Abstract: Historically, phase II trials in oncology generally had a single-arm design, constructed to distinguish between a tumor response rate felt to indicate a lack of promise (often 5%) and a rate that would indicate potential benefit (often 20%), with a one-sided type I error rate of 5% to 10% and a type II error rate of 10% to 20%. The dominant use of this design was based on the premise that an agent that could not produce a tumor response rate of 20% was not likely to produce a clinically meaningful overall survival (OS) or progression-free survival (PFS) benefit in subsequent phase III testing. Recent trends in oncology drug development have challenged this paradigm. Many phase II trials are now designed to assess the promise of a molecularly targeted agent, given either alone or in combination with another regimen. In many cases these agents are not anticipated to produce or improve tumor response rates; rather the desired outcome from their use is improved PFS or OS through means other than direct cell killing as evidenced by tumor shrinkage. In general, PFS is the preferred end point for such phase II trials, as it is more statistically efficient than OS (because it is substantially shorter and the treatment effect is not diluted by salvage treatment). However, in a situation with no effective salvage therapy and/or a disease with concerns regarding the timing of progression assessment, OS could be chosen as the endpoint. We have reviewed the history and evolution of the phase II trial over the past 50 years, in particular, in oncology trials. This review is not meant to be exhaustive, but rather to cover the primarily used designs in self-contained detail, in such a manner as to provide a primer for the young investigator and reminders for the more experienced.

Keywords: Phase II trial, phase II/III trial, randomized phase II trial, randomized screening trial, randomized selection design trial

Submitted Dec 10, 2013. Accepted for publication Jan 07, 2014.
doi: 10.3978/j.issn.2304-3865.2014.02.02
View this article at: http://dx.doi.org/10.3978/j.issn.2304-3865.2014.02.02
Introduction

Phase II studies follow phase I studies, which determine a safe dose of an agent or regimen (1). The objective of a phase II study is to determine whether the new agent or combination regimen has sufficiently promising biologic activity to warrant further (definitive) testing in a phase III study, which establishes clinical efficacy. Historically, it was believed that biologic activity would vary primarily by tumor type, and, therefore, phase II studies were restricted to a particular histology or closely related set of histologies (the uncommon exception being a study of loosely related rare histologies). This is beginning to change, as molecular characteristics, such as driver mutations and molecular pathway defects become therapeutic targets (2). In addition, to maximize the likelihood of seeing biologic activity in the initial phase II studies of an agent, the patient population should be restricted to those with favorable performance status and minimum prior chemotherapy (2). If there is effective standard therapy available for patients, it is sometimes medically justifiable to postpone it and treat patients first with one or two test courses of the experimental agent, utilizing a so-called “window of opportunity” design. After an agent proves its activity in a population with favorable prognostic characteristics, it may undergo further testing in a less favorable population.

In this paper, we outline the history and development of the phase II trial (as used, in particular, in studies of anti-cancer agents and regimens) over the past half century, attempting to elucidate the primary problems addressed and solutions proposed, so as to provide a primer for young investigators and an overview for the more experienced. Many phase II trial designs have been proposed which have, as yet, failed to achieve common use, and this paper is not meant to be an exhaustive review. For a more comprehensive review of current and prior work relating to phase II trials, please see Green (3), Mariani and Marubini (4) and Thall and Simon (5), and, to further understand the phase II trial within the context of clinical testing in phase I, II and III, please see Simon (2).

Single-armed phase II designs

In the late 1950s, there were few effective agents against most forms of cancer, with most proposed agents proving of no benefit. At that time, therefore, the primary role of the phase II trial was to screen out, as quickly as possible, with the least number of patients exposed, clinically ineffective agents (6). This required a short-term endpoint, indicative of clinical benefit and minimally affected by selection bias (the potential for particularly promising patients to be favored in accrual to the trial). Tumor shrinkage was almost universally chosen as the relevant endpoint in this setting. Such trials also required a statistical design that exposed the minimum number of patients to ineffective agents. It was generally considered that a tumor response rate less than 20% was not clinically promising, and in 1961 Gehan (7) suggested that a run of 14 patients with no response was the minimum number necessary to establish with 95% confidence that the true response rate of the agent did not attain the 20% threshold. (In other words, if the true response rate were at least 20%, there would be at least a 95% likelihood of seeing at least one response among 14 patients.) In this case, the trial would be terminated and declared negative. The standard form of Gehan’s design dictated, further, that if at least one response were observed among the initial 14 patients, then an additional 11-16 patients would be treated, to enable estimation of the response rate with a 95% 2-sided confidence interval spanning approximately the observed response rate plus or minus 0.10 (A 95% 2-sided confidence interval of response rates has the following property. In an ideal situation, if we repeat the same experiment under the exact same conditions, we will observe 95% of the time that the interval contains the true response rate).

As effective anti-cancer agents were identified in the 1960s and 1970s, it became apparent that a more comprehensive phase II statistical approach was required, since the Gehan design gave little guidance concerning how to designate an observed response rate as promising or unpromising, nor did it allow for limiting the probability of making an error in such a designation. In 1982, Fleming (8) proposed a 2-stage design that involved prospectively defining the minimum response rate (called $p_o$) that was sufficiently promising that the investigators would wish to recommend, with high probability, further testing of the agent or combination, and, likewise, the maximum response rate ($p_p$) that was sufficiently discouraging that the investigators would wish to recommend, with high probability, no further testing. Furthermore, the design allowed for limiting both the “type I error”, of calling an agent promising if the true response rate was no more than $p_o$, and the “type II error”, of calling the agent not promising when the true response rate was at least $p_p$. The design required that the total sample size of the two stages ($n_o + n_p$) be sufficiently large so that when the investigators designated the minimum number of responses ($r_o$) necessary for declaring the agent worthy of further testing, the study...
would have the following property: the probability of a false positive (that the number of responses would be at least $r_1$ when the true response rate was no more than $p_0$) and the probability of a false negative (that the number of responses would be less than $r_2$ when the true response rate was at least $p_1$) satisfied the desired type I and type II error bounds, respectively. Finally, the design provided for early stopping after approximately half the patients ($n_1$) had been accrued, if the results were dramatically positive or negative. This required designating bounds $r_1$ and $a_1$ such that if the number of responses among the initial $n_1$ patients was at least $r_1$ or at most $a_1$, the trial would be terminated early and declared positive or negative, respectively. The positive and negative bounds $r_1$ and $a_1$ were chosen to be sufficiently extreme so that the early stopping option had a minimal effect on the type I and type II error rates, which would be obtained from a one-stage trial of $n_1 + n_2$ patients.

Table 1 provides an example of a Fleming 2-stage design to distinguish between response rates of $p_1 = 20\%$ and $p_2 = 5\%$, with type I and type II error rates of 5\% and 8\%, respectively. The total sample size is $n_1 + n_2 = 40$, and the final threshold value for declaring the trial positive is $r_2 = 5$ responses (12.5\%). Interim stopping occurs at $n_1 = 20$ patients if the number of responses is $a_2 = 0$ or at least $r_2 = 4$ (20\%). We see that these bounds are sufficiently extreme so that the operating characteristics of the 2-stage trial are essentially identical to what they would be without the possibility of early termination.

In 1989, Simon (9) optimized Fleming’s 2-stage design as follows. He suggested that early stopping not be allowed for dramatically positive results, in the interest of achieving more precise estimates of the response rate by accruing to the full sample size in these cases. He also suggested that since most phase II trials were negative, it was appropriate to choose a design that minimized the average sample number (ASN) under the null hypothesis (response rate equal to $p_0$). More precisely, the Simon optimal design is the 2-stage design that minimizes the ASN under the null hypothesis, while maintaining the desired type I and type II error bounds. Such designs are easy to determine, based upon exact binomial calculations, with today’s high-speed computers, and there is a website available to derive them (http://linus.nci.nih.gov/brb/samplesize/otsd.html). Simon optimal designs are to this day considered the standard single-armed phase II design. Table 2 gives designs for four commonly chosen pairs of $p_0$ and $p_1$, with type I and type II error rates set at 0.10 (a standard choice). Based on Table 2,
the approximate characteristics shared by the designs are that early termination occurs for response rates less than \( p_0 \), which occurs with approximately 0.55-0.65 probability under the null hypothesis, and that the trial is declared positive for response rates that are observed at the halfway point between \( p_0 \) and \( p_1 \). Simon (9) also gives an alternative 2-stage “minimax design”, which minimizes the total sample size required to achieve the targeted type I and type II error bounds. In general, the total sample size of the 2-stage minimax design will be the same as the required sample size of the corresponding 1-stage design, although there are instances where the 2-stage minimax design actually requires one patient less than the corresponding 1-stage design, due to the discreteness of the binomial distribution and the greater flexibility of the 2-stage design. Simon (9) indicates that there are situations where the minimax design may be preferred over the optimal design, in particular, where the patient population is rare and the anticipated accrual rate is low.

In choosing an appropriate 2-stage design to use, study investigators have two sets of decisions to make. First, they have to define an appropriate \( p_1 \) and \( p_0 \). In cases where there are few, or no effective therapies, \( p_1 \) is generally chosen to be 20%, the conventional lower bound for a promising response rate. However, where there are a number of effective therapies available, \( p_1 \) may be set at 30-40%, or higher. In particular, if the phase II trial involves a combination, \( p_1 \) should be set 10-20% (in absolute terms) higher than what would be attainable with the most active component of the combination. The choice of \( p_0 \) is dictated by the practical necessity to keep the phase II trial relatively small. This means, in general, setting \( p_0 \) equal to \( p_1 - 20\% \) (the exception is setting \( p_0 \) to 5% when \( p_1 \) is set to 20%). The second set of decisions involves setting the desired type I (alpha) and type II (beta) error bounds. Common practice is to set both alpha and beta equal to 0.1, since it is generally accepted that in phase II trials, false negative results (which may result in termination of development of a useful agent) are at least as serious as false positive results, which result in wasted time and resources at the phase III level (2). However, in testing agents against solid tumors, where, unfortunately, a large percentage of new agents prove ineffective, many investigators prefer to use an alpha of 0.05, with a beta of either 0.1 or 0.2 (1).

There have been several extensions of the Simon 2-stage design proposed to handle special situations. In 1995, Bryant and Day (10), appreciating the need, in certain cases, for consideration of toxicity issues beyond the phase I trial setting, proposed a design that rejects the new agent if either the response rate is inadequate, or the toxicity is excessive. This design, in particular, allows for limiting accrual to the first stage if the toxicity proves excessive. In 2001, Sargent et al. (11) extended the Simon design to one for which it was possible to formally acknowledge that the response rate fell into an intermediate “borderline” zone for which other considerations were applied to determine whether or not the new agent deserved further testing. A further advantage of this design is that it reduces the required sample size for a given target response difference and given type I and type II error bounds, compared to the Simon design. Also in 2001, Dent et al. (12) proposed a dual-endpoint two-stage design that rejects a new agent if either the response rate is inadequate or the early progression rate is excessive. Analogous to the Bryant and Day design, this design allows for limiting accrual to the first stage if the early progression rate is excessive. Finally, in 2012, appreciating that certain modulating agents were not expected to (necessarily) improve tumor response rate when combined with standard therapy, but were expected to improve progression free survival, Sill et al. (13) proposed a dual-endpoint two-stage design that, in a sense, complemented that of Dent et al. This design allowed for recommending further investigation of an agent that either increased response rate or increased progression-free survival, while allowing for terminating accrual at the first stage if it was already clear that neither improvement was achieved; a characteristic of this design is that it required only modestly greater sample size than a single endpoint design with comparable statistical operating characteristics.

**Use of historical controls**

The recent rapid evolution in oncology drug development has challenged the previously accepted practice of relying on single-arm phase II trials with a tumor response rate endpoint. Many phase II trials are now designed to assess the promise of a molecularly targeted agent, given either alone or in combination with another regimen. In particular, it is not always anticipated that such agents will produce or improve tumor response rates, rather it may be expected that such agents will improve PFS or OS through means other than direct cell killing as evidenced by tumor shrinkage. In addition, for many diseases, such as lung, colon, breast, and renal cancers (14-16), tumor response has failed to predict for a survival benefit, and for other diseases, such as glioblastoma and prostate cancer, tumor response has proven difficult to measure. Finally, recent papers have
demonstrated that even with the use of standard cytotoxic therapy, patients without a tumor response benefit from superior therapy (17).

Based on these considerations, in general, PFS has become in many cases the preferred endpoint for such phase II trials, since it is more statistically efficient than OS (because it is significantly shorter and the treatment effect is not diluted by salvage treatment). For diseases with very short median OS and lack of effective salvage treatment, or where PFS cannot be reliably measured, OS may be a preferred endpoint, even in the phase II setting (18). Such trials can potentially be single-arm studies, with an endpoint of median PFS or OS, or PFS or OS may be measured at a particular time point, and then compared to that of historical controls. There are some strong reasons why statisticians and clinicians historically have favored comparisons with historical controls (over concurrent randomized controls) in phase II trials. Perhaps the strongest reason is statistical efficiency. If there is high confidence that the historical data concerning PFS or OS accurately represent what would be expected of the experimental group if treated in the standard manner, then evaluating the results with an experimental agent or regimen can be done with half the patients or less, by using historical controls rather than concurrent randomized controls. This is true even if there is not access to individual patient historical data, but only the median survival, or if the number of patients in the historic series is limited. In 1982, Brookmeyer and Crowley (19) gave methodology for comparing against historic data, and calculating the required sample size, when only the median survival is available. In 2006, Korn and Freidlin (20) showed how the approach of Rubinstein et al. (21) (who gave methodology for calculating the required sample size for randomized studies using the logrank statistic) could be extended to single-armed studies compared against historical controls, if the patient data are available.

However, the most significant concern with using historical controls to assess PFS or OS in a single-arm phase II trial of an experimental treatment is that the historical controls may not fairly represent the expected outcome of the experimental patients, if given standard treatment. In other words, the historical control patients may be inherently inferior or superior in terms of expected PFS or OS, due to differences with respect to at least three factors. First, the expected outcomes for standard of care may change over time, due to improvements in supportive care, earlier detection, differences in radiological assessment techniques, greater availability of second line therapy (if the endpoint is OS), or other reasons. Second, the inter-institution variability in outcomes has been shown to be large in many settings, thus if the new trial enrolls patients from different institutions, or in a different ratio from the same institutions, the historical data may be inaccurate. Finally, the patients on the new trial may differ from the patients in the historical studies due to differences in prognostic factors. If the important prognostic factors associated with clinical outcome in the patient population can be identified, this last problem may be partially addressed, as demonstrated by Korn et al. (22) in 2008. Using a large meta-analysis of melanoma patients treated on phase II studies, Korn et al. identified the important prognostic variables and their contributions to one-year OS and six-month PFS rates, as well as to the survival distributions for either time-to-event endpoint. This allowed them to construct tests of the observed one-year OS and 6-month PFS rates, or of the respective observed survival distributions, associated with a single-armed test of an experimental regimen, adjusting for the particular mix of prognostic factors in the experimental population. However, even in a detailed meta-analysis of individual patient data, the proportion of variability in outcomes explained by the observed covariates may be limited, which may limit the applicability of this approach.

**Randomized studies**

For several decades, there has been increased interest in randomized designs for phase II studies in oncology. An increasing number of new agents are biologic or molecularly targeted, and thus are anticipated to yield increased PFS or OS but not necessarily increased tumor shrinkage, alone or, more likely, in combination with standard regimens. PFS or OS is affected by patient characteristics (not always identifiable) which may vary between a new experimental sample and historical control patients. In addition, there is a strong argument for randomization for studies in which the endpoint has been collected differently or inconsistently in the past or is absent from historical data sets. For instance, this could be an endpoint which includes biochemical measures, such as PSA progression in prostate cancer. On the other hand, for some diseases it may be more difficult to accrue patients to a randomized study compared to a non-randomized study at the phase II stage of drug development. Also, in rare disease settings accrual is a challenge. Randomized designs generally require as much as four times as many patients as single-arm studies.
with similar theoretical statistical operating characteristics. Therefore, there has been a series of attempts to develop randomized designs that offer some protection against the uncertainties and potential biases of single-armed studies, while retaining some of the statistical efficiency.

In 1985, Ellenberg and Eisenberger (24) proposed randomizing a portion of the patients to a small reference arm. The experimental arm would not be compared to the reference arm; it would be analyzed against historical controls as if it were a single-armed study. The reference arm in this design was intended to only act as a check on the similarity of the current patients to the historical controls with respect to clinical outcome when given the standard treatment. The disadvantages of this approach are that the reference arm is too small for its outcome to truly assure comparability for the experimental group, since there is little power to reliably detect a moderate but clinically meaningful lack of comparability. If, in this design, the reference arm has outcome substantially different from that expected based on historical controls, it is difficult to interpret the outcome of the experimental arm. If the reference arm does very poorly compared to controls, an apparently negative outcome for the experimental arm may be due to inferior prognosis for the patients. Conversely, if the reference arm does very well compared to controls, an apparently positive outcome for the experimental arm may be due to superior prognosis for the patients. This is a generic problem with attempting to incorporate a randomized control arm into a phase II trial that is not large enough to allow for direct comparison, to reduce the associated cost in increased sample size.

In 1986, Herson and Carter (23) proposed randomizing the initial phase II stage is operating at the 0.50 significance level. This is a generic problem with randomized phase II/III designs; see also Goldman, LeBlanc and Crowley (28).

Selection designs

There is one context in which the use of a randomized phase II design can achieve its statistical objectives while maintaining a relatively small sample size; this is the case of directly comparing multiple experimental regimens, primarily for the purpose of prioritizing among them for subsequent phase III testing against a control. In 1982, before randomized phase II designs became popular, Simon et al. (29) formalized such pick-the-winner selection designs, where the regimen with the superior observed response rate (by any amount) was chosen, among the two or more compared, for further testing. The original designs were constructed to yield 90% power to detect the superior regimen if the true difference between the response rates was at least 15% (in absolute terms). The weakness in the original design was that it did not assure that the (sometimes nominally) superior experimental regimen was superior to standard therapy. It was occasionally argued that an ineffective experimental regimen could act as a control arm for the other regimen, but the design was not constructed to be used in this way, since, as designed, one of the two or more experimental regimens would always be chosen to go forward, even if neither was superior to standard treatment. To address this, in 2006, Liu, Moon and LeBlanc (30) proposed that each arm of the selection design be constructed as a single-armed two-stage design, to be compared separately against a historically defined response rate, a practice which is now often followed. However, that approach requires that it be possible to compare the experimental regimens to historical controls; this, as we have argued above, is not always the case.

Where the randomized phase II selection design is appropriate, it can be conducted with modest sample size. For example, Simon et al. (29) demonstrated that only 29-37
Table 3 Randomized phase II selection design trial: number of patients per treatment arm required to give 90% power to correctly select* a treatment yielding response rate 15% higher than the highest of the other arms

<table>
<thead>
<tr>
<th>Superior response rate</th>
<th>Number of treatments to be randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Two</td>
</tr>
<tr>
<td>25%</td>
<td>21</td>
</tr>
<tr>
<td>35%</td>
<td>29</td>
</tr>
<tr>
<td>45%</td>
<td>35</td>
</tr>
<tr>
<td>55%</td>
<td>37</td>
</tr>
<tr>
<td>65%</td>
<td>36</td>
</tr>
</tbody>
</table>

*, In this design, the treatment with the highest response rate is assigned the highest priority for further testing, regardless of how small the difference in response rates is, compared to the other treatments.

Table 4 Approximate required numbers of observed (total) treatment failures for screening trials with PFS endpoints, using the logrank test

<table>
<thead>
<tr>
<th>Error rates</th>
<th>Hazard ratios (Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ=1.3</td>
</tr>
<tr>
<td>(α,β) =(10%,10%)</td>
<td>382</td>
</tr>
<tr>
<td>(α,β) =(10%,20%) or</td>
<td>262</td>
</tr>
<tr>
<td>(20%,10%)</td>
<td></td>
</tr>
<tr>
<td>(α,β) =(20%,20%)</td>
<td>165</td>
</tr>
</tbody>
</table>

Note: calculations were carried out using nQueryAdvisor 5.0 software (Statistical Solutions, Saugus, MA, USA) based on methods given in Collett (36) with 1-sided α.

patients per arm will yield 90% power to detect a regimen that has response rate superior by 15% in a two armed study (see Table 3 for examples of selection designs). In 1993, Liu, Dahlberg and Crowley (31) demonstrated that this approach can be adapted to randomized phase II trials with time-to-event (PFS or OS) endpoints, where the logrank test is used to choose between the two regimens, yielding comparably small sample size requirements. Rubinstein et al. (21) show that the required sample size for such trials is proportional to \((z_α + z_β)^2\) where \(z_α\) and \(z_β\) are the standard normal values associated with the type I and type II error bounds, respectively. This means that if the type I error is set to 0.5 (\(z_α =0\)), as it is for the selection design, then, compared to a randomized study with \(z_α = z_β =0.1\) (which is standard for phase 2 designs) with the same targeted hazard ratio, the sample size is reduced by a factor of 4. This means that selection designs constructed to detect a hazard ratio of 1.5 with 90% power are generally similar in size to the original selection designs constructed to detect a response rate difference of 15% with 90% power.

Randomized phase II screening design

None of the randomized phase II designs described above fully addressed the problem outlined in the beginning of Section “Randomized studies”—the increasing need in oncology to evaluate agents that are anticipated to increase PFS or OS, but not objective tumor response, primarily in combination with standard regimens, where comparison to historical controls may be problematic. The reference arm and phase II/III designs have serious disadvantages, as outlined, and the selection design is meant for the limited situation where experimental regimens are to be compared for prioritization purposes, but, in general, each must also prove itself against historical controls. For this reason, in 2005, Rubinstein et al. (32), building on previous work by Simon et al. (33) and Korn et al. (34), [and similarly to Fleming and Richardson (35)] formalized the randomized phase II screening design. The intention was to define randomized phase II designs that yielded statistical properties and sample sizes appropriate to phase II studies. These designs were meant to enable preliminary comparisons of an experimental treatment regimen, generally composed of a standard regimen with an experimental agent added, to an appropriate control, generally the standard regimen.

Table 4 illustrates the statistical properties of such designs when the endpoint is PFS (or OS), and the logrank test is used. The table provides the required numbers of failures for various type I and type II error rates appropriate to phase II trials, and for various targeted hazard ratios. In general, it is expected that phase II studies will be conducted in patients with advanced disease, where most patients will progress within the trial period, so the required number of failures closely approximates the required number of patients. In the setting of the randomized trial, the usual limits for type I and type II errors may be relaxed; in fact, usage of type I error of 0.20 may be considered in exceptional cases, in particular, in the context of rare disease subgroups. It can also be noted that restricting the trial to a total sample size of no greater than approximately 100 patients restricts the targeted hazard ratio to be at least 1.5.

Table 5 illustrates the statistical properties of such designs
Table 5 Approximate required numbers of total patients for screening trials with PFS rate (at a specified time) endpoints, using the binomial test

<table>
<thead>
<tr>
<th>Error rates</th>
<th>PFS rates (with equivalent hazard ratios)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20% vs. 20%</td>
</tr>
<tr>
<td>(α,β) = (10%,10%)</td>
<td>256</td>
</tr>
<tr>
<td>(α,β) = (10%,20%)</td>
<td>184</td>
</tr>
<tr>
<td>or (20%,10%)</td>
<td></td>
</tr>
<tr>
<td>(α,β) = (20%,20%)</td>
<td>126</td>
</tr>
</tbody>
</table>

Note: calculations were carried out using nQueryAdvisor 5.0 software (Statistical Solutions, Saugus, MA, USA) based on methods given in Fleiss et al. (37) with 1-sided α.

when the endpoint is PFS rate, measured at a pre-specified time point, and the binomial proportion test is used. The table provides the required numbers of patients for various type I and type II error rates and for various targeted PFS rate differences (with the equivalent hazard ratios). The table demonstrates that the binomial proportion test, in general, is statistically inefficient compared to the logrank test. In fact, for the same targeted hazard ratio, the comparison of PFS rates at a particular time point requires approximately twice as many patients. Comparing PFS at a particular time point rather than across the entire survival curve means that restricting to a total sample size no greater than approximately 100 patients restricts the targeted hazard ratio to be at least 1.75. Nevertheless, comparing PFS at a pre-specified time is often done since PFS is often considered to be an endpoint that is difficult to measure, potentially subject to investigator bias, or influenced by differential follow-up between the treatment arms.

It must be emphasized that a randomized phase II study should almost never be taken as definitive evidence for the superior efficacy of an experimental agent or regimen. Rubinstein et al. (32) and Fleming and Richardson (35) suggest that the P-value must be less than 0.005 or smaller (a standard cut-off for phase III interim monitoring) for the phase II trial to preclude the necessity for conducting a definitive phase III successor study. Liu et al. (38) demonstrate that small randomized phase II studies can yield substantial false positive rates as well as substantially exaggerated estimated treatment effects. Moreover, as argued by Redman and Crowley (39), in settings where adequate historical controls exist, historically controlled phase II studies are more efficient than randomized studies.

Randomized discontinuation design

An interesting variant of the randomized phase II design, proposed by Rosner et al. (40) in 2006, is the randomized discontinuation design, which initially treats all patients with the study agent for a defined time period, and then randomizes patients with stable disease to continuation or discontinuation for a defined period to assess the effect of the drug in a population of presumably responsive and more homogeneous patients. In 2007, Freidlin and Simon (41) argued that in many settings this design is less efficient than a standard randomized study, due to the large number of patients who must be treated initially, and thus a large number of patients may be unnecessarily exposed to a potentially non-efficacious treatment. On the other hand, they also showed that for the case where a non-identifiable subgroup of patients derives benefit from the treatment, this design may be useful. However, an additional problem with this design is that it may be difficult to define an appropriate population for further study in the event the trial is positive.

PFS vs. OS in randomized phase II studies

An important concern in the design of randomized phase II studies is whether the primary endpoint should be progression-free survival (PFS) or overall survival (OS). There are significant advantages to using PFS, rather than OS, as the primary endpoint in randomized phase II studies. Time-to-progression is shorter than time-to-death, sometimes substantially, so that the PFS endpoint yields more failures and thus greater power for the logrank test. Hazard ratios for PFS are generally greater than for OS, and PFS treatment differences, unlike OS differences, are not diluted by the effects of salvage treatment, both phenomena yielding greater power for the logrank test. Finally, a positive phase II result based on PFS is less likely to complicate randomization to the definitive phase III study than a positive phase II result based on OS. There are, however, also significant disadvantages to using PFS as the primary endpoint. Sometimes PFS is difficult to measure reliably. There may also be concern that evaluation of the endpoint is influenced by investigator treatment bias or differential follow-up by treatment (if the control patients are followed more or less vigilantly, this may bias the observed time of progression). In some cases, the issues of bias can be addressed effectively by blinding the study. If this is not possible, at least the bias associated with differential follow-up can be addressed by using a
Comparison based on PFS rate at a pre-specified time, rather than using the logrank test. However, as we have demonstrated in Section “Randomized phase II screening design”, this results in substantial loss of statistical efficiency. In 2007, Freidlin et al. (42) addressed this problem by proposing a statistic based on comparing the two treatment arms at two pre-specified time points. They demonstrated that this approach, which also promises to minimize bias due to differential treatment follow-up, recovers most of the efficiency lost in comparison to the logrank test.

Discussion

The increased use of randomized phase II trials has been recommended by European (43,44) and American (32,45) investigators over the past decade, particularly for trials of experimental agents combined with standard regimens, with PFS as the endpoint. An international task force (46) recommended that in “select circumstances”, randomized phase II studies of targeted anticancer therapy are “helpful to define the best dose or schedule, or to test combinations”, but single arm phase II studies continue to be appropriate “when the likely outcomes in the population studied are well described”. In a recent editorial, Ratain et al. (47) took a stronger position, strongly recommending that randomized phase II trials “become a standard approach in oncology, especially for the development of drug combinations.”

The promotion of randomization is already having dramatic effect in the increase in the number of randomized phase II trials. A primary reason for this increase is the appreciation, in the trial design and review process, that even a modest upward drift in the historical control PFS can inflate the type I error rate approximately 3-fold (48). For example, a drift from 50% to 55% in the control 4-month PFS rate, when not accounted for, will increase the type I error of a single-arm Simon optimal (9) trial targeting a 70% 4-month PFS from 0.10 to 0.26. Coupled with this is the realization that such an upward drift over time is relatively likely for PFS as standard of care improves (49).

However, it is also widely accepted that a substantial portion of phase II trials will still be appropriately single-arm (49-52). This includes trials of agents for which tumor regression is anticipated based on mechanism of action, as well as early phase II monotherapy trials to establish a tumor response signal of biological efficacy. Additionally, monotherapy and combination trials with PFS endpoints in diseases with no effective standard therapy and established stable historical controls (e.g., recurrent glioblastoma) can be justified. For OS, an historical database for melanoma has proven useful for designing single arm studies (22). In such situations, adjustment for observed differences in the distribution of known prognostic factors between the historical database and the observed single arm study can reduce potential bias and strengthen inferences.

Importantly, expanding the use of randomization to all phase II situations in which it is appropriate will not by itself maximize the positive predictive value of phase II trials (the probability of a positive phase II trial yielding an agent or combination that is effective by phase III standards). This value is dependent not only on the type I error rates of the phase II trials, but also on the rate of effectiveness (according to the phase II endpoint) of the agents and combinations going into phase II trials for the population of interest, as well as the degree to which the phase II endpoints predict the ultimate phase III endpoints. For example, if the type I and II error bounds are both 0.10, then the positive predictive value of a phase II trial will vary between 32% and 61% in the setting in which (I) the collection of agents and combinations tested is effective, with probability varying between 5% and 15%; and (II) the phase II endpoint is a perfect surrogate for the phase III endpoint. Since stipulation (II) is never the case, the positive predictive value may be substantially less.

We therefore propose four potential approaches to maximizing the effectiveness of phase II trials as predictors for phase III success:

(I) The pool of agents and combinations going into phase II testing can be enriched for truly active agents. Enrichment may be possible through the increased use of pharmacodynamic assays in phase I and phase 0 testing (53), allowing for go/no-go decisions prior to phase II testing. Additional single arm clinical data (potentially collected at phase I or phase II) may be helpful for screening agents prior to undertaking randomization.

(II) The subpopulations in which agents and combinations are potentially effective can be better identified so that phase II testing can be limited to such subpopulations. This may be done by increased development and use of pharmacodynamic assays to better characterize the agents (53) and increased development and use of biomarkers to better identify correspondingly sensitive subpopulations of patients (51,52).

(III) Phase II endpoints that capture and predict a substantial percentage of the treatment effect...
reflected in the ultimate phase III endpoints can be identified, established, and used (51,54). Such endpoints, including new imaging endpoints, may vary by class of agent and by disease (55,56).

(IV) Even if the approaches listed above are only modestly successful in enriching the pool of phase II agents and combinations so that they are effective, with probability varying between 20% and 40%, the positive predictive value of phase II trials (to reflect true efficacy according to the phase II endpoints) could be increased to between 69% and 86%. How well these phase II trials would then predict phase III efficacy would depend upon the proportion of the phase III treatment effect captured by the phase II endpoint. However, in situations in which the above approaches are not so successful in enriching the pool of phase II agents and combinations, conducting phase II trials at the 0.05 (rather than the 0.10) significance level should be considered. In this way, even if the agents and combinations are effective, with probability varying between 10% and 20%, according to the phase II endpoint, the positive predictive value of phase II trials to reflect true efficacy according to the phase II endpoints would vary between 67% and 82%.

In conclusion, phase II trial design is currently a critically important and evolving area of research, due to the central and growing importance of phase II trials, and there are a number of current issues which we mention here, without elaboration, due to constraints of space. (I) For multi-arm, phase II trials, a number of authors have proposed outcome-adaptive randomization (weighting the randomization, as the trial proceeds, in favor of the arms with superior outcomes) and “borrowing information” across arms (altering the measured outcomes of individual arms by incorporating the results of arms with similar outcomes). Korn and Friedlin (57,58) discuss both of these approaches and cast doubt on their utility; (II) As the use of molecularly targeted therapy increases, the appropriate patient subgroups may become small, creating challenging statistical situations. Korn et al. (59) review the associated problems and potential solutions, with particular relevance to phase II trials; (III) The importance of biomarkers, both prognostic and predictive, is increasing, as a result of the increased use of molecularly targeted therapy. McShane et al. (60) review the problems and potential solutions associated with incorporating biomarkers into phase II trials.

Acknowledgements

Disclosure: The author declares no conflict of interest.

References


44. Van Glabbeke M, Steward W, Armand JP. Non-randomised phase II trials of drug combinations: often meaningless, sometimes misleading. Are there alternative

Cite this article as: Rubinstein L. Phase II design: history and evolution. Chin Clin Oncol 2014;3(4):48. doi: 10.3978/j.issn.2304-3865.2014.02.02