Review

Pharmacogenomics in Early-Phase Oncology Clinical Trials: Is There a Sweet Spot in Phase II?

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Abstract

Many clinical trials of oncology drugs now include at least a consideration of pharmacogenomics, the study of germline or acquired genetic factors governing a drug's response and toxicity. Besides the potential benefit to patients from the consideration of personalized pharmacogenomic information when making treatment decisions, the incentive is clear for oncology drug developers to incorporate pharmacogenomic factors in the drug development process, because pharmacogenomic biomarkers may allow predictive characterization of subpopulations within a disease that may particularly respond or may allow preidentification of patients at highest risk for adverse events. There is, however, a lack of agreement in actual practice about at what point in the oncology clinical drug development process pharmacogenomic studies should be incorporated. In this article, we examine the recent growth of pharmacogenomics in oncology clinical trials, especially in early-phase studies, and examine several critical questions facing the incorporation of pharmacogenomics in early oncologic drug development. We show that phase II clinical trials, in particular, have a favorable track record for showing positive pharmacogenomic signals, worthy of additional follow-up and validation, and that the phase II setting holds significant promise for potentially accelerating and informing future phase III trials. We conclude that phase II trials offer an ideal "sweet spot" for routine incorporation of pharmacogenomic questions in oncology drug development. *Clin Cancer Res; 18(10); 2809–16. ©2012 AACR.*

Introduction

Many current oncologic drug development trials consider possible genetic factors governing a drug's response or toxicity. Originally centered on single genes (pharmacogenetics), pharmacogenomics now integrates information from the entire genome and can encompass both germline differences, such as single-nucleotide polymorphisms (SNP) and acquired changes (tumor mutations; refs. 1, 2). Pharmacogenomics focuses specifically on predictive genetic biomarkers of outcomes from pharmacologic interventions, as opposed to disease genetics, in which variants describe disease subtypes or prognostic information.

There is a clear incentive to incorporate pharmacogenomic factors during the drug development process, namely, to potentially characterize subpopulations within a disease that may uniquely respond to a given drug, even if the larger population does not. Conversely, identifying genetic predisposition for drug toxicity can improve overall

tolerability of a drug through pharmacogenomic patient selection.

Although the impetus for including pharmacogenomics in oncology is clear, the development phase in which pharmacogenomics should receive attention is less clear. Should phase I and II trials routinely explore pharmacogenomic biomarkers? And, despite the sample size advantage of phase III trials, is phase III often too late? In this article, we examine the recent growth of pharmacogenomics in oncology trials, especially in early-phase studies, and examine several critical questions. We aim to show that phase II trials offer a potential "sweet spot" for routine incorporation of pharmacogenomic questions in oncology.

Oncology Clinical Trial Incorporation of Pharmacogenomics Is Rapidly Growing

To assess the prevalence of pharmacogenomics in oncology drug development, we queried MEDLINE clinical studies of "antineoplastics" combined with the search term "polymorphism." Limiting the results to studies since the year 2001 (after publication of the first human genome; refs. 3, 4) and to studies listed as phase I, II, or III clinical trials plus observational studies and meta-analyses, we found that the number of oncology studies incorporating pharmacogenomics is rapidly increasing (Fig. 1A).

To appropriately consider the timing of incorporating pharmacogenomics in oncology drug development, it is informative to evaluate phase III clinical trials first. Phase III

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Translational Relevance

The pivotal concept of using molecular variability to design oncology drug development studies has resulted in a number of well-known successes. To further this, oncology clinical trials are increasingly examining pharmacogenomics, the study of genetic factors governing a drug's response or toxicity. There is, however, a lack of agreement about at what point in the oncology drug development process pharmacogenomic studies should be incorporated. We show that phase II clinical trials, in particular, have a favorable track record for showing positive pharmacogenomic signals, worthy of additional follow-up and validation. Incorporation of pharmacogenomic endpoints into phase II trials not only has the potential of enhancing drug development through the identification of individuals most likely to respond or not respond (or most likely to experience undesirable toxicity), but also holds promise to accelerate and inform future phase III trials by reducing the size and cost of such studies.

clinical trials typically include large numbers of patients, facilitating discovery or validation of pharmacogenomic markers. We would, nevertheless, argue that phase III is too late to begin to consider pharmacogenomic effects. As an example, the role of *KRAS* mutation in anti–EGF receptor (EGFR) therapy in colon cancer is illustrative. Although anti-EGFR therapy was first approved by the U.S. Food and Drug Administration (FDA) in 2004 for use in patients with colon cancer, it was not until 2009 that a label change was instituted, stating that patients with mutated *KRAS* had no benefit from the addition of anti-EGFR therapy. The FDA label justifying the necessity of *KRAS* testing to inform anti-EGFR prescribing in colon cancer includes 7 different trials as supporting evidence; 6 of the 7 are phase III clinical trials, and 5,657 patients were included (5). Of those, only 3,287 patients had a *KRAS* result, and of those, 651 *KRAS*-mutant patients received anti-EGFR monoclonal antibody therapy, in retrospect, inappropriately (5). Clearly, many more patients were treated inappropriately in off-protocol situations during the 5 years preceding the label change. If earlier-phase trials had been able to more widely consider *KRAS* status, it is possible that fewer phase III trials would have been needed to show its importance. Not only could this have saved resources, but fewer patients would have been treated with an ineffective drug.

Consequently, we hypothesize that phase III is simply too late to consider a pharmacogenomic marker for the first time. Two other prominent oncology drug development examples recapitulate this point: Gefitinib failed commercially, in part, because predictive markers were not considered prior to the phase III studies (although in this case, the most useful predictive markers were not discovered until after the phase III studies were completed; refs. 6, 7). In

contrast, for trastuzumab (8), the pivotal phase III study was limited to patients with HER2 overexpression (9). Subsequent analyses have shown that if investigators, instead, had chosen to treat all patients with breast cancer and simply analyzed the HER2-upregulated cohort separately, a much larger (and more expensive) study would have been needed to show the effect (10).

Therefore, although large phase III studies may, in some cases, provide the only detectable signal of a pharmacogenomic marker's relevance, phase III studies are confirmatory trials of a drug in selected patients. The evaluation of pharmacogenomic biomarkers should be no different. We believe that informative pharmacogenomic questions can, and should be, asked earlier in drug development.

Pharmacogenomics in Early-Phase Trials

If phase III is too late to begin consideration of pharmacogenomic biomarkers, how early in drug development can pharmacogenomics be incorporated? We examined our prior MEDLINE search for only phase I and II clinical trials and found 83 such studies over the past 10 years (57 phase II trials and 26 phase I trials). We first considered whether phase I trials are too early to informatively assess pharmacogenomic biomarkers. In fact, we found that only 19% of the phase I trials reported a "positive" pharmacogenomic finding. In contrast, for phase II studies, 70% identified a "positive" pharmacogenomic marker (Fig. 1B). Although publication bias may preferentially affect phase II publications, these data suggest that phase I is simply too early to be routinely informative for evaluating a pharmacogenomic marker. This is likely due to the small size of phase I studies, as well as the heterogeneity of doses used and patients entered. In phase II, at least by investigator-assessed terms, pharmacogenomic markers are commonly able to be associated with some clinical phenotype or endpoint. As a final comparison, the "success" of pharmacogenomic publications derived from phase III trials that met our search criteria is also shown in Fig. 1B. The proportion of positive studies is extremely high, surely representing some publication bias, because the publications in this group were almost always separate, secondary analyses of a given biomarker or biomarkers from a previously published phase III trial. In contrast, the above-examined phase II pharmacogenomic publications tended to typically report both the clinical results of the trial and the secondary pharmacogenomic findings within the same publication.

One caveat to the above generalizations, however, is that the utility of testing pharmacogenomic biomarkers in phase I may, in part, be affected by whether the biomarker is expected to correlate with drug response in comparison with toxicity. Specifically, for toxicity pharmacogenomic biomarkers, phase I may have some unique advantages because of detailed pharmacokinetic analyses and toxicity monitoring. In contrast, for response pharmacogenomic biomarkers, phase I studies in which tumor response rates are typically <5% would likely be low yield. Additionally, in some cases, the decision about when to incorporate

Figure 1. A, published studies of antineoplastics incorporating the term "polymorphism," 2001 to 2010 (includes phase I, II, and III trials, plus observational studies or meta-analyses). It is acknowledged that some additional retrospective and case–control studies of oncology pharmacogenomics were likely not captured by our specific MEDLINE search criteria. B, the probability of "success" for showing pharmacogenomic endpoints differs substantially between published phase I and phase II trials. Interestingly, the positive pharmacogenomic results reported by 2 of the 3 "pharmacogenomically positive" phase I trials (34, 35) were, indeed, also reported as positive in separate phase II trials (36, 37). However, it is not clear that either of the findings were refined in phase II. In 1 case, the positive phase I finding (because it was reported as part of a phase I drug combination study; ref. 34) was published *after* the phase II positive finding (36). In the other case, the phase I positive finding was published first (35), but the separate phase II positive finding (published only 12 months later; ref. 37) showed the allele having the exact opposite direction of effect on the phenotype (progression-free survival). Success of contemporary pharmacogenomic analyses from phase III studies is also shown for comparison. Note that in our analyses, for the purposes of this illustrative examination, we allowed the investigators to define "success," meaning we simply reported here whether the variant being evaluated was associated in a "positive" or "negative" manner with the phenotype being studied by the authors (typically, tumor response, survival, or drug toxicity). It is important to state that in some of the reportedly "positive" trials, this does not necessarily mean that the implicated pharmacogenomic marker–phenotype relationship meets the statistical rigors of multiple testing; we simply reported whether the authors designated an association as positive or negative.
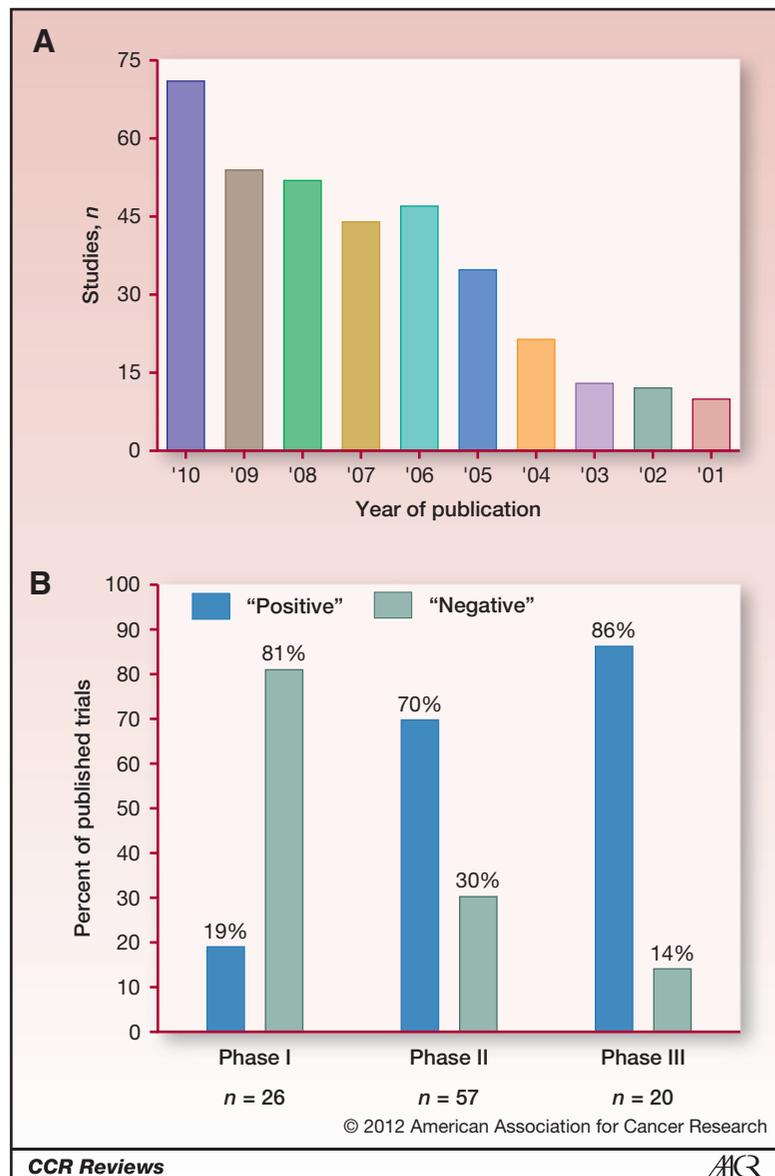
pharmacogenomic investigations may depend upon development of knowledge for specific factors, such as the mechanisms involved in drug disposition and drug action, polymorphisms in those pathways, the frequency of polymorphisms, and whether the polymorphisms of interest have shown an impact on variability in drug exposure or response for other drugs.

These nuances notwithstanding, the above data prompt us to hypothesize that phase II may be a "sweet spot" for clinical incorporation of pharmacogenomics in oncology drug development. Generally speaking, phase I trials seem to be too early for routine discovery success, too thin by sheer patient numbers and complicated by the problem of dose and patient heterogeneity, and phase III can be too late (in which patients may be inappropriately treated). Just as

for all other aspects of understanding drug activity, the appropriate "learning" phase is phase II.

Phase II Example

To examine the advantages and challenges of incorporating pharmacogenomics into phase II studies, it is informative to examine a specific case. Of the 57 published phase II studies from our search, only 1 study stated its primary objective as to "identify potential polymorphisms related to a better and safer outcome" (11). We thought that this might be an especially interesting example to examine in depth.

The study was a phase I and II trial with a 27-patient dose-finding (phase I) portion, followed by a 60-patient phase II portion. It examined oxaliplatin/irinotecan/capecitabine as

Table 1. Methods of carrying out pharmacogenomic study in early-phase oncology trials

Setting	Methods
General considerations	Universally include collection and storage of germline and tumor DNA whenever feasible
	Recognize that almost all pharmacogenomic findings in early-phase studies will need independent confirmation in a separate population, meaning endpoints will necessarily be exploratory or hypothesis generating
	Consider the expected prevalence of a given marker in the study population prior to testing; if the prevalence is expected to be very low, associations will be unlikely, and testing is therefore unlikely to be fruitful
	Recognize that testing of a large number of variants will limit statistical power to positively associate any single variant, once the penalty for multiple comparisons is properly applied
	When possible, identified pharmacogenomic markers should be verified as independent predictive factors alongside other clinical factors influencing interindividual drug-response variability, such as organ function, disease stage and/or severity, performance status, or drug–drug interactions
Phase I	Choice of variants to test might appropriately be informed by prior case reports or by preclinical information about a drug's metabolism, mechanism, and/or purported target
	Consider focusing on pharmacokinetic phenotypes in relation to rational pharmacogenomic variants, because PK data usually will be collected, and because even small sample sizes can show significant pharmacogenomic–pharmacokinetic relationships
	Consider focusing on toxicity pharmacogenomics, because disease heterogeneity of patients in phase I trials may limit drawing conclusions about tumor-related and/or response biomarkers
Phase II	May be the first opportunity, at a fixed drug dose, to extensively evaluate pharmacogenomic variants related to a given drug
	Choice of variants to test might appropriately be informed by prior case reports, phase I studies, or by preclinical information about a drug's metabolism, mechanism, and/or purported target
	Consider pharmacogenomic evaluation of toxicity, not just response, because probability of finding a positive association may be higher for a toxicity phenotype (rather than a response phenotype) if the incidence of the toxicity is more common than the incidence of response; pharmacogenomic risk stratification for toxicity could mitigate concerns about moving a drug to phase III if the highest toxicity-risk patients could be preidentified and excluded
	Randomized designs offer the advantage to specifically evaluate a marker with respect to a drug (predictive), rather than just the disease (prognostic), a step that is ultimately essential for a genetic marker to be categorized as pharmacogenomic
	Other innovative designs (such as an enrichment, or tandem, 2-step designs; Fig. 3) may accelerate confirmation of a potential marker

first-line therapy in metastatic colorectal cancer. In the phase II portion, the investigators examined 13 selected polymorphisms in 10 genes that were purportedly related to the study drugs' metabolism or efficacy (11). Only 1 of the 13 polymorphisms (located in *GSTP1*) was associated with response ($P = 0.007$); the other 12 did not meet the prespecified $P < 0.05$ significance level (11). The authors did not consider multiple testing, although they state that the results are exploratory. The issue of potential false discovery due to false association is an issue of paramount importance with pharmacogenomic data and is extensively considered elsewhere (12–14). Nevertheless, the *GSTP1* SNP association from this study was, at least, a very interesting exploratory finding.

We draw 2 conclusions from this example: 1 is that even phase II studies that posit pharmacogenomic aims as their primary purpose do not always adequately consider statistical issues. This conclusion reinforces the idea that any

finding in phase II needs confirmation. On the other hand, it is interesting that 1 of the chosen polymorphisms in this study has a potential association with response. This finding makes it worthy of additional follow-up, and in that sense, the trial achieved its stated pharmacogenomic purpose.

In many phase II situations, this will be the case. The smaller size of phase II trials means that pharmacogenomic endpoints will necessarily be exploratory or hypothesis generating. This factor will be especially true if a variant is expected to have a modest impact (as is probably the case for most variants affecting complex genetic traits; ref. 15) or if multiple variants are tested (12, 13). However, statistical power limitations are not, in our view, prohibitive, because the phase II setting may be the first opportunity (at a fixed drug dose) to extensively evaluate pharmacogenomic variants as they may relate to a drug's development (Table 1).

Randomization in Phase II Trials

Use of randomized phase II trials has been increasing (16, 17), and randomized designs intensify the importance of incorporating pharmacogenomic markers. Even if a follow-up phase III study is necessary, a pharmacogenomic marker that is not at least explored in a randomized phase II study is much less likely to be considered in the follow-up study. Randomization additionally offers a clear manner to specifically evaluate the marker with respect to drug (predictive), rather than just the disease (prognostic). This key aspect of randomization is essential for a genetic marker to be truly identified as a pharmacogenomic marker. Many published pharmacogenomic studies fail to include an untreated group and, thus, fail to convincingly show that the marker is truly predictive (18). The above study (11) is an illustration of this limitation, and it is, therefore, impossible to determine whether the GSTP1 marker is predictive of treatment response or simply prognostic for the natural course of the disease.

The randomized discontinuation trial (RDT) design (19) offers a unique and superb opportunity for incorporating pharmacogenomics. In RDTs, all patients are initially treated with the same drug and then "self-select" for continued therapy (if responding) or for randomization against placebo (if disease is stable). The design inherently invites the question of trying to better understand the response heterogeneity seen in patients with the same empiric "disease." Pharmacogenomic factors likely will eventually explain a portion of this disease-response heterogeneity in oncology, alongside other acknowledged, important sources of interindividual variability including drug–drug interactions, drug resistance, excretory organ function, compliance, and comorbidity. Nevertheless, without incorporation of pharmacogenomic questions into RDT and other randomized phase II trials, the molecular underpinnings of response variability will likely continue to remain unanswered.

Pharmacogenomic Phenotypes in Phase II Trials: Response Compared with Toxicity

It is easy to appreciate the importance of discovering response-predictive pharmacogenomic markers in the phase II setting. Tumor-specific pharmacogenomic changes certainly fall into this category, and well-described dramatic examples (like EGFR and BRAF mutations predictive of therapy benefits in lung cancer and melanoma, respectively; refs. 20, 21) have reinforced this theme. Germline variants have also been associated with treatment response outcomes in oncology (22–24).

In contrast, the value of toxicity-predictive pharmacogenomic findings in phase II may not be as obvious, but should be considered just as important. Toxicity determinants are germline variants, predictive of an increased (or decreased) risk of an adverse event due to a specific drug or drug class. The 2 most well-characterized oncology examples of germline changes predictive of toxicity are UGT1A1 polymorphisms for irinotecan (25) and TPMT polymorph-

isms for 6-mercaptopurine (26). From the standpoint of pharmacogenomic discovery within phase II trials, one could argue that the probability of finding a positive pharmacogenomic association for a given toxicity will be more likely if the incidence of the toxicity is more common than the expected incidence of response. That scenario is quite common in oncology drug development. The ultimate value of toxicity-predictive markers is improved identification of patients at highest risk for adverse events, which is useful when deciding between several apparently equivalent therapies and for drug avoidance in patients with specific comorbidities. For pharmaceutical development decisions, pharmacogenomic risk stratification could mitigate concerns about moving a drug forward to phase III (or for approval) if the highest toxicity-risk patients could be preidentified and excluded.

Study Population Challenges When Incorporating Pharmacogenomic Endpoints in Phase II Trials

In addition to the above considerations, one further specific challenge incorporating and interpreting pharmacogenomic markers in the phase II setting deserves mention: A potentially interesting or relevant pharmacogenomic polymorphism may be generally uncommon in the patient population being studied. This consideration often receives little attention, but the prevalence of the risk allele for a given polymorphism can vary considerably by ethnicity (27), or it may simply be uncommon in all populations. Falsely negative pharmacogenomic results in the phase II setting could arise because of this critical aspect. Therefore it is important to remember that when a potential pharmacogenomic marker is being selected for testing in a phase II study, if the number of patients with the susceptibility marker is expected to be low, and if the marker only confers a modest effect, then it is unlikely that a genotype–phenotype relationship will be seen. Such markers are probably simply inappropriate for testing in phase II studies. Appropriate power calculations considering the allele frequency in the intended population are, therefore, needed when designing such studies. Consideration of the expected ethnic background of the intended target population for a study should also be entertained. Phase II trial networks or cooperative groups can address this issue through increased geographic (and, therefore, hopefully ethnic) diversity. Nevertheless, it may still be impossible to appropriately power a phase II study to examine relatively uncommon pharmacogenomic variants. This challenge may be, ironically, even more true in randomized phase II studies in which only half the patients receive the drug for which the variant is potentially informative. In such cases, a common-arm approach (28) can be used (Fig. 2), although the logistical hurdles of gaining access to samples and data from the available pool of (potentially even international) trials is a practical and real limitation.
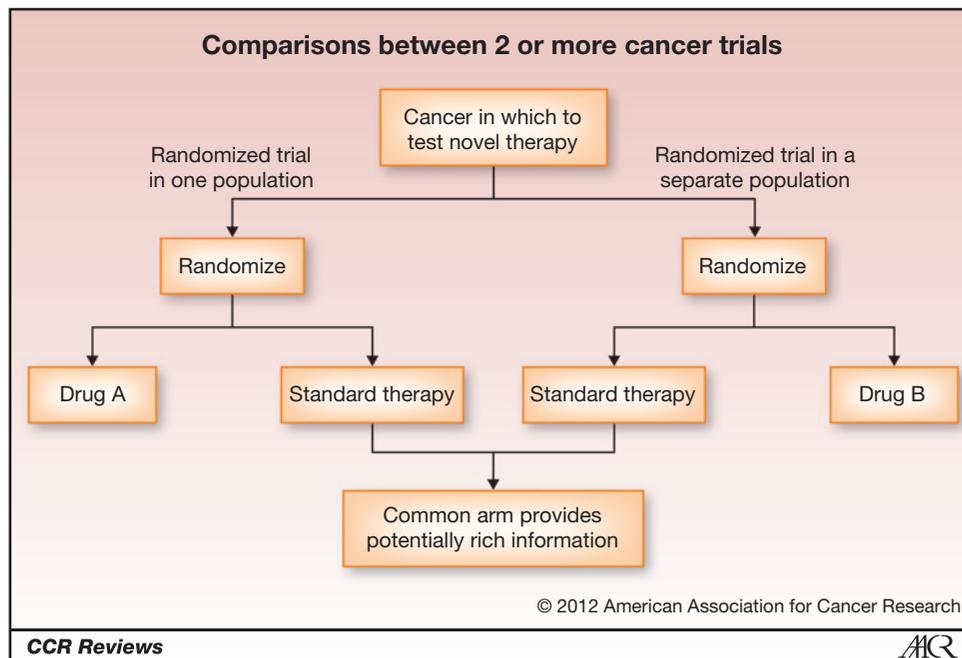
Figure 2. Common-arm approaches analyzing 2 or more common drug-treatment arms from different clinical trials can provide a rich, large data set for pharmacogenomic discovery. Common-arm approaches take advantage of the fact that several different independent clinical trials (all of which could be phase II trials) may be testing a similar common (or "standard") arm against various other arms. The investigator may be interested in a pharmacogenomic variant related to the agent used in the common arms, rather than the comparator arms. As shown, a given cancer is being tested for the development of 2 different novel therapies: drug A and drug B. In 1 randomized trial, novel drug A is being compared with the existing standard therapy. In the separate trial, novel drug B is being compared against the existing standard therapy. The existing standard therapy is, however, the same for both studies. Therefore, by combining the patients from the 2 standard therapy "common" arms from these 2 independent trials, one doubles the number of patients in which to examine a potential pharmacogenomic marker(s) for the standard therapy. In addition, the randomization feature allows one to draw conclusions that the studied pharmacogenomic marker is, indeed, potentially predictive for the therapy in the standard arm, because the novel therapy arms can serve as "control" populations having the same disease.

What's Next after a Positive Pharmacogenomic Finding in Phase II?

If a pharmacogenomic marker does show a signal of activity from a phase II trial, is a randomized prospective study always needed to confirm each potential candidate? Several authors have argued that this is neither universally necessary nor practical (29, 30), because completing a randomized prospective study for each of the candidates that has been or will be discovered in coming years would be cost prohibitive and infeasible, and in some cases, perceived as unethical (30). Cohort or case–control studies in large populations could provide confirmatory answers (29). As in the above EGFR example, entirely retrospective subset analyses of pooled data can be quite convincing.

Alternatively, innovative phase II designs within a given single study may accelerate confirmation of a potential marker. One such approach is the tandem, 2-step phase II design (Fig. 3; refs. 31, 32), also known as an enrichment design (33), which simultaneously allows one to test both a drug and a predictive pharmacogenomic biomarker in the same trial. This design is becoming increasingly used, and we believe it has the potential to inform and accelerate the incorporation of pharmacogenomic biomarkers in drug development. It, of course,

requires that the pharmacogenomic marker can be rapidly tested, such that the patient can be treated in a reasonable time frame.

Finally, it must be acknowledged that most of the nominally positive, published associations from prior phase II studies have, to date, not yet changed clinical practice or even resulted in drug label changes. This situation is likely a reflection of the high standard that has been set for validating and then incorporating a pharmacogenomic finding. Nevertheless, we argue here that ultimately increasing the number of practice-changing pharmacogenomic findings will require more routine consideration of pharmacogenomics in earlier-phase clinical trials. We have tried to show that phase II is the most logical setting for such necessary discovery work, and it is most likely to provide the initial results worthy of confirmation testing.

Conclusions

Early-phase clinical trials in oncology are increasingly examining pharmacogenomics. Just as the complete sequencing of the first human genome heralded the advent of pharmacogenomic study, the near-future ability to routinely and cost-effectively sequence every patient's germline and tumor genome will only further the key role of
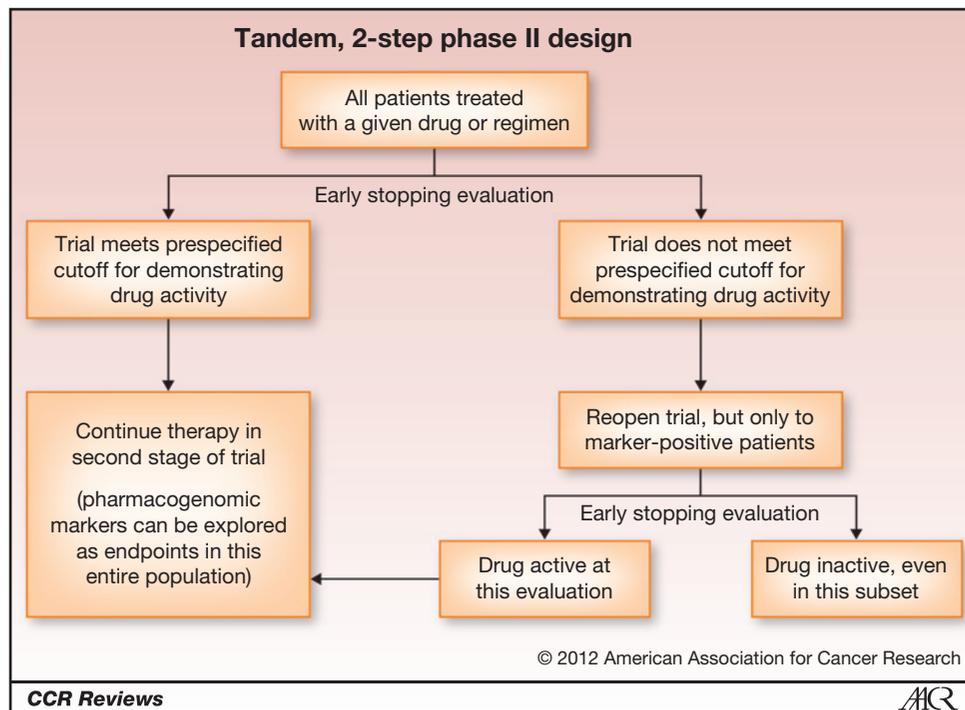
Figure 3. Tandem, 2-step phase II study design for evaluation of pharmacogenomic biomarkers. The hypothesis is that a drug will show a higher response rate in selected patients carrying the susceptibility marker. In the first stage of the tandem design, all patients meeting eligibility criteria are treated, and an early-stopping role is instituted. If adequate responses were seen at the early-stopping analysis point, then the second stage of the study would be completed with no selection of patients by the presence of a pharmacogenomic marker. If too few responses are seen in the first stage, patients will proceed on to a "limited eligibility" stage of the trial, in which only "marker-positive" patients would be enrolled and the question would be asked whether a prespecified response rate (or other outcome) is or is not met in this selected population. If too few responses are again seen, that pharmacogenomic marker would be considered invalid. If an adequate number of responses are seen in the marker-positive patients of the 2-step design, then that second stage of the study would be completed, possibly allowing a drug to be defined for a select patient population having that pharmacogenomic marker.

pharmacogenomics in oncology therapeutics. We have shown that phase II clinical trials, in particular, have a favorable track record for showing positive pharmacogenomic signals, worthy of additional follow-up and validation. This positive direction encourages us to recommend increasing incorporation of pharmacogenomic biomarkers in phase II trial designs as secondary and exploratory endpoints, to allow the earliest identification of signals of predictive information. Because phase I is likely too early and phase III may be too late, phase II should, indeed, remain the sweet spot for pharmacogenomics in cancer therapeutics.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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