increased with concentration of vandetanib reaching a plateau after 3 to 6 weeks of initiating once-daily treatment (23). Because of the positive exposure–response relationships, and the desire to evaluate whether a lower vandetanib dose would be safe and effective, the FDA requested the sponsor to conduct a small randomized prospective study to compare the efficacy (ORR) and safety (secondary endpoint) of two different daily doses of vandetanib: 150 and 300 mg (NCT01496313; ref. 24). The results from this study are pending.

## Discussion

Careful balance of benefit and risk is critical in oncology dose selection for targeted anticancer therapies. Improvement can be made to the traditional MTD approach and early

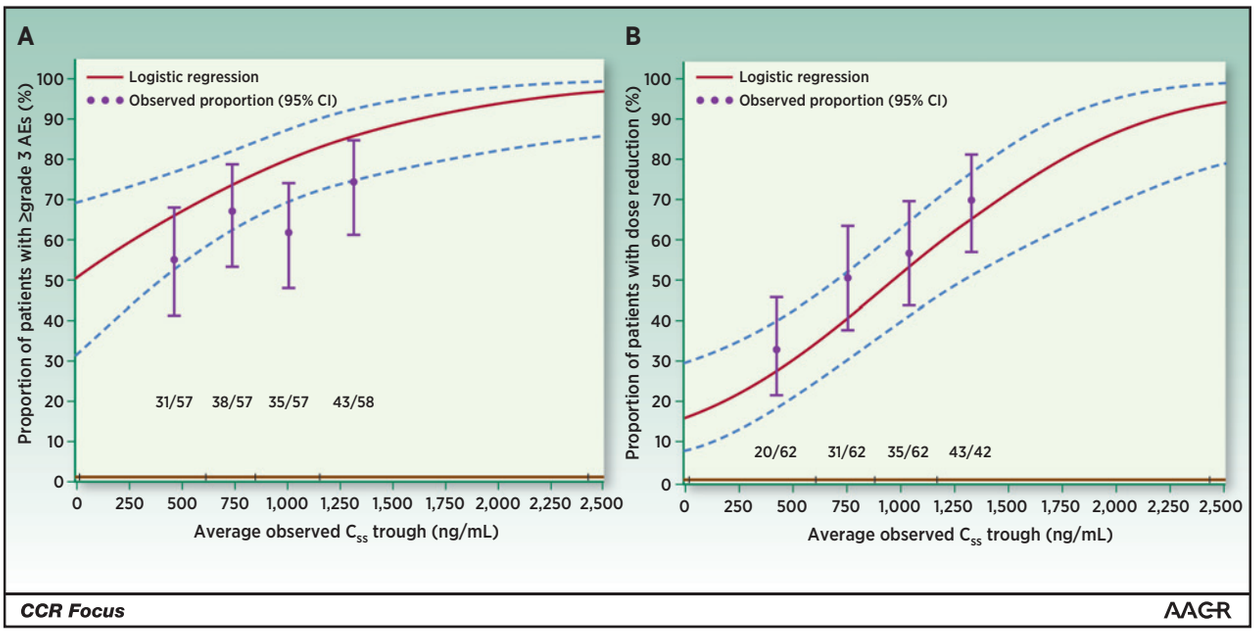


**Figure 3.**
Relationship between $C_{ss,trough}$ and the probability of ≥grade 3 AEs (A) and probability of dose reduction (B) in patients with *ALK*$^+$ tumors who were treated with ceritinib (50–750 mg daily). © Novartis Pharmaceuticals. Reprinted with permission of Novartis Pharmaceuticals. CI, confidence interval.

development strategy to optimize effectiveness, minimize toxicity, and promote adherence in patients. Not all dose-finding approaches can be extrapolated to each therapy and need to be tailored for the characteristics of each compound. Since targeted therapies entered into clinical studies in the 1990s, there have been both success and failures to inform a more educated path forward for dose selection for registration trials. Although the examples described above are a subset of the approved small molecule–targeted agents, their key learnings are important and are illustrative of many lessons from other products as listed in Table 1.

The concept of testing more than one dose in phase II or III trials is not a novel concept in drug development. Other therapeutic areas have implemented dose ranging in phase II and phase III trials; however, as oncology drug development often goes straight from FIH to efficacy trials, the informative middle stage of dose ranging and dose finding is often overlooked. However, examples such as temsirolimus (25), dasatinib (26), sonidegib (27), and nilotinib (28) confirm that an understanding of toxicity and efficacy across a range of doses can be informative in choosing a dose that improves the delicate balance of benefits and risks from the therapy (4).

All of the case examples exemplified how dose–response and exposure–response modeling approaches can be leveraged to gain a better understanding of doses and exposures that balance efficacy and toxicity. However, this goes hand-in-hand with obtaining robust pharmacokinetics in clinical trials. Incorporation of meaningful pharmacokinetics in all patients can be invaluable and, as documented in numerous FDA reviews, these analyses are often leveraged to answer questions and support labeling when dedicated studies are not available. In accelerated breakthrough therapy programs, robust pharmacokinetics sampling becomes even more important to support approval and labeling. As a case in point, the FIH trial for ceritinib was also the pivotal registration study. As designed, the ceritinib FIH trial provided a rich pharmacokinetics dataset with both intensive and sparse samples from all subjects across a wide dose range and throughout multiple cycles. In addition to the informative exposure–response analyses, the pharmacokinetics collected from this study was added to a population pharmacokinetics model, which supported labeling and use for patients with renal impairment and patients with hepatic impairment (29). The addition of ECGs time-matched with pharmacokinetics was used to support a concentration–QT analysis for ceritinib, which relieved the need for a separate study to evaluate QT prolongation (30). Similarly, even for nonaccelerated programs, the inclusion of robust pharmacokinetics can be helpful to inform the need for further dose refinement (26). Although the inclusion of pharmacokinetics sampling was not mentioned specially as a reason for slow study accrual in the review by Massett and colleagues (31), to reduce both patient and operational burden, appropriate sampling schedules, which coincide with scheduled patient visits, should be encouraged, as the knowledge gathered from such evaluations can be essential to guide and refine dosing and inform future drug development.

Incorporation of mechanistic targets and biomarkers is not typically included in the dose justification argument and instead reliance upon toxicity and efficacy is common. Although there are limitations (32, 33) to extrapolating human concentrations to *in vitro* studies, an understanding of where human concentrations are in respect to concentrations obtained *in vitro* can be useful and was employed in the nilotinib example above and was also leveraged for dasatinib (34). Characterization of primary or downstream target

biomarkers can also be useful to incorporate into dose-ranging trials to provide information on target modulation to inform dose and regimen for future studies, such as was done for temsirolimus (25) and everolimus (35), and as discussed further by Nie and colleagues (4) in this *CCR Focus*.

The nilotinib example above, in addition to data with other approved agents, such as imatinib (36), everolimus (37), and dasatinib (38), supports the idea that "one dose for all indications" is not applicable for all drugs. Different cancer types or even patients presenting for their first versus third treatment may require a different dose intensity for efficacy. Furthermore, patients may be more sensitive to drug toxicities based on the prior treatments for their cancer. Although the expectation for extensive stand-alone dose-finding studies for each indication is unrealistic, the safety and pharmacokinetics information gained from other patient populations can be used to informatively design studies in other cancers.

The need to continually evaluate dosing throughout development is becoming more common with the accelerated nature of oncology drug development. As seen in the nilotinib, ceritinib, and vandetanib examples above, approval is not the end of the dose journey, as efficacy trials can be a prime study to learn about the drug and then apply those learnings to other trials or to other indications. Incorporation of pharmacokinetics into efficacy trials can provide valuable information to select doses for future studies. In the absence of pharmacokinetics, starting the dose-finding exercise over again can be an unfortunate reality (NCT02467270; ref. 39) if the dose studied in efficacy trials leads to an imbalanced balance of benefits and risks.

Although most FIH trials base MTD on cycle 1 DLTs, all of the examples above support the need for toxicity in subsequent cycles from patients in the dose-escalation cohorts to be incorporated into the dose decision for expansion cohorts and the subsequent RP2D determination. For example, for drugs with long terminal half-lives, exposures and toxicities at steady state need to be taken into consideration, which the vandetanib development program implemented. Also, since the majority of the targeted oncologic therapies are taken daily until disease progression, an understanding of what toxicities will occur after months of dosing, and if those toxicities (even grade 2) are tolerated in the patient population, is critical. If the toxicities are not tolerable, then dose intensity and patient compliance may become issues and could have an impact on efficacy trial outcomes as well as the benefit–risk balance. This concept is further discussed in this *CCR Focus* by Nie and colleagues (4) and Jänne and colleagues (6).

Many examples cited above (ceritinib, vandetanib) support the need and value to early food effect evaluations. A food effect study conducted per the FDA guidance (40) is required for inclusion in NDA for oral anticancer agents. However, this definitive study is typically not conducted until proof of efficacy has been established. Although this is a reasonable business strategy, which reduces unnecessary spending and exposure of subjects to drugs that are not effective, the timing is not positioned to inform dosing for efficacy studies in fast-paced oncology development programs. While moving ahead and dosing efficacy trials in the fasted state can be efficient, it often is not warranted and raises the question of whether benfit–risk assessment and patient compliance may be improved (e.g., olaparib; ref. 41) if patients in clinical trials could be dosed without regard to food. Therefore, it is often recommended to evaluate the effect of food early, either within the FIH trial or in another stand-alone trial conducted prior to efficacy studies. Even a nondefinitive evaluation (i.e., one not conducted per FDA Food Effect Guidance standards) in a small subset of patients can effectively de-risk the food effect issue and be sufficient to inform a more clinically relevant dosing condition for future trials or expansion cohorts. For example, incorporation of a food effect evaluation into a cohort of the ceritinib FIH study could have been an invaluable preliminary risk assessment ahead of the dedicated food effect study. This preliminary evaluation would not necessarily have slowed down ceritinib development but could have been incorporated in the dose selection for the expansion cohorts.

Finally, the idea of therapeutic drug monitoring (TDM) to individualize and refine dosing is a well-understood approach for narrow therapeutic index drugs (e.g., warfarin and digoxin). However, incorporation of TDM into clinical trials and clinical practice can be burdensome and is limited by assay availability and turnaround. Novel and creative approaches can be used to dose patients individually in the absence of monitoring drug concentrations and should be encouraged. The concept of dose titration based on clinical tolerability implemented during the development of axitinib paid off in identifying a subset of populations who benefited from either dose escalation or deescalation based on clinical safety and tolerability.

All of these lessons learned also apply to the development of combination therapies in oncology. Whether an NME is being combined with standard of care or another NME, the concepts of translating *in vitro* target attainment and mechanistic biomarkers to human exposures and relating these exposures to toxicity and efficacy along with data generated from physiology-based pharmacokinetics modeling to predict drug interactions can streamline dose finding for combination therapies. In summary, incorporation of these lessons learned into oncology clinical development programs will enhance the understanding of the relationship between dose and exposure to efficacy and toxicity while ensuring that dose selection is an informed decision.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

**Conception and design:** J.M. Bullock, Q. Liu
**Development of methodology:** J.M. Bullock, Q. Liu
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** J.M. Bullock, A. Rahman, Q. Liu
**Writing, review, and/or revision of the manuscript:** J.M. Bullock, A. Rahman, Q. Liu
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** J.M. Bullock

## Acknowledgments

The authors thank Drs. Eric Masson, Daniel Howard, Yazdi Pithavala, and Jin Jin for their case–study contributions and participation in the May 18 to 19, 2005 FDA/AACR Dose-Finding of Small-Molecule Oncology Drugs Workshop.

Received February 17, 2016; revised March 24, 2016; accepted April 11, 2016; published online June 1, 2016.

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# Lessons Learned: Dose Selection of Small Molecule–Targeted Oncology Drugs

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*Clin Cancer Res* 2016;22:2630-2638.