Designing for the Future:
Elements in Precision Medicine Trial Design

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Dr. Conley described the elements of precision medicine trial design, including issues to consider, common designs, and master protocols.

When designing precision medicine trials, it is important to consider a variety of issues such as the intent of the trial and the target population. Numerous practical concerns must also be taken into account, including the evidence for benefit of drug, the rarity of the biomarker in the intended population, the quality of the biomarker and how it will be measured, whether fresh biopsies will be needed, methods for obtaining and transporting biospecimens, and whether or not to use a central laboratory for biomarker tests.

In precision medicine trials, molecular profiling is used to determine actionable mutations. Actionable mutations predict clinical response to specific treatments and are therefore predictive biomarkers. Actionable mutations can include activating mutations in oncogenes that up regulate signaling, as long as there is a medication available against the target mutation. Loss of function mutations in tumor suppressors and pathway inhibitors that can lead to enhanced signaling can also be actionable. Other actionable mutations may include those that predict treatment resistance and those involved in DNA repair.

Master protocols have been developed for precision medicine trials that can be used to examine different types of therapies and tumors. One issue in precision medicine is that many molecular “driver” abnormalities are expected to be relatively rare (for example, present in only 3-8% of cancer patients). Screening for each of these mutations in individual trials would result in high rates of screen failures that could be avoided by grouping the studies together and screening for different mutations at the same time. Ideally, using the master protocols will result in operational efficiency gains that will hopefully bring drugs to patients faster. There are two main types of master protocols. In umbrella trials, patients with a single cancer type are screened for a panel of molecular abnormalities then assigned to different drugs based on the results of screening. In basket trials, patients with many different tumor types are screened for a single target mutation profile. The two types of designs can be combined, as they have been in several recent trials, including MATCH.

Audience Questions and Answers

- Patients have so many acronyms and unfamiliar names to remember. Some doctors may not even know the names of the cancer drugs. Are there ways to simplify acronyms and drug names? This does sometimes get confusing when the drug doesn’t have a formal name or when we are trying to
be as generic as possible. We could give patients cards to carry that contain the name of the trial and their medications.

- **Can trials proceed faster by combining phase 1 and 2, for example?** Some trials have combined phases 1 and 2 with extensions. The FDA has been accepting of various trial designs, particularly in signal finding (early) studies.

- **In phase 1 studies, determining the maximum tolerated dose is not the same as determining the best dose. How do we get closer to the best dose?** Researchers can look at the drug’s pharmacodynamics and compare that to a response marker, if one is available.

- **What about the continuous reassessment method and accelerated titration?** The continuous reassessment method follows an algorithm that is more complex than a simple additive calculation, but it may not be superior. Accelerated titration is used more often; in this method, the first patient is given a low dose, and if they didn’t experience a toxicity more than grade 2, then the dose is escalated in the second patient, and so on. The first time a predefined toxicity level is reached, you go back to the previous dose.

- **It seems there is value in conducting retrospective analyses for older trials. Can we look at these data to identify characteristics of responders?** Yes, this method is being used, and in fact, was used in prospective/retrospective clinical trials to identify ras mutations.

- **What drives the design for better biomarkers?** There is need for more and better biomarkers, but funding has not been a priority. We do have a study section for this at NCI now. The main thing that will drive biomarker development is when it is accompanied by a drug.