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

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Statement of 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 as to where 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 demonstrating positive pharmacogenomic signals, worthy of additional follow-up and validation. Incorporation of pharmacogenomic endpoints into phase II trials not only has the potential to enhance 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.
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, there is a clear incentive for oncology drug developers to incorporate pharmacogenomic factors in the drug development process since pharmacogenomic biomarkers may allow predictive characterization of sub-populations within a disease that may particularly respond, or may allow pre-identification of patients at highest risk for adverse events. There is, however, a lack of agreement in actual practice as to where 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 demonstrating 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.
Introduction

Many current oncologic drug development trials consider possible genetic factors governing a drug’s response or toxicity. Originally centered around single genes (pharmacogenetics), pharmacogenomics now integrates information from the entire genome and can encompass both germline differences (like single nucleotide polymorphisms [SNPs]) and acquired changes (tumor mutations)(1, 2). Pharmacogenomics focuses specifically on predictive genetic biomarkers of outcomes from pharmacologic interventions, as opposed to disease genetics wherein 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 sub-populations 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.

While 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 demonstrate 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(3, 4)) and to studies listed as phase I, II, or III clinical trials plus observational studies and meta-analysis, we found that the number of oncology studies incorporating pharmacogenomics is rapidly increasing (Figure 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 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-epidermal growth factor receptor (EGFR) therapy in colon cancer is illustrative. While anti-EGFR therapy was first FDA-approved in 2004 for use in colon cancer patients, it was not until 2009 that a label change stating that patients with mutated KRAS had no benefit from addition of anti-EGFR therapy was instituted. 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 demonstrate its importance. Not only could this have saved resources, but fewer patients would have been treated with an ineffective drug.
This leads us to hypothesize that phase III is simply too late to be considering 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 (6, 7) (although in this case, the most useful predictive markers were not discovered until after the phase III studies were completed). In contrast, for trastuzumab (8), the pivotal phase III study was limited to patients with HER2 over-expression (9). Subsequent analyses have demonstrated that if investigators instead had chosen to treat all breast cancer patients and simply analyzed the HER2-upregulated cohort separately, a much larger (and more expensive) study would have been needed to demonstrate the effect (10).

Therefore, while 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 (Figure 1B). While one must consider the possibility that 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 their small size, as well as the heterogeneity of doses utilized 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 Figure 1B. The proportion of positive studies is extremely high, surely representing some publication bias since the publications in this group almost always were 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 versus 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 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 been shown to impact 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 appear 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 (wherein 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 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 one 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/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 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 \textit{GSTP1}) was associated with response (P=0.007); the other 12 did not meet the pre-specified 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 make two conclusions from this example: one is that even phase II studies which
posit pharmacogenomic aims as their primary purpose do not always adequately consider
statistical issues. This reinforces the idea that any finding in phase II needs confirmation. On
the other hand, it is interesting that one of the chosen polymorphisms in this study has a potential
association with response. This 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
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)(15) or if multiple variants are tested(12, 13).
However, statistical power limitations are not, in our view, prohibitive, since 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.

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 demonstrate 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 inter-individual 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 Versus 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 \textit{EGFR} and \textit{BRAF} mutations predictive of therapy benefits in lung cancer and melanoma, respectively\cite{20, 21}) have reinforced this theme. Germline variants have also been associated with treatment response outcomes in oncology\cite{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 two most well-characterized oncology examples of germline changes predictive of toxicity are \textit{UGT1A1} polymorphisms for irinotecan\cite{25}, and \textit{TPMT} polymorphisms for 6-mercaptopurine\cite{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 co-morbidities. 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 pre-identified and excluded.

\textbf{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 also should be entertained. Phase II trial networks or cooperative groups can address this issue through increased geographical (and therefore, hopefully ethnic) diversity. Despite this, it may still be impossible to appropriately power a phase II study to examine relatively uncommon pharmacogenomic variants. This may be, ironically, even more true in randomized phase II studies wherein only half the patients receive the drug for which the variant is potentially informative. In such cases, the use of a common arm approach(28) can be utilized (Figure 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.
What 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), since 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, two-step phase II design(31, 32) (Figure 3), 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 utilized, 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 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 pharmacogenomics in oncology therapeutics. We have shown that phase II clinical trials in particular have a favorable track record for demonstrating positive pharmacogenomic signals, worthy of additional follow-up and validation. This 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. Since 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.

**References**


Figure Legends

Figure 1. (A) Published studies of antineoplastics incorporating the term 'polymorphism', 2001-2010 (includes phase I, II, and III trials, plus observational studies or meta-analyses). It is acknowledged that there are likely some additional retrospective and case-control studies of oncology pharmacogenomics that were not captured by our specific MEDLINE search criteria. (B) The probability of "success" for demonstrating pharmacogenomic endpoints differs substantially between published phase I and phase II trials. Interestingly, the positive pharmacogenomic results reported by two of the three “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 one case, the positive phase I finding (because it was reported as part of a phase I drug combination study)(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)(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 are 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.

**Figure 2.** Common-arm approaches analyzing two or more common drug treatment arms from different clinical trials can provide a rich, large dataset 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 two different novel therapies—Drug A and Drug B. In one randomized trial, novel Drug A is being compared to 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 two standard therapy “common” arms from these two 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, since the novel therapy arms can serve as “control” populations having the same disease.

**Figure 3.** Tandem, two-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, wherein 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 two-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.
## Methods of Carrying Out Pharmacogenomic Study in Early Phase Oncology Trials

### 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 inter-individual drug-response variability, such as organ function, disease stage/severity, performance status, or drug-drug interactions

### Phase I
- Choice of variants to test might appropriately be informed by prior case reports or by pre-clinical information about a drug’s metabolism/mechanism/purported target
- Consider focusing on pharmacokinetic (PK) phenotypes in relation to rational pharmacogenomic variants, since PK data usually will be collected, and since even small sample sizes can demonstrate significant pharmacogenomic-pharmacokinetic relationships
- Consider focusing on toxicity pharmacogenomics, since disease heterogeneity of patients in phase I trials may limit drawing conclusions about tumor-related/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 pre-clinical information about a drug’s metabolism/mechanism/purported target
- Consider pharmacogenomic evaluation of toxicity, not just response, since 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 pre-identified 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 which is ultimately essential for a genetic marker to be categorized as pharmacogenomic
- Other innovative designs (such as an enrichment, or tandem, two-step designs [Figure 3]) may accelerate confirmation of a potential marker
Comparisons between two or more cancer trials

Randomized trial in one population
Randomized trial in a separate population

Randomize

Drug A
Standard therapy
Common arm provides potentially rich information
Standard therapy
Drug B
Tandem, two-step phase II design

- All patients treated with a given drug or regimen

  Early stopping evaluation

  Trial meets prespecified cutoff for demonstrating drug activity
  - Continue therapy in second stage of trial (pharmacogenomic markers can be explored as endpoints in this entire population)
  - Continue therapy in second stage of trial

  Trial does not meet prespecified cutoff for demonstrating drug activity
  - Re-open trial, but only to marker positive patients
    - Early stopping evaluation
    - Drug active at this evaluation
    - Drug inactive, even in this subset
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