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Dose Finding in Late-Phase Drug Development

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Abstract

A drug may fail or raise concerns that must be addressed in later-phase trials because of an unacceptable toxicity profile, even if the drug meets expectations for efficacy. The problem could be due to the late onset of unacceptable toxicities that were not observed in early-phase trials. We explore methodologies to find appropriate doses in situations where a drug meets the primary efficacy objective but concerns about toxicity remain. In this manuscript, we propose a general framework to design a good phase IV trial that is designed to optimize the treatment regimen. In the first step, we learn from the existing data about the dose-response and dose-toxicity relationships and further to explore and establish the relationship using a statistical model. Noting the limitations of the exploratory analyses, these analyses are not sufficient to allow us to make definitive conclusions. However, the prediction obtained from the model, either estimated efficacy metrics or safety parameters for some doses, can be incorporated in the design of the phase IV trial. In the second step, we further propose and compare design options, including options that could effectively incorporate information from these exploratory analyses, for clinical trials to find optimal doses, including trials to fulfill postmarketing commitments or requirements.

Keywords

dose-response, dose-toxicity, Bayesian design, marginal structure model

Introduction

The primary objective of earlier-phase clinical trials (eg, phase I or II) in oncology is to identify the recommended doses for pivotal or registrational clinical trials, ideally based on nonclinical data, pharmacokinetics (PK) / pharmacodynamics (PD), toxicity, and preliminary evidence of efficacy. However, these early dose-finding trials are often abbreviated, with the goal of identifying the maximum tolerated dose (MTD) in a phase I trial, the highest dose with an acceptable risk of toxicity, and possibly followed by a phase II trial of the treatment at the MTD aiming for regulatory approval.[1]

In later-phase trials, unacceptable toxicity may be observed that was not observed in early-phase trials due to late onset of toxicity events. If a drug has favorable efficacy and late onset of unacceptable toxicity, then it is critical to find the right dose in development so that the risk and benefit can be adequately balanced. For example, Ponatinib is a tyrosine kinase inhibitor indicated for the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia and chronic myeloid leukemia. Ponatinib (45 mg) was approved by FDA on December 14, 2012, as a treatment of adult patients with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia and who are resistant or intolerant to prior tyrosine kinase inhibitor therapy, or Philadelphia chromosome-positive acute lymphoblastic leukemia and who are resistant or intolerant to prior tyrosine kinase inhibitor therapy. Approval was based on the results observed in a single-arm trial. Ponatinib dosing was reduced or interrupted in most of the patients in this trial due to adverse events. The Sponsor voluntarily suspended marketing of the product from October 31, 2013, to December 18, 2013, due to a high percentage of vascular occlusive events, leading to questions about whether the studied and approved dose of 45 mg was the optimal dose. Similar dose reductions and discontinuations occur in clinical trials of many other drugs, for which additional trials were conducted to fulfill postmarketing commitments or requirements to find optimal doses.

Here we explore methodologies to find the appropriate dose after a drug meets the primary efficacy objective in late-phase testing. In this manuscript, we propose a general framework to design a good phase IV trial that aims to optimize the treatment regimen. In the first step, we learn from the existing data about the dose-response and dose-toxicity relationships through a novel graphic tool and further to explore and establish the relationship using a statistical model. We will discuss some

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exploratory tools to learn from available data about the dose-response and dose-toxicity relationship. These tools include graphic illustrations of the dose-response and dose-toxicity relationship, as well as model-based exploratory data analyses to establish dose-response and dose-toxicity relationships. Noting the limitations of the exploratory analyses, these analyses are not sufficient to allow us to select the optimal regimen. However, the prediction based on the relationship obtained from the model can be used and the estimation can be incorporated in the design of the phase IV trial. In the second step, we further discuss some design options for various different purposes and the results demonstrate that some options which incorporate the prediction has major advantages. Exploring these options is especially important, because although many trials were conducted to fulfill post-marketing commitments or requirements to find optimal doses, most of them were not able to achieve the goal because of inadequate design or inadequate study power. We expect that this new framework could significantly improve the trial design.

This paper is organized as follows: we first discuss the Ponatinib case study as background and then present graphical illustrations of daily dose use for all patients enrolled in a hypothetical trial and briefly discuss some exploratory analyses. Then we discuss how the results obtained from the exploratory analyses may be integrated into future trials and when they are appropriate.

Background

Ponatinib is a tyrosine kinase inhibitor indicated for the treatment of patients with chronic myeloid leukemia or Philadelphia chromosome–positive acute lymphoblastic leukemia who have been unable to tolerate prior tyrosine kinase inhibitor therapy or whose cancer is resistant to prior tyrosine kinase therapy. Ponatinib was approved on December 14, 2012, under accelerated approval regulations based on the objective response rate observed in a single-arm trial of Ponatinib administered at a daily dose of 45 mg. However, 59% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy. The commercial sponsor voluntarily suspended marketing of the drug on October 31, 2013, because at least 27% of Ponatinib-treated patients had adverse events, including fatal and life-threatening myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. The high percentage of vascular occlusive events raised the question of whether the daily dose of 45 mg was appropriate. During the marketing suspension, Ponatinib was made available to more than 400 patients through emergency and single-patient investigational new drug (IND) applications, which were reviewed and approved by the FDA on a case-by-case basis.[2]

On December 19, 2013, Ponatinib marketing was resumed with the modification of the indication. However, the commercial sponsor was required to conduct postmarketing trials to evaluate whether a lower dose could achieve similar efficacy with less toxicity. The data from the phase II trial PACE,[3] supported by the phase I dose escalation trial[4] (both included in the initial marketing application), provide some information of the dose-response relationship.

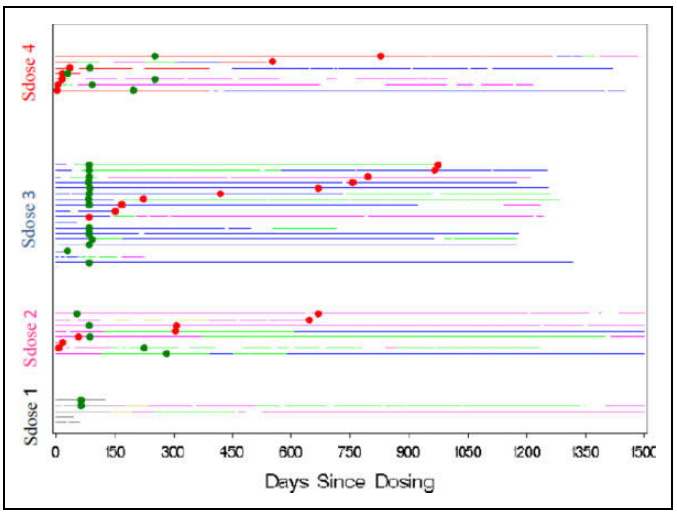

Figure 1. A typical plot of daily dose use for all patients enrolled in a trial with time of response and the first occurrence of a toxicity event. (Lines: red = starting dose 4 [40 mg]; blue = starting dose 3 [30 mg]; magenta = dose 2 [20 mg]; grey = starting dose 1 [10 mg]; green = reduced dose between doses 2 and 3 [25 mg]; orange = reduced dose between doses 1 and 2 [15 mg]). A red dot represents occurrence of a toxicity event and a green dot represents response occurrence.

Exploratory Analyses

Our exploratory analyses mainly consist of 2 parts: graphical presentation of the data and exploratory data analysis to establish dose-response and dose-toxicity relationships. We will discuss the usefulness and limitation of these tools, acknowledging the need for further research.

Graphical Presentations of Dose Reduction, Response, and Toxicity

In our proposed graphical presentation, as shown in Figure 1 for a plot of an illustrative phase I dose finding trial, we plot detailed information about the daily dose of all patients enrolled in the trial, time when objective response was observed, and time when a toxicity event of specific interest for each patient occurred. The code is available from the first author upon request.

In Figure 1, each horizontal line represents the daily dose level of a single patient. For each line, the time at which a response was observed (green dots) and when a specific toxicity event was first observed (red dots) are shown. The x-axis is time in days since the start of treatment and y-axis is the identity of all patients. Lines are colored according to the starting dose, or an intermediate dose that represented an increase to achieve greater efficacy or a decrease to achieve tolerability. Plots are sorted by starting doses from the lowest to the highest and within each dose by time to the first toxicity event of interest.

In the patients, there is increasing toxicity with increasing dose levels. The patient represented by the first horizontal line from below (patient 1) started at the lowest dose, and stopped the treatment at day 60, without response or a toxicity event. Patient 4 started with the lowest dose (starting dose 1) and responded on day 65. The dose for this patient was increased to the next level but eventually was changed to starting dose 2, and this patient did not experience toxicity. Eight patients started starting dose 2 represented by magenta line, the majority of whom achieved response and experienced toxicity. However, most of these toxic events were not observed before doses were further escalated to a higher dose level (starting dose 3, green line), and then to the highest dose level (starting dose 4, red line) in the trial. Patients that were receiving starting dose 4 experienced the most toxicity events and many of their toxicity events occurred rapidly, and dose reductions occurred quickly or the treatment was stopped. In the dose 3 cohort, although the response rate was high, the toxicity event rate was also high. Note that a symbol could be added to the graph to indicate that subjects were censored for any specific event.

Similar plots could also be used to illustrate dose reduction, together with time to efficacy and toxicity, of an experimental treatment versus matching placebo in randomized blinded trials. See Figure A1 in the appendix as one example.

The graphic tools presented above are useful to explore the dosing pattern and its relation to response and toxicity including late onset of toxicity. By sorting the graph by variables of interest, for example, predictive variables, we may further link the predictive variables to dose change, dose-response, and the dose-toxicity relationship. This tool is for exploratory purposes, to visualize the data and to generate hypotheses.

Exploratory Data Analyses: Methods, Challenges, and Limitations

The characterization of dose-response relationships plays an important role for successful drug development. Using the data from multiple doses presented in Figure 1, we further explore the dose-response and dose-toxicity relationships.

One can explore the relationship using the starting doses without considering the dose reduction and modification. Because of the lack of randomization (eg, in the phase I dose escalation trial), confounding factors can exist. Some confounding factors are not measured, which are thus hard to deal with because of the lack of randomization. Some other confounding factors exist, such as age and baseline disease characteristics. Consistent with our experience with the data analyses in the dose-response and dose-toxicity relationship, therapeutic benefits are generally smaller than differences in baseline characteristics[5] in early-phase clinical trials. We may perform model-based exploratory analysis by including likely confounders measured at baseline into the models using methods such as regression analysis as well as propensity score methodologies. The limitations of this method are that (1) the method cannot include unmeasured confounders and (2) some response and toxicity outcomes may not be directly caused by the starting dose but by the following dose after a dose change.

Another method is to calculate the posttreatment doses including the average and total dose in each patient and then explore the relationship between the doses and response and/or toxicity. Sophisticated methods are needed to deal with the time-dependent confounders,[5] and as pointed out by Robins and colleagues, traditional regression models "may fail to adjust appropriately for confounding due to measured confounders"[6] when the dose is time varying. The failure is due to the fact that the traditional regression model cannot deal with time-dependent relationship between cumulative or average doses and response and/or toxicity for the following reasons, as Robin et al have explained.[6] On one hand, these time-dependent confounders are confounders of the later doses, dose response, and toxicity. Thus, the traditional regression model must adjust these time-dependent confounders by including them as regressors. On the other hand, these time-dependent confounders are affected by earlier doses, and thus they should be considered as "outcomes" of earlier doses. A traditional regression model cannot include these "outcomes" as regressors.[6] A more appropriate method, such as the marginal structure model (MSM), could be used to deal with the complication.[3,6] In addition to the likely confounders measured at baseline, this method incorporates potential time-varying confounders, such as blood pressure, neutrophil counts, platelets counts, and glucose levels.

MSMs can adjust for time-dependent confounding factors through inverse probability weighting. However, MSMs do not control for potential unmeasured confounders. In addition, because a large number of covariates are involved, extreme weights may be obtained and these extreme weights may lead to the unstable estimation of treatment effect. As an additional limitation, the selection of time points used to calculate the weights and models selected is considered exploratory in nature, because the time points are generally identified in a post hoc fashion.

Through these exploratory analyses, we are able to establish the dose-response and dose-toxicity relationships, which allow us to predict the efficacy and safety of a particular dose. For example, we could predict the objective response rate of a specific dose with estimated standard error.

A general question to be answered here is how we can efficiently make use of the existing data to design a future trial to identify an optimal dose. One approach is to generate appropriate prior information for the doses using a Bayesian approach.

We next consider designing a confirmatory trial integrating the information obtained from the exploratory analyses.

Clinical Trial Designs for Dose Finding After Phase 2 Trials

Consider a scenario where a response rate of 50% in a single-arm trial was observed when a high dose of an experimental

drug A was administered. Suppose drug A at the high dose also contributed to an unfavorable toxicity event at an unacceptable high rate of 30%. Because of the high response rate observed, it is worthwhile to conduct an additional randomized trial to compare a lower dose of drug A with the high dose used in the single-arm trial to see if the lower dose is associated with a reduced rate of toxicity. Although the following discussion of options for designs in this scenario focuses on comparing 2 doses, the methods can be generalized to compare more doses.

For ease of presentation, we assume that we are interested in making an inference for one binary efficacy endpoint representing response and one safety endpoint representing toxicity. Let y_{ij} be the total numbers of responses ($j = e$) and toxicity events ($j = t$) from n_{ij} subjects included in the high ($i = 1$) and low ($i = 0$) dose groups, respectively. We assume that $y_{ie} \sim Binomial(n_{ie}, p_{ie})$ and $y_{it} \sim Binomial(n_{it}, p_{it})$ for $i = 0, 1$.

In all the designs, an important consideration is that the 2 endpoints may not occur at the same time. For example, some safety signals may occur much later than the efficacy outcome. Thus, the design should take the appropriate follow-up time into consideration.

Design Option 1

Consider a design in which patients are randomized to the high- and low-dose arms and there are 2 co-primary endpoints, response rate and toxicity rate, and the plan is to test non-inferiority of the low dose vs high dose with respect to response and superiority of the low dose vs high dose with respect to toxicity:

$$H_{0e}: p_{0e} \le p_{1e} + \delta_e \text{ vs } H_{1e}: p_{0e} > p_{1e} + \delta_e$$
$$H_{0t}: p_{0t} = p_{1e} \quad \text{vs } H_{1t}: p_{0t} > p_{1t}$$

Here δ_e is the non-inferiority margin for the efficacy endpoint and p_{0e}, p_{1e}, p_{0t}, p_{1t} are the response rates in the low- and high-dose groups and the toxicity rates in the low- and high-dose groups, respectively. The results obtained from the exploratory data are used to set the assumptions for p_{0e}, p_{1e}, p_{0t}, p_{1t} and calculate the sample size.

This design may be preferred when we believe (based on the exploratory analysis of available data) that the low dose leads to a relatively good response compared to the high dose and is less toxic than the high dose. This scenario would apply, for example, when the efficacy plateaus at a low dose level; therefore, increasing the dose does not increase the efficacy but increases toxicity.

Suppose the exploratory analysis of existing data suggests that the high dose is superior to the low dose with respect to efficacy. In this scenario, we may consider an alternative design to test superiority of the high dose versus the low dose in response and non-inferiority in toxicity

$$H_{0e}: p_{1e} = p_{0e} \quad \text{vs } H_{1e}: p_{1e} > p_{0e}$$
$$H_{0t}: p_{1t} > p_{0t} + \delta_t \text{ vs } H_{1t}: p_{1t} < p_{0t} + \delta_t$$

(where δ_t is the non-inferiority margin for toxicity).

Using this design, the required sample size could be very large, as the trial includes a non-inferiority component. The design is based on a frequentist approach for confirmatory trials and does not make use of the large amount of information obtained in previous trials. As an alternative, a Bayesian trial design integrating the existing information may be considered. For the above scenario, if we consider a Bayesian trial, which uses information obtained from the previous exploratory analyses, the power greatly improves and sample size can be significantly reduced as illustrated in the next section.

Design Option 2: A Bayesian Approach

Based on the existing data and exploratory analyses, p_{ik}(k=e, t) can be estimated with $\hat{p}_{ik}$, and let the standard error of the estimate be s_{ik}. These estimates and standard errors will be used to construct prior distributions for the parameters in the models.

Assuming that $\hat{p}_{0e}$ and $\hat{p}_{1e}$ are independent, and assuming that $\hat{p}_{0t}$ and $\hat{p}_{1t}$ are independent, we generate the informative prior $Beta(\alpha_{ik}, \beta_{ik})$ for p_{ik}. The calculation of α_{ik}, β_{ik} is based on the following relationship:

$$\hat{p}_{ik} = \frac{\alpha_{ik}}{\alpha_{ik} + \beta_{ik}};\ \hat{s}_{ik}^2 = \frac{\alpha_{ik}\beta_{ik}}{(\alpha_{ik} + \beta_{ik})^2(\alpha_{ik} + \beta_{ik} + 1)}$$

Given potential differences between the early-phase trials and the new trials, discounting the information, for example, $100\pi\%$ information obtained from the exploratory data analyses can be considered. For example, discounting the information obtained by $100\pi\%$, α_{ik}, β_{ik} can be calculated using

$$\hat{p}_{ik} = \frac{\alpha_{ik}}{\alpha_{ik} + \beta_{ik}};\ (1-\pi)\hat{s}_{ik}^2 = \frac{\alpha_{ik}\beta_{ik}}{(\alpha_{ik} + \beta_{ik})^2(\alpha_{ik} + \beta_{ik} + 1)}$$

When $\hat{p}_{0e}$ and $\hat{p}_{1e}$ are not independent or $\hat{p}_{0t}$ and $\hat{p}_{1t}$ are not independent, the dependence structures will need to be considered, but the details are beyond our scope here.

A major advantage of the Bayesian approach is its use of existing information. As a result, the sample size needed for the trial may be greatly reduced. Please refer to Joseph et al[7] for some examples as to the magnitude of sample size reduction that can be achieved.

Although the Bayesian approach is attractive with its ability to borrow information from previous trials, designs of such trials are necessarily more complex in, for example, sample size calculation. In addition, setting the prior distribution could be controversial: different people may have different opinions on how the prior distribution should be set up and on how much information we could actually borrow from the existing trials. Further research and discussion are needed to make the Bayesian approach easily accessible.

Note that the randomization ratio may depend on the prior information that is available for the high and low doses.

Design Option 3: Benefit and Risk Analysis

In this design, we may test the efficacy endpoint against a threshold that is minimally clinical meaningful,

$$H_{0ie}: p_{ie} = p_e \text{ vs. } H_{1ie}: p_{ie} > p_e$$

Any arm i that fails to reject H_{0ie} will be considered a failure. If null hypotheses are rejected in both arms, that is, the response rate in both arms demonstrate efficacy, we shall use a benefit-risk analysis to find a better dose between them.

Benefit-risk analysis can be done using a frequentist or Bayesian approach. In our cases, the benefit and risk analysis will assess the responses as the efficacy endpoint and a specific toxicity event as the toxicity endpoint. Design and analyses for the benefit-risk analysis are substantially discussed in early phases for dose finding based on efficacy and toxicity.[7-13] These analyses can also be used in the confirmatory trials as a tool for benefit and risk analysis.

This design can give a relatively quick assessment of the benefit: risk of reasonable doses in an exploratory manner. The major advantage is that this trial can be done with a smaller sample size.

The trial with this design is exploratory in nature and the goal could be hypothesis generation. In addition to the planned benefit and risk analysis, an integrated approach can take into consideration all the available data (including nonclinical data, PK/PD, dose-response, safety, and earlier clinical data) and choose the appropriate dose for further testing and confirmation.

Concluding Remarks

We propose a general framework to design a good phase IV trial that is designed to optimize the treatment regimen. In step 1, we proposed and illustrated exploratory tools to learn from existing data and to establish a dose-response relationship. When late-onset toxicity occurs, some ideas presented in the predicted-risk-of-toxicity method, modified EM algorithm, and Bayesian data augmentation[14-16] may be utilized. In step 2, we illustrate some options for clinical trial designs to confirm the safety and efficacy results of selected doses for further investigation. Although we expect that our proposed designs will improve design for post marketing commitments or requirements to find optimal doses, we acknowledge their limitations and call for further research.

Our proposed Bayesian approach integrates data mostly from late-phase clinical trials (eg, phase IIb or phase III). However, we caution against the use of a naïve approach, and for the Bayesian approach, we note 2 important considerations: First, because previously conducted trials may be very large, the information derived from the exploratory analyses could be substantial. If one were to use all the information to derive the prior, the software may suggest that a very small sample size is needed in the confirmation trial. As a consequence, the existing information can drive the final results even if the results are different in the confirmatory trial. In this situation, we recommend appropriately adjusting the sample size by discounting the information obtained from the existing data. There should be a balance between the existing information and information to be collected in the prospective study. Second, the Bayesian approach to borrow information from existing trials is straightforward when the sources of the existing data are "similar," for example, in terms of trial conduct and the standard of health care. If trial conduct, for example, risk management and dose reduction/modification, and the knowledge base and standard of care is expected to be different in the future, then the role of Bayesian design and how one should determine priors for parameters could be controversial and challenging. Further research is warranted. As one reviewer suggested, these issues may be mitigated by utilizing power priors[17] and commensurate power priors approaches.[18] The amount of borrowing, for both methods, would be determined by the similarity between the existing and the newly obtained data.

This paper is motivated by drugs with a large proportion of patients who experienced dose reductions, discontinuations, or severe adverse events during the clinical trials. It highlights a major problem in the current oncology drug development. For further understanding of the problem and potential solutions, the readers are also referred to the discussion of the best practice in oncology drug development in the FDA-AACR workshop http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Pages/dose-finding-of-small-molecule-oncology-drugs.aspx.

When step 1 is applied to early-phase clinical trials including phase I and II trials, the results could be utilized to help with designing phase III clinical trials including biomarker selection and potential enrichment.

Appendix

Figure A1 illustrates another example from a randomized blinded trial of an experimental treatment versus matching placebo. The color green represents a higher dose of treatment or matching placebo and pink reduced dose. The graph is sorted by time to first reduction/interruption of treatment. It is visible that treatment arm experienced much more dose reductions than the control arm.

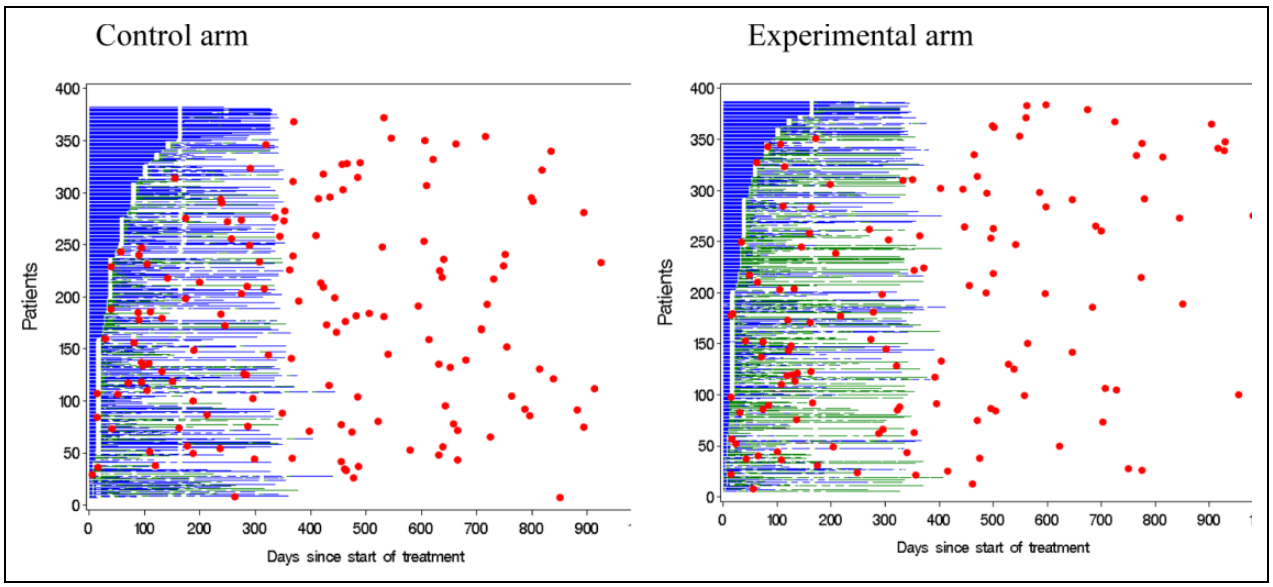

Figure A1. Illustration of dose changes and time to toxic events (red dot) for all patients enrolled in a trial.

Author Note

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

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Declaration of Conflicting Interests

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