Review

A review of perspectives on the use of randomization in phase II oncology trials

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Abstract

Historically, phase II oncology trials assessed a treatment's efficacy by examining its tumor response rate in a single-arm trial. Then, approximately 25 years ago, certain statistical and pharmacological considerations ignited a debate around whether randomized designs should be utilized instead. Here, based upon an extensive literature review, we review the arguments on either side of this debate. In particular, we describe the numerous factors that relate to the reliance of single-arm trials on historical control data, and detail the trial scenarios in which there was general agreement on preferential utilization of single-arm or randomized design frameworks, such as the use of single-arm designs when investigating treatments for rare cancers. We then summarize the latest figures on phase II oncology trial design, contrasting current design choices against historical recommendations on best practice. Ultimately, we find several ways in which the design of recently completed phase II trials does not appear to align with said recommendations. For example, despite advice to the contrary, only 66.2% of the assessed trials that employed progression-free survival as a primary or co-primary outcome used a randomized comparative design. In addition, we identify that just 28.2% of the considered randomized comparative trials came to a positive conclusion, as opposed to 72.7% of the single-arm trials. We conclude by describing a selection of important issues influencing contemporary design, framing this discourse in light of current trends in phase II, such as the increased use of biomarkers and recent interest in novel adaptive designs.

Keywords: Cancer; Progression-free survival; Screening; Selection; Single-arm; Tumor response.

Abbreviations: MTA: Molecularly targeted agent; PFS: Progression-free survival.

Classical phase II oncology trial design

The classical paradigm of oncological drug development comprises three phases of clinical trials. In phase I, a treatment's toxic effects are assessed and the recommended dose(s) for subsequent trials determined. Phase II provides the first assessment of a regimen's efficacy, with success typically resulting in a confirmatory phase III trial being conducted. Phase II trials thus play a pivotal role, providing the principal evidence for deciding whether to carry out a large phase III trial. The consequences of an incorrect decision at this time can be far-reaching: halting the development of an effective regimen could deprive future patients of a valuable treatment option, whilst continuing to develop a futile regimen could waste substantial resources. Accordingly, the optimal approach to conducting phase II trials has received much attention.

Historically, given the scarcity of effective anti-cancer agents in the 1950s, the accepted perspective was that phase II should act as a screening process to efficiently weed out inactive regimens [1,2]. For this, a short-term surrogate endpoint for long-term clinical benefit was required. A binary tumor response indicator, later formally defined via RECIST [3], became the endpoint of choice [2]. Furthermore, Gehan offered in 1961 a design that would long remain the primary approach to phase II oncology trial design [1]. Based upon the belief of the day that a response rate of less than 20% was not promising, he recommended that 14 patients be recruited and observed for tumor response. If no response was observed, this would ascertain with 95% confidence that the true response rate was below 20%. With at least one response observed, a second stage of recruitment and observation would be conducted to accurately estimate the true response rate.

Unfortunately, Gehan's design provided no guidance on whether the observed response rate was clinically meaningful. Consequently, as the number of available effective oncology drugs increased during the 1970s, phase II trials shifted to demand a higher standard of evidence of potential clinical benefit [2]. The prevailing techniques for achieving this were Simon's two-stage single-arm designs [4], which were constructed to allow a formal hypothesis test to be conducted on the tumor response rate. Simon's designs, like Gehan's, experienced a sustained period of time as the preferred approach in phase II. Thus, unlike in many disease settings, phase II cancer trials were traditionally non-randomized. Moreover, they almost all used tumor response as their primary outcome [5]. By the mid-1990s, however, questions over the optimality of this convention began to arise.

In this article, we focus on these questions, in particular examining opinions on the role of randomization in phase II. To provide a comprehensive overview of this subject, we base our discourse on a completed narrative literature review (see **Supplementary Methods and Supplementary Tables 1-5** for details on this review). We proceed by describing one of the primary reasons for the now evident changes in phase II design. We then discuss the arguments put forth for and against the use of randomization, along with the real-world evidence and statistical investigations that complicate this debate. Our discourse then turns to consider the current design of phase II oncology trials, and how such design aligns with past opinions on best practice. We conclude by highlighting current issues that are likely to influence changes in the design of future phase II trials.

Changing phase II design: molecularly targeted agents suggest a new paradigm is needed

Arguably the principal driver of change in phase II oncology trial design was the advent of molecularly targeted agents (MTAs). Classic anti-cancer agents were cytotoxic, thus it was considered reasonable to assess their efficacy via their ability to shrink tumors, and the fact that tumors do not typically spontaneously shrink meant many accepted the lack of a randomized comparator arm. However, it was anticipated that the new MTAs may often be cytostatic; delaying tumor progression, rather than leading to tumor shrinkage [6,7]. Accordingly, it was feared that the use of tumor response as a primary endpoint may lead to many novel regimens, which do increase clinical benefit, being rejected from further consideration [8-11]. Thus, it was contended that a new approach was required in phase II for cytostatic agents.

Initially, the proposed approaches varied greatly, with some authors even suggesting that phase II be skipped [12]. Unsurprisingly, such suggestions were not widely favored. It was acknowledged that whilst this may seem a desirable means of reducing development plan sample sizes, the ever-rising cost of phase III studies, and the scarcity of available patients to enroll in trials, would make it impossible to test all regimens in this manner [9,13,14]. Further, given a preliminary efficacy assessment could be acquired in phase II using a relatively small number of subjects, it would be unethical to expose large numbers of patients to a regimen for which little evidence of efficacy exists [9].

More reasonably, calls for the use of an alternative primary endpoint in phase II trials of cytostatic agents soon grew [13,15]. In particular, progression-free survival (PFS) was much advocated, as an assessment of time until disease progression would more accurately capture the benefits of cytostatic agents. Furthermore, PFS, it was argued, would be more

efficient to estimate than overall survival and would not be affected by salvage treatment. However, PFS is highly dependent on a disease's natural history. It was thus contended that with this necessary change in endpoint, so came a necessary change in design to utilize randomization [11,16-19]. With this, one of the primary reasons randomization has been advocated for in phase II was apparent.

Arguments for and against the use of randomization in phase II

Along with changes proposed to phase II design because of the rise of MTAs, appeals for the use of randomization no matter the regimen under investigation, or the chosen primary endpoint, also increased. Here, we discuss the arguments for and against randomization that have appeared in the literature, providing an overview in **Table 1**. Note that we concentrate our discussion on randomization as a means to formally comparing treatments using a hypothesis test, as the majority of articles have focused on the use of randomization for this purpose. Thus, for brevity when we now refer to randomized designs, we mean randomized comparative designs. However, many of the following points are also relevant to a debate on the utility of randomized non-comparative designs.

At the center of most discussions on phase II design has been the key assumption of a single-arm trial: the historical controls used to design the current study provide a fair representation of the probable outcome for patients in the new trial, if they were given the same control treatment. Many have noted that due to improvements in the standard of care, earlier detection rates, institutional variabilities, and differences in prognostic factors, only in rare scenarios would historical controls provide such a representation [20-23].

Potential differences in prognostic factors between historical controls and concurrent participants was seen as particularly problematic, as it was well-recognized that unknown prognostic factors can profoundly affect a single-arm trial's error-rates [23,24]. A modelling-based approach was suggested as a possible solution to accounting for such prognostic variables [25]. However, whilst proponents of randomization acknowledged that this could improve upon simple unadjusted comparisons to historical controls, given the majority of inter-individual variability remains unexplained after accounting for all measured predictors [8,16,26,27], they argued that such adjustment procedures were not widely applicable or reliable [20,26]. So too did others note that the desire for a new agent to 'look good' could manifest itself in setting the historical response rate too low [28,29], or the enrollment only of patients who 'look promising' [30]. Each of these problems, it was maintained, would not be an issue in a randomized trial [17,18,20,22-24,26,30-33].

Nonetheless, numerous publications still argued in favor of single-arm designs [23,34-37], claiming that they can be readily utilized given high enough confidence in the historical data [23,34]. A melanoma overall survival database was in particular a heralded means through which successful single-arm studies had been conducted [25]. In addition, those in favor of single-arm designs noted flaws in the supposed advantages of randomization, arguing that the purported ability of randomized phase II trials to balance prognostic factors was an illusion, as the majority of such trials used simple randomization, which would be unlikely to provide balance for typical phase II sample sizes [23,36,38-40]. Moreover, as was feared about single-arm trials, randomized phase II trials could also feature highly selected patients [17], and easily fall foul of differential loss to follow-up or

patient drop-out [41]. As a counterpoint, it was argued that randomization was a better way to handle many sources of bias, and actually the only way to make detection and quantification of imbalances possible [23].

Randomized phase II trials have also been viewed as troubling because of the possibility that investigators will mistakenly treat their results as though they are from a phase III trial [42]; a claim arguably supported by the large number of comparisons performed at the end of non-comparative trials [38]. This though, others claimed, should not be an argument against randomization, and in fact a highly statistically significant p-value from a randomized phase II trial could provide enough evidence for a licensing claim, which is not in general possible from a single-arm study [23].

Perhaps the most common argument against randomizing was its associated cost and complexity, with many fearful of the resultant requisite sample size, the fact that randomized trials can be more complex for patients to understand, and that it may be difficult to find patients willing to be randomized [23,34,35]. This viewpoint was supported by a review that found 27% of conducted randomized phase II studies had encountered 'sizeable problems' [23]. Those in favor of randomization, however, argued that in general randomization would provide more reliable data [8], and since 'you get what you pay for' [33] the increased cost should be accepted [13]. Furthermore, this argument ignored the fact that randomizing in phase II could decrease the cost of a project overall [20,26,43], and that whilst it may seem appealing to utilize single-arm trials to develop drugs quickly, or to allow expedient publication, in the long term we all had more to gain from well-designed, randomized phase II trials [33].

Advocates of randomization further attacked the issue of larger requisite sample sizes by arguing for one-sided hypothesis tests and allowance for increased type-I error-rates [9,14,16,17,20,29]. Given the purpose of phase II is to screen and select, this was claimed to be entirely appropriate [16], and also logical for ethical reasons [17]. As a counterpoint, it was noted that the advantages of increasing error-rates to reduce sample sizes in phase II are negated by the cost associated with conducting more phase III trials with inactive agents. However, pro-randomization researchers contended that some control is better than none and highlighted that the type-I error-rate in single-arm trials is actually unknown [23,26].

Arguments in favor of single-arm designs were also made on ethical grounds, with some desiring to provide all enrolled patients with the experimental regimen [34]. Others, though, stated that randomizing may be more ethical, as the experimental treatment could be inferior [26], contending that in most cases there is equipoise [33].

Several authors were critical of the approach randomization implies about our method of identifying new treatments. Most prominently, Stewart and Kurzrock argued that using randomized designs in phase II to balance for characteristics that might confound efficacy assessment is the antithesis of personalized medicine, and that unless the target required for drug activity is very common or we know for each patient whether their tumor expressed the required target, randomization could produce misleading results [44]. This argument, though, was not logical to all, with it noted that any experienced group of investigators would identify a subgroup of patients with exceptional outcomes within a randomized trial [33].

Finally, it is important to note that deliberations on what should become the typical primary endpoint in a phase II trial have long inter-weaved the debate around randomization; a consequence of a desire for improved endpoints to select treatments upon [10,45-50]. Here, though, we have limited our discussions to our primary interest: the suitability of single-arm designs in phase II. For an in-depth history of endpoints that could be utilized in oncology trials, we refer the reader to Wilson et al. [51].

Practical evidence on the outcome of utilizing randomized or non-randomized designs

Along with the discussions outlined above, several authors have provided evidence on the result of utilizing different design frameworks in phase II, in practice. In particular, much evidence has suggested that the classical approach has contributed to the failure of phase II trials to predict long-term survival benefits. Kola and Landis [52] highlighted that 60% of regimens that had 'promising' activity in single-arm phase II trials failed to demonstrate superiority in phase III. Zia et al. [53] identified that response rates were regularly lower in phase III trials than in their preceding phase II studies. Maitland et al. [54] analyzed all phase II combination therapy trials published in 2001-02 and found that despite 72% being deemed successful, the likelihood that an ensuing trial would demonstrate important effects within 5 years was only 3.8%. Ratain [55] pointed to the extremely low positive predictive value of classical phase II trials. Finally, Vickers et al. [29] identified that 46% of surveyed phase II studies that required historical data, did not cite the source of this data. Even more troubling was their finding that those trials that failed to cite prior data suitably were more likely to declare an agent to be active. For many, this was evidence that a higher bar now

needed to be set for progressing to phase III. The solution to attaining this higher bar, it was

argued, was randomization in phase II [13,17,20,30,33,56].

Complicating the picture, though, were the many results that favored the use of

single-arm designs and tumor response. Goffin et al. [57] identified that higher overall

response rates in phase I and II were predictive of regulatory approval in a range of cancer

types. Moreover, El-Maraghi and Eisenhauer [50] established, in 89 surveyed phase II trials,

higher response rates were predictive of regulatory approval for MTAs. Tsimberidou et al.

[58] noted that of 31 drugs approved in 1973-2006 without a randomized trial, 30 remained

fully approved. Finally, Chan et al. [59], in examining all phase III trials of targeted therapies

against advanced cancers from 1985-2005 and their preceding phase II studies, found that

randomization in phase II was not more likely to lead to a positive phase III result.

Consequently, it was argued that success issues in phase III were not due to the use

of single-arm trials in phase II, but to how these trials were planned and interpreted, and

thus we should focus on conducting high quality single-arm trials [23]. Not all were

convinced by these presentations however [20,60], with Gan et al. [23] in particular noting

that such reviews are biased as many trials are never published, and it is likely that a higher

proportion of randomized phase II trials would be published because of their greater

intrinsic value.

**Statistical investigations of randomized and non-randomized design operating
characteristics**

Thus, arguments for and against classical phase II designs could readily be made based upon the available evidence from design use in practice. Hoping to clarify purely statistical recommendations, several publications have provided quantitative figures on optimal phase II design.

Firstly, Mariani and Marubini noted that the error-rates of single-arm, but not randomized trials, are highly sensitive to the historical control rate assumptions [61]. Baey and Le Deley conducted a similar analysis and argued in favor of randomized designs [62]. Providing a less favorable view of randomization, Sharma et al. [63] re-sampled data from a positive and a negative phase III trial. They considered a variety of endpoints and designs, finding that randomized designs performed better for PFS at predicting a positive result for the positive trial, but that they had a higher false-negative rate for the negative trial.

Taylor et al. [64] compared single-arm and randomized designs using a simulation study. They found that a randomized design of equal size to a single-arm trial made the correct decision more often, and that increasing the sample size was more beneficial to randomized than to single-arm trials. They concluded that in the presence of uncertainty around the historical response rate, and when a larger sample size is possible, a randomized design should be used. Similarly, Tang et al. [65] simulated single-arm and randomized phase II trials using data from a colorectal cancer study. They found that the false positive rate of single-arm trials was 2-4 times higher under modest drift of several considered patient selection factors, but that randomized phase II trials came at a cost of 2-4 times the sample size. They also argued that given enough patients, a randomized design was preferable. Sambucini later came to similar conclusions, having taken a Bayesian approach

to design comparison [66]. However, Pond and Abassi [67], using a simulation study that

modelled numerous potential sources of variability, argued that single-arm and randomized

designs were both warranted in certain circumstances.

Consensus opinions on phase II design

Thus, in spite of much debate, no consensus on the optimal design of phase II trials

emerged. Nonetheless, several areas of general agreement are apparent; being for the most

part described in two articles released following committee discussions [68,69], and in a

table provided by Gan et al. [23]. In particular, it was widely accepted that both single-arm

and randomized designs have a part to play in phase II [23,37,69-71], with it typically agreed

that the number of randomized phase II trials should increase and PFS should become the

conventional endpoint of choice [37].

Most authors believed that single-arm trials were acceptable for single, especially

novel, agents when tumor response was expected [17,19,23,69]. They would also be useful

for rare cancer types, where it may be challenging to enroll enough patients to conduct a

randomized trial [23,34,72], in late disease and salvage settings, and when no standard

treatment exists [68,69]. Additionally, if data suggested a response rate that was

dramatically higher than that for available therapies, we may forego randomization [72].

They could also be logical in, the admittedly rare, situations in which a robust historical

database exists [68].

In contrast, randomized designs would be required for combination therapies, as it

would otherwise be difficult to distinguish the contribution of the experimental agent from

the established component [14,68,73]. They would be needed for time-to-event endpoints [3,17,23,69], when there is a lack of available suitable historical data [9,68,72], or when the target population is unclear or heterogeneous [69,74,75]. However, investigators were cautioned against conducting small randomized trials, with it propositioned that in general we may need to accept an increase in the size of phase II trials [68].

Finally, many papers agreed that alternative endpoints, outside of tumor response, should be given greater consideration, and ultimately be deployed in randomized trials [68,70]. Nonetheless, it was also well-recognized that although they were promising, many alternative endpoints required additional evaluation and validation before they could be utilized as primary outcomes in phase II [76], and thus the choice in practice would often remain between tumor response and PFS.

Figures on the contemporary design of phase II oncology trials

The number of available phase II designs is now extensive, with an overview of many provided by Brown et al. [77]. Consequently, several articles have sought to examine how frequently particular designs have been utilized. Together, they provide evidence that arguments for the increased use of randomization have permeated through to practice. Mariani and Marubini found that of 308 phase II trials published in 1997, only 4 (1.3%) were controlled [5], whilst Stone et al. examined publications in the Journal of Clinical Oncology between 1999 and June 2003 and identified only 23 randomized phase II trials out of approximately 250 studies [16]. However, Rubinstein et al. noted in 2011 that 69 (28%) of the then active National Cancer Institute sponsored phase II trials were randomized [19]. In

addition, Thezenas et al. [78], Ivanova et al. [79], and Langrand-Escure et al. [80] have all since conducted reviews of phase II trials, each identifying a large proportion incorporated randomization.

Here, we focus on re-analyzing the data from Langrand-Escure et al. [80], who examined 557 trials published in three top oncology journals from 2010-2015. In **Table 2** we present an assessment of several design characteristics, by design type: single-arm, multi-arm non-randomized, randomized non-comparative, and randomized comparative studies, which form the main types of design in this dataset. Whilst in **Table 3** we summarize the choice of primary and co-primary endpoints by the type of treatment under investigation. Our analyses reveal several important figures in relation to the aforementioned opinions on best-practice. We provide a summary of these in **Box 1**.

Firstly, against prevailing opinion, a smaller proportion of targeted therapies were tested using randomized comparative designs (13.7%) than cytotoxic therapies (23.1%), and 102 (32.4%) of the single-arm trials were of combination therapies (**Table 2**). Recommendations on the utilization of randomization with PFS appear to have been better heeded, with 47 (66.2%) of the trials employing PFS as a primary or co-primary outcome being randomized comparative. However, 18 (5.7%) single-arm trials had PFS as a primary or co-primary outcome.

The randomized comparative trials on average analyzed approximately three times as many patients (median = 131, IQR = 89, 182) as single-arm trials (median = 43, IQR = 34, 58), exemplifying an ability in many circumstances to overcome concerns around increased requisite sample sizes (**Table 2**). Additionally, though there is evidence that different type-I

error-rates have been used across the four design types (Kruskal-Wallis test, P = 0.04; see **Table 2** and **Supplementary Figures 1-2**), the lower-quartile, median, and upper-quartile values used in the single-arm and randomized comparative trials are equal, suggesting calls for randomized comparative trials to utilize increased error-rates may not have been realized in the way many authors desired.

Importantly, **Table 2** highlights that amongst the trials which reported a conclusion, the analyzed randomized comparative trials less frequently come to positive conclusions (29/103 trials, 28.2%) than single-arm (152/209, 72.7%), multi-arm non-randomized (25/30, 82.3%), and randomized non-comparative trials (39/55, 70.9%). This, in particular, raises concerns over the choice of historical controls, and specification of the hypotheses, in the single-arm trials.

Finally, in **Table 3** we observe that more than 50% of cytotoxic, combination, and targeted therapy trials have utilized either tumor response, PFS, or a dichotomized version of PFS, as a primary or co-primary outcome, with tumor response the most commonly utilized endpoint for all three treatment types. Also, perhaps surprisingly given previous recommendations, tumor response was used more than twice as often as PFS for targeted therapies.

Contemporary factors influencing phase II design

Whilst the use of randomized designs in phase II has increased, an open question exists as to what this has taught us about randomization's applicability, particularly given it does not appear to have improved success rates in phase III [81]. Furthermore, whilst there has been

much interest in the use of novel endpoints, this has not materialized in the way many hoped it would [82]. We may therefore still question whether poor performance in phase III is down to the methods typically used in phase II. Careful design choice in phase II thus remains paramount. In addition, several contemporary articles highlight additional important considerations for future phase II trials.

Firstly, despite historical agreement on the suitability of single-arm designs for rare cancers, whether this should be universally accepted has recently been challenged [83,84]. It has been argued that the field of oncology performs a disservice to patients with rare tumors when we accept medications using inferior levels of evidence. It has also been maintained that whilst randomized trials are difficult to conduct in rare tumors, large randomized trials have been conducted for even ultra-rare tumors, providing reliable results to important questions [83]. Thus, randomization has more to do with our expectations than tumor incidence. Accordingly, we should not accept that randomization is not required for rare conditions. Whether randomization can, and will, be more commonly utilized in rare cancer types remains to be seen.

Moreover, in recent years, there has been increased interest in the use of novel adaptive designs in phase II, such as umbrella and basket designs [85]. How this complicates the debate on the use of randomization, and the preferred primary endpoint, remains unclear. Many of the available adaptive designs applicable in phase II are non-randomized in nature, yet one may expect that adaptation might improve trial efficiency in a way that randomization becomes more feasible. Furthermore, adaptive designs typically require a

primary outcome that can be evaluated quickly. This implies that PFS, which has been much argued for historically, may be difficult to utilize with such designs.

Perhaps most important are considerations around the design of trials that utilize biomarkers, given their evident increased use [80]. It has long been argued that randomization would be needed for biomarker-guided trials, not only as historical data would be unavailable, but also because of the requirement to validate the biomarker as a predictive marker of efficacy [33,86-88]. However, it has been pointed out that conducting randomized trials in pre-specified subgroups with very low frequency biomarkers may be difficult [89], and that randomized assignment may be unnecessary if tumor shrinkage is the primary endpoint, as only predictive factors would be expected to correlate with shrinkage [37].

This debate is further complicated by the emergence of several drugs with extremely high response rates in novel biomarker-guided patient subgroups. Given these remarkable response rates, it has been argued that randomized trials may be unnecessary and unjustifiable on ethical grounds [69,90]. However, it has been noted that this remains an extremely unusual situation [33,89,91]. Thus, only in rare cases would it be unethical to randomize, and we should not let such findings guide our overall development strategy [33,88], with several authors even advocating for randomized designs to be used more often in phase I [88,92]. Nevertheless, Selaru et al. describe a variety of settings in which dramatic activity would be enough to license a monotherapy MTA on the basis of a single-arm trial [93]. So too has Simon et al. described the potential future role of tumor response as a basis for licensing [72]. They emphasize, though, that the utilization of classical phase II designs

remains reliant on the choice of historical controls. Thus, guidelines from regulatory bodies on how to achieve appropriate use of historical comparator groups will be paramount to future trials.

Discussion

Many years have now passed since the beginnings of the debate on optimal phase II oncology trial design and yet it remains a subject of on-going deliberation (see, e.g., Grossman et al. [94] for a recent examination in the context of glioblastoma). Furthermore, whilst this debate has contributed to an increase in the number of randomized phase II trials, phase II design for cytotoxic and targeted therapies remains similar, and we remain without evidence that the use of randomized designs in phase II has improved outcomes in phase III.

Little has changed in terms of the importance of resolving this debate. Accordingly, all new guidance on phase II oncology trial design remains extremely valuable. Such guidance will be key to the effectual design of future studies.

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References

[1] Gehan EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. *J Chron Dis*. 1961;13(4):346–353.

[2] Rubinstein L. Phase II design: history and evolution. *Chin Clin Oncol*. 2014;3(4):48.

[3] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors (RECIST Guidelines). *J Natl Cancer Inst*. 2000;92(3):205–216.

[4] Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989;10(1):1–10.

[5] Mariani L, Marubini E. Content and quality of currently published phase II cancer trials. *J Clin Oncol*. 2000;18(2):429–436.

[6] Markham M. Challenges associated with evaluating the clinical utility of non-cytotoxic pharmaceutical agents in oncology. *J Cancer Res Clin*. 1997;123(11–12):581–582.

[7] Twardowski P, Gradishar WJ. Clinical trials of antiangiogenic agents. *Curr Opin Oncol*. 1997;9(6):584–589.

[8] Stadler WM, Ratain MJ. Development of target-based antineoplastic agents. *Invest New Drug*. 2000;18(1):7–16.

[9] Korn EL, Arbuck SG, Pluda JM, et al. Clinical trial designs for cytostatic agents: Are new approaches needed? *J Clin Oncol*. 2001;19(1):265–272.

[10] Michaelis LC, Ratain MJ. Measuring response in a post-RECIST world: from black and white to shades of grey. *Nat Rev Cancer*. 2006;6(5):409–414.

[11] Morabito A, Di Maio M, De Maio E, et al. Methodology of clinical trials with new molecular-targeted agents: where do we stand? *Ann Oncol*. 2006;17(Suppl 7):128–131.

[12] Mick R, Crowley JJ, Carroll RJ. Phase II clinical trial design for noncytotoxic anticancer agents for which time to disease progression is the primary endpoint. *Control Clin Trials*. 2000;21(4):343–359.

[13] Ratain MJ, Eckhardt SG. Phase II studies of modern drugs directed against new targets: If you are fazed, too, then resist RECIST. *J Clin Oncol*. 2004;22(22):4442–4445.

 [14] Rubinstein LV, Korn EL, Freidlin B, et al. Design issues of randomized phase II trials and a proposal for phase II screening trials. *J Clin Oncol*. 2005;23(28):7199–7206.

[15] Sharma MR, Maitland ML, Ratain MJ, et al. RECIST: No longer the sharpest tool in the oncology clinical trials toolbox. *Cancer Res*. 2012;72(20):5145–5150.

[16] Stone A, Wheeler C, Barge A. Improving the design of phase II trials of cytostatic anticancer agents. *Contemp Clin Trials*. 2007;28(2):138–145.

[17] Cannistra SA. Phase II trials in journal of clinical oncology. *J Clin Oncol*. 2009;27(19):3073–3076.

[18] Mandrekar SJ, Sargent DJ. Randomized phase II trials: time for a new era in clinical trial design. *J Thorac Oncol*. 2010;5(7):932–934.

[19] Rubinstein L, Leblanc M, Smith MA. More randomization in phase II trials: Necessary but not sufficient. *J Natl Cancer Inst*. 2011;103(14):1075–1077.

[20] Ratain MJ, Sargent DJ. Optimising the design of phase II oncology trials: The importance of randomisation. *Eur J Cancer*. 2009;45(2):275–280.

[21] The Protocol Review Committee. Phase II trials in the EORTC. *Eur J Cancer*. 1997;33(9):1361–1363.

[22] Wieand HS. Randomized phase II trials: What does randomization gain? *J Clin Oncol*. 2005;23(9):1794–1795.

[23] Gan HK, Grothey A, Pond GR, et al. Randomized phase II trials: Inevitable or inadvisable? *J Clin Oncol*. 2010;28(15):2641–2647.

[24] Bajorin D. The phase III candidate: Can we improve the science of selection? *J Clin Oncol*. 2004;22(2):211–213.

[25] Korn EL, Liu P-Y, Lee SJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. *J Clin Oncol*. 2008;26(4):527–534.

[26] Buyse M. Randomized designs for early trials of new cancer treatments - An overview. *Drug Inf J*. 2000;34(2):387–396.

[27] Flaherty LE, Liu PY, Unger J, et al. Comparison of patient characteristics and outcome between a single-institution phase II trial and a cooperative-group phase II trial with identical eligibility in metastatic melanoma. *Am J Clin Oncol*. 1997;20(6):600–604.

[28] Thall PF, Estey EH. A bayesian strategy for screening cancer treatments prior to phase II clinical evaluation. *Stat Med*. 1993;12(13):1197–1211.

[29] Vickers AJ, Ballen V, Scher HI. Setting the bar in phase II trials: The use of historical data for determining "go/no go" decision for definitive phase III testing. *Clin Cancer Res*. 2007;13(3):972–976.

[30] Sargent DJ, Taylor JMG. Current issues in oncology drug development, with a focus on phase II trials. *J Biopharm Stat*. 2009;19(3):556–562.

[31] Estey EH, Thall PF. New designs for phase 2 clinical trials. *Blood*. 2003;102(2):442–448.

[32] Ratain MJ, Humphrey RW, Gordon GB, et al. Recommended changes to oncology clinical trial design: Revolution or evolution? *Eur J Cancer*. 2008;44(1):8–11.

[33] Sharma MR, Stadler WM, Ratain MJ. Randomized phase II trials: A long-term investment with promising returns. *J Natl Cancer Inst*. 2011;103(14):1093–1100.

[34] Gehan EA, Freireich EJ. Non-randomized controls in cancer clinical trials. *New Engl J Med*. 1974;290(4):198–203.

[35] Yothers G, Wieand HS, Freireich EJ. Pro/con: Randomization in phase II clinical trials. *Clin Adv Hemat Oncol*. 2006;4(10):776–778.

[36] Redman M, Crowley J. Small randomized trials. *J Thorac Oncol*. 2007;2(1):1–2.

[37] Stewart DJ. Randomized phase II trials: Misleading and unreliable. *J Clin Oncol*. 2010;28(31):649–650.

[38] Lee JJ, Feng L. Randomized phase II designs in cancer clinical trials: Current status and future directions. *J Clin Oncol*. 2005;23(19):4450–4457.

[39] Betensky RA, Louis DN, Cairncross JG. Influence of unrecognized molecular heterogeneity on randomized clinical trials. *J Clin Oncol*. 2002;20(10):2495–2499.

[40] Booth B, Glassman R, Ma P. From the analyst's couch: Oncology's trials. *Nat Rev Drug Discov*. 2003;2(8):609–610.

[41] Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15(5):615–625.

[42] Liu PY, LeBlanc M, Desai M. False positive rates of randomized phase II designs. *Control Clin Trials*. 1999;20(4):343–352.

[43] Van Glabbeke M, Steward W, Armand JP. Non-randomised phase II trials of drug combinations: often meaningless, sometimes misleading. Are there alternative strategies? *Eur J Cancer*. 2002;38(5):635–638.

[44] Stewart DJ, Kurzrock R. Fool's gold, lost treasures, and the randomized clinical trial. *BMC Cancer*. 2013;13:193.

[45] Eisenhauer EA. Phase I and II trials of novel anti-cancer agents: Endpoints, efficacy and existentialism. The Michel Clavel Lecture, held at the 10th NCI-EORTC Conference on New Drugs in Cancer Therapy, Amsterdam, 16-19 June 1998. *Ann Oncol*. 1998;9(10):1047–1052.

[46] Stadler W. New trial designs to assess antitumor and antiproliferative agents in prostate cancer. *Invest New Drug*. 2002;20(2):201–208.

[47] George SL. Selection bias, phase II trials, and the FDA accelerated approval process. *J Natl Cancer I*. 2003;95(18):1351–1352.

[48] Roberts TG, Lynch TJ, Chabner BA. The phase III trial in the era of targeted therapy: Unraveling the "go or no go" decision. *J Clin Oncol*. 2003;21(19):3683–3695.

[49] Dowlati A, Fu P. Is response rate relevant to the phase II trial design of targeted agents? *J Clin Oncol*. 2008;26(8):1204–1205.

[50] El-Maraghi RH, Eisenhauer EA. Review of phase II trial designs used in studies of molecular targeted agents: Outcomes and predictors of success in phase III. *J Clin Oncol*. 2008;26(8):1346–1354.

[51] Wilson MK, Karakasis K, Oza AM. Outcomes and endpoints in trials of cancer treatment: the past, present, and future. *Lancet Oncol*. 2015;16(1):e32–e42.

[52] Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov*. 2004;3(8):711–715.

[53] Zia MI, Siu LL, Pond GR, Chen EX. Comparison of outcomes of phase II studies and subsequent randomized control studies using identical chemotherapeutic regimens. *J Clin Oncol*. 2005;23(28):6982–6991.

[54] Maitland ML, Hudoba C, Snider KL, et al. Analysis of the yield of phase II combination therapy trials in medical oncology. *Clin Cancer Res*. 2010;16(21):5296–5302.

[55] Ratain MJ. Phase II oncology trials: Let's be positive. *Clin Cancer Res*. 2005;11(16):5661–5662.

[56] Seruga B, Ocana A, Amir E, et al. Failures in phase III: Causes and consequences. *Clin Cancer Res*. 2015;21(20):4552–4560.

[57] Goffin J, Baral S, Tu D, et al. Objective responses in patients with malignant melanoma or renal cell cancer in early clinical studies do not predict regulatory approval. *Clin Cancer Res*. 2005;11(16):5928–5934.

[58] Tsimberidou AM, Braiteh F, Stewart DJ, et al. Ultimate fate of oncology drugs approved by the US Food and Drug Administration without a randomized trial. *J Clin Oncol*. 2009;27(36):6243–6250.

[59] Chan JK, Ueda SM, Sugiyama VE, et al. Analysis of phase II studies on targeted agents and subsequent phase III trials: What are the predictors for success? *J Clin Oncol*. 2008;26(9):1511–1518.

[60] Leff R, Andrews M. Predicting success in phase III studies from phase II results: A new paradigm is needed. *J Clin Oncol*. 2008;26(21):3653–3654.

[61] Mariani L, Marubini E. Design and analysis of phase II cancer trials: A review of statistical methods and guidelines for medical researchers. *Int Stat Rev*. 1996;64(1):61–88.

[62] Baey C, Le Deley MC. Effect of a misspecification of response rates on type I and type II errors, in a phase II Simon design. *Eur J Cancer*. 2011;47(11):1647–1652.

[63] Sharma MR, Karrison TG, Jin Y, et al. Resampling phase III data to assess phase II trial designs and endpoints. *Clin Cancer Res*. 2012;18(8):2309–2315.

[64] Taylor JMG, Braun TM, Li Z. Comparing an experimental agent to a standard agent: relative merits of a one-arm or randomized two-arm phase II design. *Clin Trials*. 2006;3(4):335–348.

[65] Tang H, Foster NR, Grothey A, Ansell SM, Goldberg RM, Sargent DJ. Comparison of error rates in single-arm versus randomized phase II cancer clinical trials. *J Clin Oncol*. 2010;28(11):1936–1941.

[66] Sambucini V. Comparison of single-arm vs. randomized phase II clinical trials: A Bayesian approach. *J Biopharm Stat*. 2015;25(3):474–489.

[67] Pond GR, Abbasi S. Quantitative evaluation of single-arm versus randomized phase II cancer clinical trials. *Clin Trials*. 2011; 8(3):260–269.

[68] Booth CM, Calvert AH, Giaccone G, et al. Design and conduct of phase II studies of targeted anticancer therapy: Recommendations from the task force on methodology for the development of innovative cancer therapies (MDICT). *Eur J Cancer*. 2008;44(1):25–29.

[69] Seymour L, Ivy SP, Sargent D, et al. The design of phase II clinical trials testing cancer therapeutics: Consensus recommendations from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. *Clin Cancer Res*. 2010;60(1):186–196.

[70] Adjei AA, Christian M, Ivy P. Novel designs and end points for phase II clinical trials. *Clin Cancer Res*. 2009;15(6):1866–1872.

[71] Rubinstein L, Crowley J, Ivy P, Leblanc M, Sargent D. Randomized phase II designs. *Clin Cancer Res*. 2009;15(6):1883–1890.

[72] Simon R, Blumenthal GM, Rothenberg ML, et al. The role of nonrandomized trials in the evaluation of oncology drugs. *Clin Pharmacol Ther*. 2015;97(5):502–507.

[73] Eskens FALM, Verweij J. Clinical studies in the development of new anticancer agents exhibiting growth inhibition in models: facing the challenge of a proper study design. *Crit Rev Oncol Hemat*. 2000;34(2):83–88.

[74] Rosner GL, Stadler W, Ratain MJ. Randomized discontinuation design: Application to cytostatic antineoplastic agents. *J Clin Oncol*. 2002;20(22):4478–4484.

[75] Freidlin B, Simon R. Evaluation of randomized discontinuation design. *J Clin Oncol*. 2005;23(22):5094–5098.

[76] Dhani N, Tu D, Sargent DJ, et al. Alternate endpoints for screening phase II studies. *Clin Cancer Res*. 2009;15(6):1873–1882.

[77] Brown SR, Gregory WM, Twelves CJ, et al. Designing phase II trials in cancer: a systematic review and guidance. *Br J Cancer*. 2011;105(2):194–199.

[78] Thezenas S, Duffour J, Culine S, et al. Five-year change in statistical designs of phase II trials published in leading cancer journals. *Eur J Cancer*. 2004;40(8):1244–1249.

[79] Ivanova A, Paul B, Marchenko O, et al. Nine-year change in statistical design, profile, and success rates of phase II oncology trials. *J Biopharm Stat*. 2016;26(1):141–149.

[80] Langrand-Escure J, Rivoirard R, Oriol M, et al. Quality of reporting in oncology phase II trials: A 5-year assessment through systematic review. *PLOS One*. 2017;12(12):e0185536.

[81] Monzon JG, Hay AE, McDonald GT, et al. Correlation of single arm versus randomised phase 2 oncology trial characteristics with phase 3 outcome. *Eur J Cancer*. 2015;51(17):2501–2507.

[82] Wahl RL, Jacene H, Kasamon Y, et al. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. *J Nucl Med*. 2009;50(Suppl 1):122S–150S.

[83] Prasad V, Oseran A. Do we need randomised trials for rare cancers? *Eur J Cancer*. 2015;51(11):1355–1357.

[84] Lasch F, Weber K, Chao MM, et al. A plea to provide best evidence in trials under sample-size restrictions: the example of pioglitazone to resolve leukoplakia and erythroplakia in Fanconi anemia patients. *Orphanet J Rare Dis*. 2017;12:102.

[85] Renfro LA, Sargent DJ. Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. *Ann Oncol*. 2017;28(1):34–43.

[86] Ratain MJ. Bar the windows but open the door to randomization. *J Clin Oncol*. 2010;28(19):3104–3106.

[87] Yap TA, Sandhu SK, Workman P, De Bono JS. Envisioning the future of early anticancer drug development. *Nat Rev Cancer*. 2010;10(7):514–523.

[88] Saad ED, Paoletti X, Burzykowski T, et al. Precision medicine needs randomized clinical trials. *Nat Rev Clin Oncol*. 2017;14(5):317–323.

[89] Grothey A, Sargent DJ. Reply to D.J. Stewart. *J Clin Oncol*. 2010;28(31):652–653.

[90] Harmon A. New drugs stir debate on rules of clinical trials. New York Times, September 19 2010.

[91] Gan HK, Pond GR, Moore MJ, et al. Reply to D.J. Stewart. *J Clin Oncol*. 2010;28(31):2010–2011.

[92] Mozgunov P, Jaki T, Paoletti X. Randomized dose-escalation designs for drug combination cancer trials with immunotherapy. *J Biopharm Stat*. 2018;29(2):359–377.

[93] Selaru P, Tang Y, Huang B, et al. Sufficiency of single-arm studies to support registration of targeted agents in molecularly selected patients with cancer: Lessons from the clinical development of crizotinib. *Clin Transl Sci*. 2016;9(2):63–73.

[94] Grossman SA, Schreck KC, Ballman K, Alexander B. Point/counterpoint: randomized versus single-arm phase II clinical trials for patients with newly diagnosed glioblastoma. *Neuro-Oncology*. 2017;19(4):469–474.

Tables

Table 1. A summary of the key arguments/counterpoints that have historically been put forward for and against the use of randomization in phase II oncology trials

Consideration	For randomization	Against randomization
Molecularly targeted agents may often be cytostatic, and not in general lead to tumor shrinkage.	Progression free-survival should be the preferred primary outcome for cytostatic agents, which in turn makes randomization preferable.	The use of tumor response is still appropriate, as several cytostatic agents have led to statistically significant tumor regression.
Success in phase II should reliably predict that clinical benefit will be observed in phase III.	The classical single-arm paradigm has performed poorly in predicting clinical benefit in phase III; randomized designs would perform better.	No evidence is available to suggest the use of randomization in phase II has improved success in phase III.
Randomized phase II designs appear more similar to phase III designs, than conventional phase II designs.	A highly statistically significant p-value from a randomized trial would provide a strong case for seeking regulatory approval.	Investigators may incorrectly interpret the results of randomized phase II trials as though they are from a large phase III study.
Single-arm trials use historical control data to specify their design.	Reliance on historical control data for setting target response makes the results of single-arm trials unreliable.	For several diseases well-established resources do allow for the determination of the historical response to treatment.
Prognostic factors can differ substantially between patients, and these are often strong predictors of response to treatment.	Randomization should balance prognostic factors between arms, allowing for a more reliable assessment of efficacy. Attempts to account for such covariates in single-arm data using modelling are unreliable.	Randomization cannot guarantee prognostic factors will be balanced, especially in smaller trials, and modelling can be used to account for such variables in single-arm studies.
There is a trade-off between trial complexity and quality.	In conducting a randomized trial, you 'get what you pay for', with better quality data accrued.	Single-arm trials are simpler and easier to conduct.
Clinical trials should be conducted with as few participants as are required to control type-I/II error-rates to specified levels.	One-sided testing with increased type-I/II error-rates allows randomized trials to be conducted with achievable sample sizes. Only in a randomized trial are these error-rates ever known.	Single-arm trials require a much smaller sample size and modifying error-rates to reduce that required by a randomized trial would only increase failure in phase III.

Single-arm designs should be preferred from an ethical standpoint.	In general, there is equipoise, making randomized trials entirely appropriate.	Randomized trials are not ethical when large responses have been observed previously, as not all participants have access to a potentially better treatment.

Table 2. A summary of the characteristics (e.g., treatment type, primary/co-primary endpoint, patients analyzed) of phase II oncology trials by type of design used (e.g., single-arm, randomized non-comparative), based on a re-analysis of the data from Langrand-Escure et al. [80]*

Characteristic	Single-arm, % (IQR)	Multi-arm non-randomized, % (IQR)	Randomized non-comparative, % (IQR)	Randomized comparative, % (IQR)	*P*-value†
Type of therapy					
Cytotoxic	84 (26.7)	13 (26.5)	24 (31.6)	27 (23.1)	0.02
Combination therapy	102 (32.4)	11 (22.4)	27 (35.5)	53 (45.3)	
Targeted therapy	62 (19.7)	17 (34.7)	8 (10.5)	16 (13.7)	
Other	67 (21.3)	8 (16.3)	17 (22.4)	21 (17.9)	
(Co-)Primary endpoint‡					
Tumor response	129 (41.0)	18 (36.7)	26 (34.2)	18 (15.4)	–
Dichotomized PFS	23 (7.3)	6 (12.2)	9 (11.8)	5 (4.3)	
PFS	18 (5.7)	1 (2.0)	5 (6.6)	47 (40.2)	
Other	159 (50.5)	26 (53.1)	38 (50.0)	54 (46.2)	
Positive result	152 (72.7)	25 (83.3)	39 (70.9)	29 (28.2)	< 0.001
Median type-I error-rate (IQR)	5 (5-10)	5 (5-10)	7.1 (5-10)	5 (5-10)	0.04
Median type-II error-rate (IQR)	14 (10-20)	10 (9.8-12.5)	10 (10-20)	20 (15-20)	< 0.001
Median patients analyzed (IQR)	43 (34-58)	72.5 (49.8-111)	92 (72.8-135)	131 (89-182)	< 0.001

* Note that the dataset from Langrand-Escure et al. [80] comprises 557 trial reports.

† In addition, *P*-values for either a chi-squared test of row-column independence or a Kruskal-Wallis test of stochastic dominance, as appropriate, are reported for each of the characteristics. All statistical tests were two-sided.

‡ The percentages for the (co-)primary characteristic section do not add up to 100% because the categories are not mutually exclusive given the allowance for co-primary endpoints, and consequently a *P*-value is omitted for this section.

Table 3. A summary of the choices of primary/co-primary endpoints (e.g., tumor response) in phase II by the type of treatment under investigation (e.g., cytotoxic), based on a re-analysis of the data from Langrand-Escure et al. [80]*

(Co-)Primary endpoint	Cytotoxic No. (%)	Combination therapy No. (%)	Targeted therapy No. (%)
Tumor response	69 (46.6)	53 (27.5)	35 (34.0)
Dichotomized PFS	5 (3.4)	18 (9.3)	16 (15.5)
PFS	10 (6.8)	38 (19.7)	16 (15.5)
Other	67 (45.3)	92 (47.7)	44 (42.7)

* The percentages do not add up to 100% because the categories are not mutually exclusive given the allowance for co-primary endpoints.

Box 1. A summary of the key findings, in light of historical recommendations, from the re-analysis

of the data from Langrand-Escure et al. [80]

Finding
102 (32.4%) of the single-arm trials were of combination therapies.
47 (66.2%) of the trials employing progression-free survival as a primary or co-primary outcome used randomized comparative designs.
18 (5.7%) of the single-arm trials used progression-free survival as a primary or co-primary outcome.
The median number of patients analyzed in the randomized comparative trials was 131, compared to 43 for the single-arm trials.
29 (28.2%) of the randomized comparative trials came to a positive conclusion, compared to 152 (72.7%) of the single-arm trials.
More than 50% of the trials of cytotoxic, combination, and targeted therapies utilized either tumor response, PFS, or a dichotomized version of progression-free survival as a primary or co-primary outcome.
35 (34%) of the trials of targeted therapies used tumor response as a primary or co-primary outcome, whilst 16 (15.5%) used progression-free survival.