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 understanding 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.

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 usefulness of these assays in individualizing treatment, and possibly lead to the incorporation of the diagnostics into treatment guidelines.

cont. on pg 20 >>

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Among industry experts, there is agreement that the ideal entry point for new biomarker tests is in the phase 1 stage so that data can mature by the time the phase 3 study is concluded. Gordon Gochenauer, Senior Consultant at Kantar Health, a global consultancy and marketing insights company, explains the test can be validated at phase 2, "so that you know what you have once you get to phase 3."

But, part of the problem with relying on a retrospective study is that the FDA may not approve the data. "Hoping that the regulatory authorities are lenient in letting you submit data retrospectively is the best case scenario," he says. "[However,] there's no question that regulatory authorities would prefer the data from a prospective phase 3 trial."

Gordon Gochenauer

One of the benefits biomarkers can have on a new therapy is that the duration of treatment is likely to be increased among patient populations for whom a drug is effective. Several years ago, Tarceva [erlotinib, Genentech/OSI] was approved as a second-line therapy for non-small cell lung cancer and was typically administered for 3 months. However, with the discovery of the epidermal growth factor receptor (EGFR) and K-ras mutation, Tarceva is now approved for first-line treatment with an average duration of therapy approaching one year. "That's the best argument for companies to not shy away from biomarkers," says Gochenauer. "You get drugs into earlier lines of therapy and you can more than double the duration of therapy."

An additional benefit of including a biomarker study early in clinical trials is the possibility of higher response rates. "There is a great desire to increase response rates and an expectation from regulatory bodies [to do so]," says Christopher Ung, Vice President of Strategic Business and Operations, Oncology, at Quintiles. As Ung explains, the response rate bar is set much higher today than it was in the past, when treatment options and validation techniques were fewer and farther between. If the target patient population is identified early on, then response rates will be higher, thereby increasing the likelihood of a drug being approved—and making marketing of the drug that much easier.

Christopher Ung

However, having an effective biomarker does not eliminate market risk completely when there are competing drugs for the same niche market. "If the response rate is high, it's a self-marketing program," says Ung. "But if it is similar [to other drugs], then...you could back yourself into a corner." Still, cancer drug development is clearly heading in a more personalized direction, and companies holding onto the hope of a blockbuster panacea could be left behind. "I think that needing and wanting to search for a blockbuster has in some ways held back biomarker development in the clinic up to this point," says Gochenauer.

Keeping Pace and Changing Dynamics

Although the pharmaceutical industry may need to shift into higher gear when it comes to including diagnostics into clinical trials, experts cite a similar need on the regulatory side. Both Ung and Gochenauer see Europe and Japan as far ahead of the U.S. in this regard. The K-ras mutation was incorporated into European treatment guidelines for colorectal cancer almost immediately after the data showing its connection to Erbitux therapy were reported. "[The U.S.] took about a year and a half," says Ung.

Similarly, Japanese investigators embraced the evaluation of the EGFR as a biomarker for Iressa [gefitinib; ImClone] therapy early on, conducting two prospective, phase 3 clinical trials. "In the West, we had only retrospective data looking at EGFR mutations," says Gochenauer.

Moving things forward will likely mean increased collaboration among public and private interests. Currently in the U.S., the Biomarkers Consortium stands out as a pioneer. The Consortium is bringing together the National Institutes of Health, the FDA, members of the Pharmaceutical Research and Manufacturers of America, Centers for Medicare and Medicaid Services, and the Biotechnology Industry Organization in an effort to speed up the process of identifying, developing, and qualifying potentially effective biomarkers.

Ung cites the Consortium's I-SPY 2 clinical trial as an example of the kind of approach that is needed if the promise of personalized medicine is to be realized. In I-SPY 2, treatment decisions for breast cancer patients are being made based on tests for a

series of well-known biomarkers. The goal is to test the idea of tailoring therapy based on these diagnostics. Remarkably, several pharmaceutical companies, including Abbott, Amgen, and Pfizer, among others, are cooperating in the study with government agencies, and others may join as the trial proceeds.

I-SPY 2 Trial Study Procedures

"What I'm impressed by in this trial is that there is a vision," says Ung, "a vision of looking at profiles of patients and pulling together the drugs from a variety of companies that have relevance to that biomarker profile." Based on their biomarker test results, patients will be treated with investigational new drugs (Table 1) plus neoadjuvant chemotherapy with paclitaxel, doxorubicin, and cyclophosphamide. This approach (Fig. 1) could potentially spare patients from unnecessary procedures as well as side effects from ineffective drugs. OBR published an article on the I-SPY 2 trial in its January 2010 issue.

A Future Worth the Effort

Clearly, the cancer drug development industry is ramping up its efforts where biomarkers are concerned. From McClure's NCCN vantage point, she sees a host of new diagnostics on the nearby horizon, and among the most intriguing new tests, according to her, are one for EGFR mutations to select lung cancer patients who are appropriate candidates for EGFR-targeted small molecule inhibitors, and one for B-RAF mutations in melanoma patients indicating potential response to treatment with B-RAF inhibitors. "The data are maturing as we speak," she says.

Ung, who works with pharmaceutical companies worldwide, has seen an uptake in the inclusion of biomarkers into drug development programs. "It's almost impossible to find a development program, especially if it relates to a targeted therapeutic, where biomarkers are not involved," he says. "The tide has definitely changed, and I don't see that ever receding."

Still, ushering in the era of personalized medicine is going to depend on finding the ways to obtain the most robust data possible for biomarkers that are tied to specific patient outcomes. "The successful ones will be those that are not just reproducible and consistent, but which are linked to a clinical decision," emphasizes Burstein. Only when the data are solid will guideline panels consider recommending them for patient care.

The odds of getting that high-quality, infallible data are vastly improved by collaboration among the many facets of cancer care. Cooperation among pharmaceutical companies, diagnostic test developers, regulatory bodies, and investigators is integral to the future of biomarkers—and thus the future of personalized medicine. The effort is formidable, but the payoff will be well worth it. "If we are clever enough in the design of trials and [are] open to other adaptive methods...I think we all stand to benefit a lot," says Ung. And that's a future everyone can agree with. JW

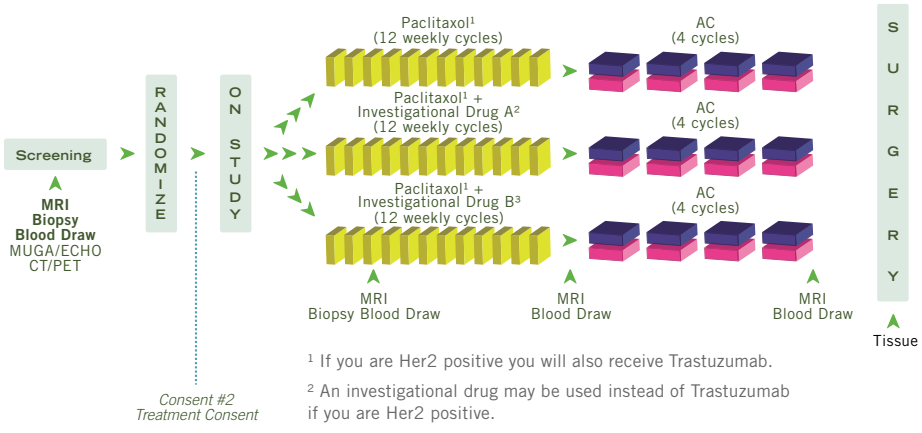

Figure 1. I-SPY 2 Trial Study Procedures. Source: www.ispy2.org/about

Table 1. I-SPY 2 Investigational Drugs*

ABT-888 (veliparib): A PARP inhibitor developed by Abbott Laboratories
AMG 655 (conatumumab): an APO-TRAIL inhibitor developed by Amgen
AMG 386: An angiogenesis inhibitor developed by Amgen
CP-751,871 (figitumumab): An IGFR inhibitor developed by Pfizer, Inc.
HKI-272 (neratinib): A pan-ERbB inhibitor developed by Pfizer, Inc.

*As of 3/17/2010. Source: www.cancer.gov/ncicancerbulletin/032310/page2