How to Develop Treatments for Biologically Heterogeneous "Diseases"

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Running title: Developing treatments for heterogeneous “diseases”

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Summary

The standard paradigm for the design of phase III clinical trials is not suitable for evaluation of molecularly targeted treatments in biologically heterogeneous groups of patients. Here we comment on alternative clinical trial designs and propose a prospective discovery/evaluation framework for using tumor genomics in the design phase III trials.

In this issue of Clinical Cancer Research, Redman et al. describe the design of a new phase III clinical trial of cetuximab in NSCLC. Clinical trials are generally designed to test a single null hypothesis for all randomized patients with eligibility defined by histology, stage and amount of previous treatment. Rejection of the null hypothesis can lead to regulatory approval of the drug for patients who satisfy the eligibility requirements of the trial. In many cases, this paradigm no longer provides a scientifically sound or economically sustainable basis for phase III clinical trials. Not scientifically sound because most histologic diagnoses are heterogeneous in oncogenesis, pathogenesis and sensitivity to molecularly
targeted therapy. Not economically sustainable because approving drugs based on very small average treatment effects for broad populations creates a heavy economic burden².

We are in search of a new paradigm for therapeutics development in oncology³. Although there is uncertainty on what this new paradigm should be, the inadequacies of the existing paradigm are illustrated by the development of cetuximab for patients with NSCLC. There is substantial evidence that EGFR signaling is of importance for some NSCLC tumors⁴ and two large phase III trials have been conducted. FLEX reported a statistically significant 1.2 month increase in median survival for the cetuximab arm. BMS 099 reported a non-significant 1.3 month increase in median survival for the cetuximab arm and a 0.5 month improvement in median PFS. Neither trial selected patients or even evaluated tumors for genomic alterations in EGFR. These clinical trials are representative of the current paradigm in which large clinical trials are conducted without detailed prospective biological characterization of the tumors and without prospective archiving tumor specimens on all patients to enable discovery.

Redman et al. provide a nice analysis of the relative merits of 4 design options they considered for design of a new phase III trial to evaluate EGFR amplification as a predictive biomarker for benefit from cetuximab. The first option is to repeat the “all comers” design used in the two previous phase III trials in which evaluating cetuximab in the subsets based on EGFR amplificaton is only exploratory. Exploratory generally means that none of the 5% type I error for the trial is reserved for that subset analysis, the trial may not be sized for the subset analysis, and submission of tumor specimens for analysis is not a condition for enrolment. One clearly doesn’t need another trial of that type.

The second design option considered by Redman et al. is the “strategy design” in which patients are randomized to either have their tumor tested for EGFR amplification or not. If not, they receive standard of care chemotherapy. If tested,
they would receive cetuximab augmented chemotherapy only if their tumor was found to be EGFR amplified. Strategy designs are generally a very poor choice\textsuperscript{5}. They require an enormous sample size because many patients receive the same treatment regardless of the arm to which they are randomized.

The third design option is the “enrichment design” in which only patients with EGFR amplified tumors would be eligible\textsuperscript{6}. Enrichment can be very efficient with regard to minimizing the required number of randomized patients and the cost of the trial. Although it seems clear from the previous phase III trials that the patients without EGFR amplification as a group do not benefit meaningfully from cetuximab, including such patients would enable re-analysis of the results of the trial with regard to candidate biomarkers discovered later, using the “prospective-retrospective” design\textsuperscript{5}.

The multiple hypothesis designs considered by Redman et al. were described previously by Simon\textsuperscript{7} as a single design in which the 5\% type I error (alpha) of the clinical trial is partitioned among the various hypotheses that are tested. How the 5\% alpha is split-up can depend on the degree of confidence one has in the marker or it can be optimized to achieve the desired power for each hypothesis to be tested with a minimum total sample size. Simon provided a website where investigators can evaluate several specific analysis plans and partitions of the alpha (http://brb.nci.nih.gov). The key features of this design are that the analysis plan must be specified in detail in the protocol, that the total study-wise type I error be preserved at 5\% and that the trial is sized to obtain adequate power for each hypothesis of interest.

Redmond et al. selected the multiple hypothesis design for their trial with their hypotheses of interest being the null hypothesis of no benefit for all randomized patients and the null hypothesis of no benefit for the EGFR amplified patients. The first null hypothesis has been already tested in two previous large phase III trials however. A second concern is the large number of patients without EGFR
amplification likely to be enrolled. Karuri and Simon\textsuperscript{9} recently published a Bayesian design to better protect test negative patients. The study-wise type I error is protected but it monitors for futility in test negative patients more aggressively than the design proposed by Redmond et al.

An additional design option that should be considered for many phase III trials is the “Adaptive Signature Design”\textsuperscript{9} illustrated in Figure 1. It is a discovery design based on the admission that we don’t know enough about the factors that influence response to cetuximab in NSCLC and should try to prospectively ensure that the phase III trial extends that knowledge. The previous phase III clinical trials already conducted for cetuximab indicate that the improvement in median survival for EGFR amplified patients is unlikely to exceed 4 months. The proposed trial is sized to detect an increase in median PFS of less than 2 months in EGFR amplified patients. Is it worthwhile to detect such small effects? We need to better understand what aspects of the genetic background of lung tumors determine whether a patient is likely to benefit from cetuximab treatment. The Adaptive Signature Design is structured to do discovery based on a more comprehensive genomic characterization. At the time of final analysis, the patients are partitioned into a training set and a validation set. The genomic characterization and outcome data in the training set is analyzed to train a multivariate classifier that identifies the genomic characteristics of patients who benefit from cetuximab. That classifier is tested on the validation set. This design can also be implemented sequentially in time as described by Sher et al.\textsuperscript{10} and the statistical power of the approach can be substantially enhanced by using cross-validation rather than sample splitting as described by Freidlin et al.\textsuperscript{11} and by Simon\textsuperscript{3}.

Redman et al. have provided an analysis that will be useful for planning clinical trials of treatments and pre-specified predictive biomarkers. An important aspect of the design of many such phase III clinical trials, however, is to ensure that tumor samples or tumor DNA are preserved for all randomized patients for future
analysis. Our understanding of the interactions among signaling pathways is still rudimentary and the discovery objective of phase III clinical trials warrants increased emphasis.

Legend for Figure 1:
Schematic for the Adaptive Signature Design(Freidlin, 2005 #307). The tumors of all randomized patients are molecularly characterized with regard to a trial specific set of discovery features to be evaluated. Eligibility is not restricted by the molecular characterization. At final analysis patients are randomly partitioned into a training set and validation set. A binary classifier is trained to identify patients for whom the difference in outcomes between the treatment arms is maximum. The binary classifier is tested on the validation set. The design uses a predictive classifier discovery and evaluation framework, not a multiple hypothesis testing framework. Trial is sized for discovery and validation as illustrated in Sher et al.(Sher, 2011 #844)


Partition into training set T and validation set V

Declared effectiveness for classifier positive patients

Yes

p<.05 in subset?

Compare outcomes for E vs C in classifier + patients of V

Extensive analysis of biological characterizations in T to develop optimal single multivariate predictive classifier

Perform final analysis

Follow-up

Extensive biological characterization of tumors for all randomized patients

Randomize n patients to rx E or control C
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