Rendering the 3 + 3 Design to Rest: More Efficient Approaches to Oncology Dose-Finding Trials in the Era of Targeted Therapy

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Abstract

Selection of the maximum tolerated dose (MTD) as the recommended dose for registration trials based on a dose-escalation trial using variations of an MTD/3 + 3 design often occurs in the development of oncology products. The MTD/3 + 3 approach is not optimal and may result in recommended doses that are unacceptably toxic for many patients and in dose reduction/interruptions that might have an impact on effectiveness. Instead of the MTD/3 + 3 approach, the authors recommend an integrated approach. In this approach, typically an adaptive/Bayesian model provides a general framework to incorporate and make decisions for dose escalation based on nonclinical data, such as animal efficacy and toxicity data; clinical data, including pharmacokinetics/pharmacodynamics data; and dose/exposure–response data for efficacy and safety. To improve dose-ranging trials, model-based estimation, rather than hypothesis testing, should be used to maximize and integrate the information gathered across trials and doses. This approach may improve identification of optimal recommended doses, which can then be confirmed in registration trials. *Clin Cancer Res; 22(11); 2623–9. ©2016 AACR.*

See all articles in this *CCR Focus* section, "New Approaches for Optimizing Dosing of Anticancer Agents."

Introduction

A primary goal of early-phase clinical trials is to identify the recommended doses for later phases. Phase I clinical trials are conducted to select doses for further development based on all relevant information, including nonclinical, pharmacokinetics, pharmacodynamics, biomarker characterization, and clinical information. Outside of the oncology disease area, phase II clinical trials are conducted to characterize dose/exposure–response relationships for efficacy and safety to inform dose selection for the registration trials.

However, in the era of breakthrough for development of oncology products, for which a balance needs to be maintained between optimal dose selections before approval versus rapid access to effective medications by patients, a sequential phase I–III trial paradigm may not be feasible or practical. Therefore, selection of a recommended dose may occur in an abbreviated manner, perhaps involving a single trial. In these cases, the historical approach of selecting the maximum tolerated dose (MTD) as the recommended dose, often using the 3 + 3 "up and down" algorithm, may no longer be appropriate, and a revisit to this approach is urgently needed. It is worth noting that the MTD approach to dose selection was designed to maximize the activity for cytotoxic chemotherapeutic agents. Other approaches for the more targeted agents being developed in the current era should be considered, because the MTD may be higher than needed for maximal efficacy.

In reality, many nonoptimal doses are taken into late development, with a high rate of dose interruptions and reductions observed in registration trials. In addition, frequent postmarketing requirements to study lower doses or alternate regimens are needed to optimize use of the drug (1). Identification of the "right dose" before approval is the goal; however, it is sometimes challenging to conduct adequate dose-ranging trials when the biology of the target is not well understood and/or there is an unmet medical need to make the drug available to patients quickly. On the other hand, postmarketing trials to inform appropriate labeling may be challenging to complete in a timely manner (1–4).

On May 18–19, 2015, the FDA and the American Association for Cancer Research (AACR) cosponsored a public workshop to discuss dose-finding strategies, with a focus on small-molecule oncology drugs. Experts from academia, industry, and regulatory agencies gathered together to discuss the best practices related to dose finding in the development of oncology products. The intent of this article is to stimulate further discussion of alternative approaches and advanced methods around the topic of dose finding, particularly for oncology drugs in development.

Lessons Learned from Currently Used Methods

The high rate of dose interruptions and reductions in the initially approved dose of oncology drugs points out the importance and need for improvement to current dose selection strategies that are based on the MTD/3 + 3 method. For example, the FDA approved

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ponatinib at 45 mg once daily in December 2012 as a treatment for adult patients with chronic myeloid leukemia (CML; ref. 5). Vascular occlusions (arterial and venous thrombosis and occlusions) occurred in at least 27% of treated patients. The adverse events included fatal myocardial infarction, stroke, stenosis of large cerebral arterial vessels, and severe peripheral vascular disease, often resulting in the need for urgent revascularization procedures (5). Ponatinib, once daily at 45 mg, was determined as the MTD in a phase I dose-escalation study using the 3 + 3 design (6), and no clear understanding was reached of the dose–response relationship for these vaso-occlusive events. Eventually, the FDA revised the label to explicitly indicate that the optimal dose of ponatinib in this patient population had not been identified and provided an option to lower the dose in patients with chronic or accelerated-phase CML who had achieved a major cytogenetic response with the initial dose of 45 mg. In another example, the FDA approved cabozantinib in November 2012 for the treatment of progressive, metastatic medullary thyroid cancer (7). The dose approved was 140 mg once daily, which was also the dose studied in the registration trial. This led to dose modifications in 86% of the patients. In addition, exposure–response analyses indicated that lower average exposures were not associated with reduction in progression-free survival. The analyses also showed that higher exposures were related to early-dose modifications. All the evidence suggests that a lower dose might be effective with improved tolerability. For both ponatinib and cabozantinib, postmarketing trials to characterize the efficacy and safety of lower doses were recommended by the FDA.

In an additional example, the dose of decitabine 1,500 to 2,000 mg/m^2 per course was determined to be the MTD in a phase I study. High doses used in phase II studies showed disappointing efficacy (8). With a better understanding of the compound's mechanism of action, later clinical trials focused on identifying a dose based on pharmacodynamic markers rather than an MTD, leading to approval of a dose of 15 or 20 mg/m^2 per day, which is 1% of MTD originally determined in phase I trial (9). As demonstrated in the pivotal trial of decitabine 15 mg/m^2 for treatment of patients with myelodysplastic syndromes, the overall response rate was 17% in decitabine-treated patients and 0% in the standard care group.

The potential problems and findings from these examples highlight the need for better dose selection during drug development. In the examples above, the conventional MTD/3 + 3 approach identified doses that were subsequently found to be nonoptimal, likely due to (i) inefficient use of data from the preceding cohort to select the dose for the next cohort of patients; (ii) use of only short-term safety data from a single cycle; (iii) lack of incorporation of information other than dose-limiting toxicity (DLT); (iv) lack of accounting for interindividual variability in exposure and response; and (v) poor statistical properties.

For at least 12 recently approved oncology products, postmarketing trials have been recommended to characterize efficacy and/or safety of alternate dosage or dosage regimen. This highlights the need to advance methodology for dose selection. In addition, it has been estimated that in approximately 50% of noncytotoxic drugs (total of 82 noncytotoxic studies), the MTD could not be determined (10). In addition, of the remaining 50% of drugs for which an MTD could be determined, in only 30% objectively quantifiable clinical toxicity was reported.

The paradigm of determining a single dose, often the MTD, to investigate in phase II studies was initially developed in the era of cytotoxic therapies but has since been used for targeted therapies as well. In most cases, only a single dose of a drug, which is generally determined on the basis of tolerability in a phase I dose-escalation trial, is used in the pivotal trials. The conventional objective of these phase I oncology studies is determination of the MTD, which is then selected for study in phase II trials. However, the determination of recommended phase II dose(s), which is often an explicitly stated objective of phase I studies, should always be the primary objective, not determination of the MTD.

To improve upon this paradigm, it is necessary to have a good understanding of the limitations of the conventional approach, particularly with respect to targeted therapies. MTD is conventionally defined as a dose with an observed DLT rate no greater than a fixed value, typically 1 of 3 patients or 2 of 6 patients, and DLT in turn is defined as a serious toxicity that occurs within a specified period of time (usually the first treatment cycle of 28 days). The 3 + 3 approach does not have good statistical properties and has been shown to have poor targeting of true MTD, to lack flexibility to target alternate DLT rates, and to involve a small number of patients, which may result in the selection of doses that can be unacceptably toxic when studied in a larger number of patients. In addition, restriction to a 28-day observation period for DLTs may miss relevant delayed toxicities. However, it may not be possible to follow all subjects enrolled in phase I oncology studies for sufficiently long periods to determine DLTs that develop beyond cycle 1, as many patients enrolled in phase 1 studies have late-stage disease, and those who progress rapidly drop out of the study. In an evolving field where DLT cannot be relied on alone for the determination of recommended phase II doses (RP2D), the use of 3 + 3 is simply no longer tenable. We propose alternate approaches in the next section.

New Approaches

One possible change in methodology for determination of the RP2D is to focus on determining an efficacious dose range, rather than a single dose based on tolerability. The efficacious dose range could be selected based upon a pharmacodynamic biomarker specific to the agent. It is important, however, to ensure that there is a good understanding of the relationship between the target and the biomarker. The use of tumor size can be an important effect marker especially when continuous tumor size reduction is used as a continuous variable rather than a categorical variable as in the RECIST categories (11, 12). The proposed approach could target a wide range of doses (5-fold or greater) that includes a minimal effective dose and an MTD. This approach will provide important information about interindividual variability in response. In cases for which an MTD cannot be reliably established or when a pharmacologic understanding of the target has been established, proposed clinical doses could be based on pharmacokinetics/pharmacodynamics and explore a wide dose range, using endpoints such as change in tumor size for early-response assessment. Preclinical data can also help to identify the relevant target (ALK inhibition rather than MET inhibition in the case of crizotinib) and degree of inhibition of the target needed for tumor growth inhibition. Clinical pharmacokinetics/pharmacodynamics and preclinical data were useful to model and select optimal biologic doses for everolimus (13). For idelalisib, pharmacokinetics, *in vitro* data and clinical

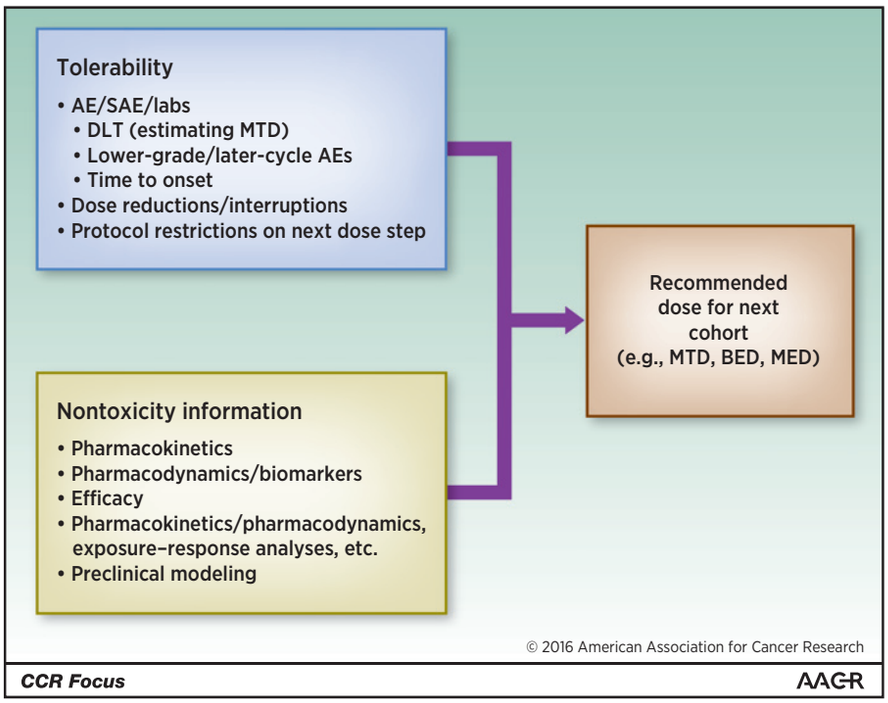

Figure 1.
Data supporting recommended dose stratification. AE, adverse event; BED, biologically effective dose; MED, minimally efficacious dose; SAE, serious adverse event.

exposure–response data were used by the sponsor to select the dose, whereas in the case of axitinib for the treatment of renal cell carcinoma, hypertension-based dose titration was employed in the clinical drug development program to maximize the chance of efficacy and safety in individual patients (14, 15).

Other examples with adaptive dose modification algorithms have been implemented in the drug development programs, and accordingly, instructions have been included in the label. Such approaches offer the benefit of dose individualization to maximize chances of efficacy while ensuring acceptable safety (4). The key idea is to bring an evaluation of drug activity and safety into the dose selection process earlier for phase II studies, moving away from an exclusive focus on toxicity and the MTD. Although, randomized dose-finding studies are not routinely conducted in oncology, there is evidence that when conducted they help in rational dose selection (16).

Approaches for dose-escalation trials

The main goal of a phase I clinical trial is to identify the RP2D, historically driven by toxicity with nonclinical data, pharmacokinetics/pharmacodynamics, and preliminary evidence of efficacy as supporting information. The singular focus on toxicity as the driver for decisions primarily came from the chemotherapy development paradigm, but novel treatments (e.g., small molecules, immunotherapies) require the weighting of information to be more flexible.

An integrated approach refers to use of all available information to select optimal doses for phase II trials (including appropriate formulations and schedules). This information includes activity from animal studies, *in vitro* and *in vivo* studies, dose/exposure–response measured by efficacy or biomarker/pharmacodynamics markers and pharmacokinetics parameters, tumor shrinkage, and safety (e.g., adverse events, preclinical safety, DLT, tolerability, dose–toxicity relationship; see Fig. 1).

Although DLT remains an important parameter to protect patients, it should not be the sole or primary endpoint in dose-finding studies. Establishing dose–response (including efficacy and toxicity) relationships and determining a minimum effective dose are equally important. Furthermore, it is not necessary to identify MTD in all cases, and it is not always true that a higher dose can result in higher efficacy than a lower dose.

The integrated approach requires incorporation of preclinical or historical information, drug–drug interaction for drug combinations, and also flexibility to adapt information as it becomes available during the clinical trial itself. This is optimally done with a Bayesian/adaptive design that incorporates new information as it becomes available. However, a statistical model should not be relied on without the context of clinical data. The model should provide a support framework to the review of the totality of data, by integrating the information obtained in the study in context

Box 1. Recommended approach to dose finding in phase I studies

1. Predefine dose levels for escalation as if for a "3 + 3" design.
2. Select a target DLT rate, typically 30% or 25%, and a cap for the total number of patients to be treated at a given dose, typically 12–14.
3. Use an adaptive/Bayesian method to identify a dose with the targeted DLT rate.
4. These methods allow doses to be increased or decreased in groups of patients to enable convergence to the targeted DLT rate.

with the other available information. The integrated approach is also a tailored approach that considers the specific development plan of a drug with a specific mechanism in a specific disease. The specificity will depend on the challenges, such as orphan drug status, in which the enrollment could be a major problem; lack of efficacy endpoints/surrogate endpoint/biomarkers; and late onset of toxicities.

In two recent examples, we illustrate some adaptive/Bayesian study designs (see Box 1 and ref. 20). These designs, as well as many other adaptive/Bayesian approaches, could serve as an integrated strategy with suitable modifications and improvement.

Example 1. In a phase I study with the primary objective of determining the MTD of AUY922 in patients with advanced solid tumors, an adaptive Bayesian logistic regression model (BLRM) was used to guide dose-escalation decisions (17, 18). On the basis of available preclinical data, the starting dose was established to be 2 mg/m^2. The dose was escalated to 2, 4, 8, and 16 mg/m^2 without observing any DLTs. One of 4 patients with a next dose level at 22 mg/m^2 experienced DLT; however, no DLTs were observed in another 5 patients with this dose and in the next dose cohort of 28 mg/m^2. Two of 7 patients with a next dose level of 40 mg/m^2 experienced DLTs. A traditional 3 + 3 would stop the trial and declare the MTD to be 28 mg/m^2. However, the adaptive Bayesian logistic regression model allowed recruitment of additional patients to 40 mg/m^2, given that the probability of a true DLT rate above 33% was less than 0.25, as estimated by the model. Additional cohorts were then enrolled at a dose of 40 mg/m^2 without observing additional DLTs. Subsequently, the dose was escalated to 54 and 70 mg/m^2, at which point the final RP2D was declared and an observed DLT rate of 8.7% was observed (2 DLTs in 23 evaluable patients).

In this example, dose escalation was guided by an adaptive Bayesian logistic regression model, while the decisions to continue recruitment at 40 mg/m^2 and subsequently escalate to the final RP2D of 70 mg/m^2 were made by incorporating information from biomarker, pharmacokinetics/pharmacodynamics, and tumor response as measured by CT and PET scans from all dose levels at each decision point. The adaptive/Bayesian methods (e.g., refs. 19–21) can easily accommodate dose change based on other integrated information, addition of new doses, and change of cohort size, while maintaining acceptable statistical properties.

Example 2. In a dose-escalation phase I study of continuous oral treatment with MK-2206, MK-2206 was administered on alternate days in 28-day cycles to fasting patients in 5- and 25-mg tablets (22). The study used a two-stage design. The first stage followed a standard 3 + 3 design. Cohorts of 3 to 6 patients were to be treated at preplanned dose levels of 30, 60, and 90 mg on alternate days. The second stage employed a modification of the toxicity probability interval method (23, 24).

In stage 1, dose escalation proceeded through alternate-day dose levels of 30, 60, and 90 mg. Four of 7 patients receiving a dose of 90 mg experienced DLTs. In stage 2, an intermediate dose of 75 mg ($n = 3$) was evaluated, with DLTs observed in 3 patients at this dose level. An additional 3 patients were then enrolled at a 60-mg dose on alternate days to confirm the safety of this dose level, with no additional DLTs observed. Fourteen patients were then enrolled in an expansion cohort at the alternate-day MTD that mandated paired tumor biopsies for detailed biomarker studies.

The toxicity probability interval method is a model-based dose-finding design that is as simple, transparent, and intuitive as the algorithm-based design but possesses good small and large sample statistical properties. It can be easily adapted to accommodate dose change based on other integrated information, dose insertion, and change of cohort size.

These two examples demonstrate single-agent dose-escalation approaches, but designs such as those discussed above can be easily extrapolated to the combination setting (25), an increasingly important area of focus in the treatment of cancers. In the combination space, the incorporation of single-agent data is critical to efficient dose escalation, and the risk from potential drug–drug interaction (DDI; both due to pharmacokinetic-DDI or safety interaction known from preclinical studies or combinations of similar classes of compounds) can be built into the respective models or decision framework (26). In this setting, a range of combination RP2Ds may be determined for study in expansion groups or subsequent phase II dose-ranging studies.

A common criticism for adaptive/Bayesian model–based approaches is their complexity, including the requirement of experienced statistical support to be available for the design, execution, and reporting of the phase I study or that the designs appear more like a black box to investigators who are uncertain about the reason a dose is considered acceptable. Here, the onus is on the statistical community to do better in communicating these approaches, removing much of the statistical jargon and putting summaries into a clinical framework; "posterior risk for the true DLT rate to exceed the DLT threshold" can be rephrased as "risk of overdose" or "risk of being above MTD." Similarly, ensuring that decisions are seen as a combination of clinical and statistical justification, e.g., BLRM defines a window of potential doses, lower-grade/later-cycle adverse events narrow the window further, and modeling of pharmacokinetics, pharmacodynamics, and/or pharmacokinetics–pharmacodynamics relationships then help focus on whether we should use the upper boundary of that window or a lower dose.

An additional concern reflects the sample size for adaptive studies, seemingly taking more patients than traditional 3 + 3 designs in a number of cases. Traditional approaches use few patients to answer just one question on cycle 1 DLT rates, though generally leading to poorly estimated MTDs requiring subsequent dose finding in phase II (see the following section) or major risk to a development program. Adaptive/Bayesian designs allow us to answer many of the critical early development questions in a single trial without the need for multiple amendments, mitigating the risk of dose changes in late development and possibly reducing overall cost, and accelerating the speed to a development program.

Approaches for dose-ranging phase II trials

In the 3 + 3/MTD approach, the important dose-ranging clinical trials have not been performed routinely. Thus, development occurs in an abbreviated manner, assuming that the MTD achieves the maximum benefit in patients with cancer.

The main goal of a phase II dose-ranging clinical trial is to identify the recommended phase III doses, ideally based on comprehensive understanding of the dose/exposure–response

relationship for efficacy and safety. Understanding the dose/exposure–response relationship and identifying the appropriate dose for phase III clinical trials are probably the most critical, and yet most challenging, components of the clinical development program for a new therapy. Inappropriate dose selection for these trials can result in unacceptable toxicity or adverse events when the chosen dose is too high or insufficient evidence of effectiveness when it is too low. Even when evidence of effectiveness/safety is shown for a selected dose, inadequate knowledge of the dose–response relationship often provides little evidence about its relative value with regard to other doses.

Despite these important goals, phase II dose-ranging trials have often been designed using a very small number of doses narrowly focused on the upper end of the dose–response relationship due to an MTD-oriented phase I dose-escalation trial. The emphasis of this type of phase II trial has been on hypothesis testing, rather than on estimation: The *P* values corresponding to comparisons of the different doses to control are used to drive dose selection (i.e., the smallest dose that is statistically significant from control). Multiple comparison methods often play an important role in this pairwise comparison hypothesis-testing context.

As a change from the hypothesis test approach for dose selection, phase II dose-ranging trials following model-based estimation approaches that are focused on understanding and properly characterizing the dose–exposure response may be more useful. Although many methods have been described, we briefly introduce one, multiple comparison procedures and modeling (MCP-Mod; ref. 27), which has received a positive qualification opinion from the European Medicines Agency Committee for Medicinal Products for Human Use (28).

To account for the inherent model uncertainty involved in this type of estimation (which could lead to overfitting and other inferential issues, if not taken into consideration), a dose-finding method combining multiple comparison procedures and modeling is used. The first step (MCP step) of MCP-Mod, characterizes the prior knowledge, or lack thereof, about the true underlying dose–response relationship through a set of candidate model curves. The candidate models are translated into optimal model contrasts that are applied to the observed data to produce a multiplicity-adjusted test of dose–response signal (i.e., any of the candidate shapes corresponding to a statistically significant signal). This is a different type of hypothesis test procedure than the pairwise comparisons to control mentioned earlier. Although the latter controls the type I error for claiming effective (acceptable) doses, the former controls the type I error for dose–response signal detection.

If a statistically significant dose response signal is established in the MCP step of MCP-Mod, the approach proceeds to model-based estimation of a target dose (or doses). The model families (e.g., Emax family) corresponding to the significant models in the MCP step are fitted to the observed data. Then, either the best-fitting model (selected according to model-fitting criteria, such as AIC or BIC) or a model average estimate of the dose–response profile (derived from the fitted models) is used to estimate the dose, producing a target effect, if one exists (e.g., MED, ED_{90}). The model-based estimation can also produce confidence intervals for the selected dose and its corresponding expected effect.

Through extensive simulation studies, MCP-Mod has shown superior performance when compared with ANOVA-like approaches based on pairwise comparisons of doses to control, and it has comparable, or better, performance when compared with alternative model-based dose-finding approaches, such as Bayesian model averaging and nonparametric modeling (29, 30).

Conclusions

The historical approach to the development of oncology products of selecting the MTD as the recommended dose, often using the 3 + 3 algorithm, is not optimal for many contemporary oncology drugs.

The tension between speeding up drug development and taking time in dose finding is real. Because of the life-threatening nature of the disease (cancer), some drug toxicity is acceptable if the drug shows promising efficacy; thus, speed in making a drug available at an effective dose can take precedence over identifying the optimal dose. However, it is possible to improve overall efficiency in dose finding without slowing down overall development. We offer suggestions on how to streamline the drug discovery and development process by identifying the correct dose early.

An integrated approach, which synthesizes nonclinical data, including animal efficacy and toxicity data, with clinical data, including pharmacokinetics/pharmacodynamics data, dose–response and dose–toxicity relationship, and safety data from multiple cycles that potentially incorporate long-term and delayed toxicities is needed. Such an appropach can be expected to improve dose selection in oncology drug development, allowing the benefits and risks of a drug to be better understood earlier. Exposure–response analysis for both efficacy and safety should be routinely conducted to identify the target therapeutic window, and then dose(s) should be selected that produce exposures within the target range (31).

Model-based methods, which could incorporate all information in phase I and/or phase II trial designs, should generally be used. The 3 + 3 design, which does not adequately use this information, should be replaced with advanced model-based adaptive/Bayesian approaches that have better statistical properties. We highlight the importance of conducting phase II dose-ranging trials to identify the recommended dose(s) for registration trials. The implementation requires collaboration with experts from all disciplines and effective communication, so that all information can be translated into good statistical modeling and inferences. The communication should occur through the whole process of dose finding, rather than only in planning and conclusion phases. To facilitate this communication and collaboration, the description of model-based analysis, including Bayesian/adaptive designs, should be made as simple as possible.

It is generally recognized that appropriate doses should be identified before approval. However, in some scenarios, specifically in cases where there is a significant unmet medical need and the drug is safe and efficacious at the tested dose, the optimization of doses could be carried further into the post-approval setting.

For further discussion on dose finding in clinical trials, refer to the other articles in this *CCR Focus* section (32–34) and refs. 26 and 35.

Disclosure of Potential Conflicts of Interest

A. Roy has ownership interest in Bristol-Myers Squibb. No potential conflicts of interest were disclosed by the other authors.

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