

▶ Taking It Personal: When to Add Biomarkers to Treatment Guidelines

By Jessica Wapner



With the mounting evidence showing the capacity for biomarkers to improve outcomes among patients with cancer, the role of diagnostics in the future of cancer drug development is tantamount to the personalization of therapy. As with any nascent approach to cancer care, the field of biomarkers is still taking shape; and with each newly found mutation, new pathways are being considered. However, numerous issues surround the incorporation of biomarkers into treatment guidelines. Questions arise, including what features are needed to warrant inclusion? Why is it important to include biomarkers into guidelines? And, when is the right time to add a biomarker into treatment guidelines for a particular cancer type?

Undoubtedly, making the era of personalized medicine a reality will increasingly require faster test results, feasibility of routine use of biomarker testing in practices, and more effective incorporation of biomarkers into cancer treatment guidelines. Therefore, understanding when to incorporate biomarkers into treatment guidelines means understand-

ing the host of clinical and regulatory issues apparent to their use; achieving this, could bring broad changes to cancer drug development.

Linking Outcomes With Biomarker Detection

What separates the biomarker success stories from the unsuccessful stories are improved outcomes. It has been established that patients with breast cancer who are HER2-positive benefit from Herceptin [trastuzumab; Genentech]. Similarly, Gleevec [imatinib mesylate; Novartis] efficacy is tied to the presence of the Philadelphia chromosome mutation in patients with chronic myeloid leukemia. And, most recently, only those advanced colorectal cancer patients without the K-ras mutation have been found to benefit from treatment with Erbitux [cetuximab; Bristol Myers Squibb/ImClone/Lilly] and panitumumab [Vectibix; Amgen].

According to Harold Burstein, a member of the breast cancer treatment guidelines panel of the National Comprehensive Cancer Network (NCCN) and co-chair of the aromatase inhibitor guidelines for the

American Society for Clinical Oncology, and associate professor of medicine at Harvard Medical School, “If the marker is prognostic but does not link itself to a clinical treatment or intervention, then it’s irrelevant.”

Joan McClure, NCCN’s Senior Vice President of Clinical Information states likewise, “We are looking for actionable results from having the [biomarker] test done.” Since the NCCN evaluates new biomarker candidates as part of the review and update of its cancer treatment guidelines, candidates are held up to the same scrutiny as new treatment options—by a panel of physicians with collective expertise in the treatment of a given disease.

The cyclin d2 mutation serves as a useful example of a biomarker that did not qualify for inclusion in treatment guidelines. Breast cancer patients harboring this mutation have a slightly poorer prognosis than those who do not. As Burstein explains, this particular information is useless when it comes to patient management. “[It] doesn’t help with treatment decisions,” states Burstein.

GUIDELINES

Because the marker was not linked to any particular intervention, it did not warrant inclusion in the NCCN's breast cancer treatment guidelines.

Biomarker candidates must have tangible results and biomarker tests must be reliable and reproducible. "You would never want to make a treatment decision based on a technique that very few people could do, or that couldn't be [repeated] time after time," says Burstein. Equally vital is having robust data to back up any claims of a biomarker's efficacy. Data based on small, single-center studies are generally not robust enough to grab a guideline panel's attention. "You want to be able to point to a sufficient data experience that gives you confidence that you can use this test," says Burstein.

Biomarkers on Trial

Requirements for inclusion of a biomarker diagnostic into treatment guidelines naturally raise questions about clinical trials data. Must the data be prospective? What data does the U.S. Food and Drug Administration (FDA) need in order to approve a new diagnostic?

Past experience shows that retrospective data can be acceptable for inclusion. For example, the Oncotype Dx assay developed by Genomic Health was approved in January '04 based on retrospective analysis from a clinical trial that was begun long before the assay was created. The assay assists in the selection of chemotherapy for estrogen receptor (ER)-positive, node-negative breast cancer patients. The ASCO tumor marker guidelines' inclusion of ER testing as an important biomarker for estrogen therapy was also based mainly on retrospective analyses of breast cancer patients who did or did not benefit from tamoxifen therapy.

Similarly, the discovery of the K-ras mutation's role in deciding whether or not to treat a patient with colorectal cancer with Erbitux was made retrospectively. That being said, updates to the package labels for both Erbitux and Vectibix—whose efficacy is also linked to the absence of the K-ras mutation—were hindered by the fact that the pivotal data initially presented at ASCO '08 were retrospective.

Currently, many of the diagnostic approvals are being followed by prospective studies. The TAILORx study is a 10-year clinical trial with a 20-year follow-up that will evaluate the power of the Oncotype Dx assay to aid in chemotherapy decisions for patients



with breast cancer. Results from these types of follow-up studies will confirm (or not) the [cont. on pg 20 >>](#)

FULL LENGTH PDFs ARE AVAILABLE TO PRINT SUBSCRIBERS ONLY.

Send requests to editor@oncbiz.com or subscribe today at www.oncbiz.com