Use of Predictive Biomarkers in Phase 2 Trials

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H&O What are the different ways in which biomarkers can be used in clinical trials?

JD Biomarkers can help us in a number of different ways, depending on the phase of the trial and on the specific research questions. They can be surrogate endpoints, which sometimes are used instead of traditional clinical endpoints. One example is measuring the objective tumor response as a surrogate for an antitumor effect and overall survival. In early-phase trials, biomarkers also can be used as pharmacodynamic markers, which may help us make dosing decisions. In late-phase trials, particularly phase 3 trials, there are 2 types of biomarkers used to evaluate and predict outcome, called prognostic and predictive markers. Prognostic markers are independent of treatment and correlate with patient outcome. They commonly are used to determine whether the patient should be treated with further therapy. Predictive markers are used to determine whether a subset of patients might benefit from a specific treatment, usually a therapy targeted toward that marker. Predictive biomarkers have become more common in the past 15 years as our ability to test for biomarkers improves, and our knowledge of disease biology leads to targeted drug treatments that interfere with abnormal biochemical pathways within cancer cells.

H&O Are there differences in how biomarkers are used in phase 2 trials vs other phases?

JD Phase 2 trials in oncology are designed to determine whether a drug is likely to have sufficient anticancer activity to improve patient outcomes compared with standard of care. In this setting, biomarkers are generally used in 1 of 2 ways. Traditionally, they are used as surrogate endpoints.

The endpoint in a phase 2 trial is, in some respects, used as an intermediate endpoint. For example, we might measure objective tumor response, which we use as a way of assessing an antitumor effect that might subsequently, in a phase 3 trial, lead to an improvement in overall survival compared with standard of care.

But increasingly, we are looking at phase 2 trials in cancer not just to determine whether there is an anticancer effect, but also to look for markers that might correspond to whether a patient will benefit. Predictive markers are increasingly being embedded into phase 2 trials so that we potentially can identify which patients are most likely to benefit from treatment. Subsequent phase 3 trials can then confirm not only the treatment effect, but also the predictive biomarker effect.

H&O Currently, how common is the use of predictive biomarkers in phase 2 trials?

JD A significant number, possibly a majority, of phase 2 trials have secondary objectives that assess potential predictive markers. Some phase 2 trials are designed to assess for treatment effect only in the group of patients with cancers that have the predictive marker. For example, there are studies focusing specifically on whether targeted inhibitors are effective in patients with BRAF mutations in melanoma or HER2 amplifications in breast cancer.

H&O What are the benefits of using predictive biomarkers?

JD With a good predictive biomarker, we can limit the patients enrolled in a trial to the subset of those who are
most likely to respond to a certain treatment. There are 2 benefits to this. First, fewer patients are needed in the trial to demonstrate improvement, which can result in reduced cost and recruitment time. Second, the clinical effect might be larger in this subgroup of patients, as patients who are unlikely to benefit from treatment are removed from the study population. Therefore, it could be possible to detect efficacy in a small group of patients who otherwise would have been overlooked if the general population were tested.

**H&O What are some examples of successful studies using predictive biomarkers in phase 2 trials?**

**JD** One example is the use of trastuzumab (Herceptin, Genentech) in breast cancer. Approximately 20% of the breast cancer patient population harbors a mutation in HER2, which is associated with a more aggressive cancer. Trastuzumab is an antibody against the human epidermal growth factor receptor (HER2), and was found to improve overall survival in late-stage metastatic breast cancer compared with standard therapy. Later, benefit also was shown in early-stage breast cancer. The example of trastuzumab is particularly interesting because testing this drug in the general patient population might not have yielded significant results; however, by testing only the group with HER2 mutations, it was possible to see an effect.

Another example is the use of a BRAF inhibitor, vemurafenib (Zelboraf, Genentech/Daiichi Sankyo), in late-stage melanoma. Specifically, the common BRAF V600E mutation, which occurs in about 60% of the population, was targeted. Treatment with vemurafenib resulted in increased response rate, progression-free survival, and overall survival compared with standard chemotherapy.

Predictive biomarkers were also used in non–small cell lung cancer trials with crizotinib (Xalkori, Pfizer), which inhibits anaplastic lymphoma kinase (ALK) and ROS1. In about 7% of patients, there is a chromosomal rearrangement resulting in a fusion of the genes EML4 and ALK. This fusion was used as a predictive biomarker in the trial. Treatment with crizotinib in patients with this biomarker resulted in increased progression-free survival and overall response rate compared with standard therapy.

**H&O What is required for a predictive biomarker to be successful?**

**JD** Multiple components have to align for a biomarker to be successful. First, the drug has to be active. Second, we must have a good understanding of why the drug is active in a group of patients. Third, we have to find a marker that correlates with drug activity. Finally, we must have a good test to measure that marker, meaning we have to appropriately define positive and negative test results. To do this, we must be able to determine the level at which the biomarker sufficiently correlates with drug effect. Essentially, we must have the correct drug, the correct patient population, an understanding of how the drug works, and an accurate test to measure the drug’s benefit. If those attributes align we will have success, but if any one of those is incorrect, we will not.

**H&O What are the current risks or challenges associated with using predictive biomarkers in phase 2 trials?**

**JD** The main risk is that the hypotheses are wrong. A phase 2 study that incorporates a predictive biomarker is designed around 2 hypotheses: that the drug is active, and that we can show a correlation between presence of the biomarker and drug activity. Therefore in the phase 2 trial, a hypothesis could fail if the drug is not active, or it could fail because the biomarker does not correlate with drug activity. The biomarker may not show a correlation with drug activity if the patient population is incorrect, or if the biomarker test is inaccurate. There is also the risk that the drug actually is effective in the general population, and using the biomarker unnecessarily limits the number of patients treated.

Another challenge arises from statistical issues. In general, phase 2 trials are designed to identify a treatment effect, determine the likelihood that the treatment effect will occur, and confirm the appropriate dosing schedule. Phase 2 trials typically are small in order to limit the number of patients treated in the case that a drug is not effective. However, because of this small sample size, there may be insufficient numbers to show a strong correlation between a biomarker in a subset of patients and treatment benefit.

**H&O Do you know of any studies that highlight these risks?**

**JD** One example is a class of drugs called JAK2 inhibitors; ruxolitinib (Jakafi, Incyte Pharmaceuticals) is an example. Some myeloproliferative disorders—for example, myelofibrosis—are characterized by JAK mutations. The assumption was that a JAK inhibitor would be active in patients where these mutations occurred, and it would treat this disease. And in fact, they do provide benefit to patients with this disorder. However, the activity does not correlate with JAK mutation; even patients who do not have the mutation benefit from JAK inhibitors. There are different hypotheses as to why this occurs. It could be that the pathways are active even without JAK mutations, or that the patient benefit is not directly related to the drug’s action on the mutated JAK pathway.
Another example is the development of an antibody for colon cancer, cetuximab (Erbitux, Bristol-Myers Squibb/Lilly), which targets the epidermal growth factor receptor (EGFR). It was thought that the presence of EGFR, measured with immunohistochemistry, would correlate with cetuximab benefit in that patient. However, the researchers found evidence of patient benefit even in patients whose tumors tested negative for EGFR. In this example, it is likely that the immunohistochemistry test was not successful at detecting what were low—but still biologically significant—levels of EGFR expression. In this instance, the hypothesis that cetuximab is beneficial to patients with EGFR is correct, but the ability to detect biologically relevant levels of EGFR is limited. Interestingly, cetuximab was later shown to be ineffective in colon cancer patients with KRAS mutations, so this is currently being used as a predictive marker that correlates with lack of benefit.

**H&O** What do you think is the future of predictive biomarkers in phase 2 trials?

**JD** I think we will continue to use predictive biomarkers in phase 2 trials. Our ability to successfully identify markers in phase 2 will improve, because we will learn from our mistakes. We will develop phase 2 trials at the right time, using the right tools and the right design, so that drugs will show activity in phase 2. We will have tests based on a more enriched understanding of cancer biology, so that they are more sensitive and accurate in measuring biomarkers associated with drug sensitivity and drug resistance. The experience of the last 15 years is going to lead to better-designed phase 2 trials with better drugs and better predictive markers.

**Suggested Reading**


