

Issues in the Design of Translational Research Trials

Faculty Presenter

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Scholars' Summaries

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Translational research encompasses several domains of investigation which similarly aim to bring basic science into early phase clinical trials. Such investigation includes, for example, biomarker studies and new drug development. Often these studies involve collaboration between academia, government, and industry.

A biomarker may be used to aid in risk assessment, diagnosis, prognosis, prediction of treatment benefit, pharmacodynamics or dose adjustment, and/or as a surrogate endpoint for disease progression or response. Some biomarkers may only be prognostic and not treatment guiding (e.g. treatment benefits all) vs. treatment guiding but not prognostic (e.g. treatment benefits only marker positive patients). Biomarkers can have various roles in studies: the biomarker may be *integral*, as an eligibility criterion or treatment assignment, *integrated*, in which a biomarker is being validated, or *ancillary or exploratory*, in which trial data is used to develop a biomarker and to understand its biology.

The process of biomarker development involves 1. *analytic validation*, in which assay performance is shown, 2. *Clinical validation*, in which the association between test result and pathophysiologic state is shown, and 3. *Clinical utility*, in which the effectiveness, uptake, and an improved clinical outcome with its use is demonstrated.

In studies with biomarkers as endpoints it is important to note that interval outcomes provide "more bang for the buck" in demonstrating clinical differences for a given sample size. Caution should be given to interpretation of subgroup analysis. Additionally attention should be given to investigators' determination of the "optimal" cut point for a new biomarker to ensure that results do not only seem significant due to chance. Thus, in summary, it is advised that investigators of biomarker studies pre-specify hypotheses to be tested with an appropriate sample size, plan for interim looks, adjust for multiple comparisons or estimate false discovery rates, and treat post-hoc analyses as exploratory.

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In her talk at the Society of Translational Oncology Fellow's Forum 2017, Dr. Susan Hilsenbeck discussed critical issues in the design of translational research development. The process of translational research study design is complex; it can include choosing appropriate biomarkers to select patients or choosing appropriate endpoints such as response rate or progression free survival.

But let's first discuss the background of translational research. In fact, there is not a true definition of translational research. Rather, the term "translational research" indicates the goal of the research, which is to improve patient care by applying basic science and lab findings to benefit patient care. When we consider translational research, we can consider it a continuum of the research process from basic science discovery to wide adoption of the discovery in clinical practice. In her talk, Dr. Hilsenbeck focused primarily on the process of early drug discovery.

Clinical Trials:

She initially discussed the phases of clinical trials. Phase I studies have the primary goal of finding the dose safety and exploration of biomarkers. Phase II studies evaluate whether larger studies are warranted. Phase III studies primarily assess efficacy.

What Are Biomarkers?

In the creation of primarily early translational trials, the issue of biomarkers becomes paramount. The key questions to address are

1. What is a biomarker?
2. What function does it predict?, and
3. When is it used?

As Dr. Hilsenbeck said, "A biomarker is a characteristic that is objectively measured as an indicator of normal biologic processes, pathogenic processes, or pharmacologic response to a therapeutic intervention". Biomarkers are most often validated in a lab and, as a result, are compared to clinical validation. Therefore, their role is to demonstrate the association between test result and pathophysiological state.

The next step in biomarker development is determining clinical utility. This is the process by which the biomarker utility is investigated in a real-world setting. There is an important difference between clinical validation and clinical utility. A key example is a warfarin test, which has high clinical validation but little utility, in part due to the fact that there are many easier ways to assess the effects of warfarin.

Prognostic Versus Predictive Biomarkers:

When utilizing a biomarker, it is important to consider the setting of biomarker use. Most often, biomarkers are utilized in two settings: 1) to determine the prognosis or natural history of

disease, and 2) in predicting treatment benefit. One can also consider biomarker use in early readouts, surrogate endpoints, disease progression PD/dose adjustment, diagnosis, and determining disease susceptibility. There is a difference between prognostic versus predictive (i.e., treatment-guiding) biomarkers. If you have a biomarker that perfectly predicts long-term outcomes, how would it be best to use this clinically? A clinician may be tempted to drop adjuvant treatment in those patients who appeared to have favorable prognoses and to be more aggressive if a biomarker returned with unfavorable outcomes. However, this may be a pitfall for researchers and clinicians, as treatment may be complicated by the setting of therapy and ultimately may make predicting the role of that biomarker impossible without more testing. Developing background information that is able to inform, with high clinical competence, a clear role of the biomarker is key. Prognostic biomarkers demonstrate survival and are of significance to all patients in the population being studied. However, a treatment-guiding but not prognostic marker indicates that a drug may only benefit the marker-positive group.

The Role of Biomarkers in Clinical Trials

There are two main types of marker-enriched trial designs. Integral trial designs test for the marker and may only treat in biomarker positive, usually randomizing individuals with a positive marker to treatment versus no control. Adaptive or multi-stage trial designs may treat both marker positive or negative patients and may stop arms of the study if there are fewer efficacies in a certain population. In phase II trials, the key role of biomarkers is to find further information toxicity and evidence of efficacy, select a right schedule, or even to be used as a companion biomarker. They may also predict phase III outcomes.

Important terms regarding biomarkers include integral, integrated, and ancillary or exploratory biomarkers. An integral biomarker is involved in the eligibility, treatment assignment, or group stratification and is a substantial part of the treatment choice. An integrated biomarker has a pre-planned analysis but does not alter which treatment patients get. Exploratory or ancillary biomarkers are used to develop biomarkers or assays and understand the agent biology.

The Selection of Endpoints and Specimens

Another key part of trial design is the selection of endpoints and biospecimens. The continuum of trial design ranges from diagnosis to neoadjuvant therapy, adjuvant therapy, 1st line, 2nd line, and beyond. There are many time points to consider for data collection, such as after surgery or at first relapse. Alternatively, endpoints for data collection can be mobile, such as at the time of overall response driven by predictive effects, disease-free survival, progression free survival, or overall response driven by predictive and prognostic effects.

Sample Size Selection

Sample size is another important issue with development of translational studies. Single arm studies may only need half the sample size as a study with 2 parallel arms, and a comparative

study evaluating a single endpoint such as overall survival may need a sample size four times larger. However, for a 2 parallel arms trial with comparative interval assessment (such as those that utilize a biomarker), a smaller group is needed.

Multiplicity

Multiplicity is another pitfall of clinical trial design and may lead to small variations in findings that are ultimately not representative of the larger patient population as a whole. For example, competing studies of adjuvant 5-FU and leucovorin versus observation demonstrated differing results, such as benefits only in certain populations, whereas other studies demonstrated overall benefit in all populations.

Optimal Cutpoints

Optimal cutpoints are also a vital consideration in translational trials. If given infinite endpoints, cutpoints can be by chance suggestive of false significant differences in treatment arms. In order to avoid this false suggestion, pre-specify endpoints, avoid multiplicity, and keep in mind that post-hoc analyses may over-represent data due to the numerous cutpoints being drawn from the data.

Conclusions

In conclusion, there are many aspects of translational research to take into consideration in regards to clinical trial initiation. These can include trial design with adequate controls, biomarkers (whether predictive or prognostic), sample size calculations, elimination of multiplicity, and finding of optimal endpoints.

*Authored by **Sheng Yang, MD**, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Translational research bridges basic sciences and clinical practice. Dr. Hilsenbeck focused her informative and inspiring lecture on trials of early translation, including phase I/II trials.

Biomarkers are critical for translational research trials. Biomarkers Definition Working Group of National Institutes of Health defined a biomarker as “a characteristic that is objectively measured as an indicator of normal biological processes, pathogenic processes, or pharmacological response to a therapeutic intervention”. Biomarkers are widely investigated for various purposes: to predict susceptibility, prognosis, or treatment efficacy, to assist diagnosis, to monitor disease progression, to guide drug dose adjustment, or to serve as

surrogate endpoints. The development process of biomarker initiates with analytic validation (demonstration of assay performance), proceeds to clinical validation (demonstration of association between test result and pathophysiologic state), and concludes with clinical utility (demonstration of effectiveness, uptake, improved clinical outcome).

Subsequently, Dr. Hilsenbeck put biomarker development into a frame of clinical studies. The roles of biomarkers in a clinical study can be categorized as: integral, integrated, and ancillary or exploratory.

- Tests of integral biomarkers are carried out for the trial to proceed. Integral studies are inherent in the design of the clinical trial from the onset and are done in real time for the conduct of the trial. If integral markers are to be used to make individual patient decisions, then CLIA regulations apply.
- Integrated biomarker tests are intended to identify or validate assays or markers that are planned for use in future trials. In this setting, trials are designed to test a hypothesis and include complete plans for specimen collection, laboratory measurements, and analysis. Also, statistical design and analysis should be prespecified.
- When studying an ancillary or exploratory biomarker, trial data are used to develop biomarkers and/or assays or to better understand therapeutic agent potential, so biomarker data are not fundamental to the successful completion of the phase I or II trial.

Dr. Hilsenbeck then suggested some design strategies for phase 2 trials, such as enrichment design. In addition, she summarized how to choose endpoints and optimize bio-specimen timing in the clinical course of a patient.

From her perspective of statistician, Dr. Hilsenbeck exemplified the impact of trial design on sample size and addressed multiplicity issues, such as multiple looks for early decision making, overinterpreting the subgroup analysis, trying many cut-points for a positive p value (instead of analyzing according to a pre-specified threshold), and testing multiple genes without statistical adjustment. Finally, she provided valuable suggestions for the design of translational research

trials. It is desirable to pre-specify hypotheses to be tested (and to plan appropriate sample size accordingly), to plan for 'interim' looks, to adjust for multiple comparisons or estimate false discovery rates, and to keep in mind that post-hoc analyses should always be regarded as exploratory.

*Authored **Deborah Blythe Doroshov, MD, PhD**, Fellow in Hematology/Oncology, Yale-New Haven Hospital, New Haven, CT, USA*

In this presentation, Dr. Hilsenbeck addressed the challenges of early translational work in oncology. A large portion of her talk focused on the development of biomarkers, which require both analytic and clinical validation as well as demonstration of clinical utility. Biomarkers can be used to assess risk, diagnosis, and prognosis; they can predict treatment benefits; and they can be used to assess disease progression or serve as surrogate endpoints. Prognostic biomarkers, she explained, might or might not have clinical relevance, depending on whether they would affect clinical management. It is critical to differentiate between prognostic and predictive biomarkers. In designing a study, it is critical to differentiate among integral biomarkers, which are necessary in order for a trial to proceed and must be done in a CLIA certified lab, integrated biomarkers which have preplanned analysis plans intended to validate assays, and exploratory biomarkers, which are much looser and might use trial data to understand the biology of a new agent. Choosing an evaluable endpoint is also critical in study design, and should be based on the disease natural history as well as the setting of that study (e.g. neoadjuvant or adjuvant therapy or treatment for metastatic disease). Finally, Dr. Hilsenbeck encouraged caution when performing subgroup analyses, as spurious results can be interpreted as meaningful when in fact they portend no clinical significance.