

Jul 10 2009, 12:00 AM EST

Sutent: Would Biomarkers Have Helped?

Special Report

Patricia F. Dimond, Ph.D.

While kinase inhibitors have proven remarkably effective in treating previously intractable cancers, the rush to discover the next post-Gleevec-like blockbuster provides many cautionary tales. Both failures and successes in cancer drug development show that proceeding without biomarkers is risky business. Implementing biomarker research and validation, though, remains tricky because a range of mutations and characteristics can affect tumor as well as patient responses.

Take [Pfizer's](#) cancer drug Sutent, for example. It has failed three label-expanding Phase III trials and succeeded in one. [In April](#) the firm said that the drug would not significantly improve progression-free survival when given as a single agent to patients with advanced breast cancer who had failed prior treatments. [Then in June](#) the firm stopped another trial evaluating Sutent with paclitaxel in the same indication.

[The first success](#) came later that month in patients with advanced neuroendocrine-type pancreatic islet cell tumors. [This was followed, however, by more bad news](#) with the company discontinuing its evaluation of Sutent plus Folfiri versus Folfiri alone for the first-line treatment of metastatic colorectal cancer.

Sutent is currently approved to treat gastrointestinal stromal tumors that are refractory to or have relapsed after Gleevec treatment and for advanced renal cell carcinoma. It is an orally available small molecule that inhibits multiple tyrosine kinases. These are key signaling molecules that control multiple cellular functions like angiogenesis, cell growth, and survival, all functions that go severely awry in cancer cells. Pfizer is studying Sutent in multiple Phase II and III trials for various solid tumors.

"Biomarkers are becoming increasingly crucial components of the drug development process, and we all recognize that most of our drugs work in only a subset of the treated patient population," remarks Pfizer's Dominic Spinella, Ph.D., vp, translational and molecular medicine. "That may be somewhat frightening to our commercial colleagues who may be reluctant to cut the market size down. But we also all recognize that if we can really tailor the drugs to the right patient population, not only will the trials be smaller, more efficient, and cheaper, but one can command a premium price for a drug that is much more likely to work in the patients who receive it."

[AstraZeneca's Biomarker Strategy](#)

The story of [AstraZeneca's](#) Iressa makes another good case for going into preclinical development and clinical trials armed with definitive markers. The FDA initially sanctioned Iressa in 2003 under its accelerated approval program for non-small-cell lung cancer (NSCLC) patients in whom two or more chemotherapy courses had failed. In Phase III trials, though, Iressa failed to produce a survival benefit among NSCLC patients compared to placebo.

The FDA thus issued a new label for Iressa in 2005 limiting its use to “patients with cancer who in the opinion of their treating physician are currently benefiting or have previously benefited from Iressa treatment.” This label resulted in a reduction of 58% in new prescriptions written for Iressa, and 86% of physicians treating NSCLC modified their treatment practice.

Retrospective tumor analyses, however, by scientists from the [Massachusetts General Hospital](#) (MGH) and the [Dana-Farber Cancer Institute](#) showed that eight of nine NSCLC patients who had responded to Iressa had EGFR mutations. No mutations were detected among the seven patients who did not respond to the drug. To analyze the effect of these mutations, the MGH team developed cultures of cells expressing two mutated receptor proteins and then studied the cell responses to growth factor; cells with mutant EGFR exhibited a two- to threefold increase in activation; mutated receptors were also 10 times more sensitive to Iressa inhibition than normal receptors.

In reality, it turns out that a number of mutations and genetic characteristics influence both tumor and patient responses to Iressa. “This (Iressa) was a targeted therapy before the target was really known,” remarked Matthew Meyerson, M.D., Ph.D., a member of the Dana Farber team that analyzed the tumors. As recently as July 1 AstraZeneca reported that the European Commission approved Iressa for locally advanced or metastatic NSCLC with activating mutations of EGFR-TK.

Additionally, on June 25 results of a Phase I trial published in the *New England Journal of Medicine* (*NEJM*) with AstraZeneca’s Olaparib, a small molecule enzyme inhibitor, showed that the drug shrank or stabilized tumors in 12 of 19 patients with breast, ovarian, and prostate cancers, all of whom carried the BRCA1 or BRCA2 mutations. Olaparib was designed to take advantage of abnormalities in DNA repair mechanisms in cancer cells carrying these mutations by inhibiting the enzyme poly (ADP-ribose) polymerase (PARP).

BRCA1 and BRCA2 mutations in cancer cells partially disable one of two major DNA repair mechanisms known as homologous recombination. Excision repair, the second mechanism, compensates for that loss in these cells. Olaparib’s inhibition of PARP-1 effectively prevents excision repair, leading to cancer cell death while sparing normal cells. The editorial accompanying the *NEJM* paper emphasized the potential value of biomarkers: “There are almost certainly other tumors with defects in homologous recombination that should make them targets for PARP inhibition therapy.”

One Size Not Likely to Fit All

Therein, however, lies another potential pitfall in one size fits all tumor biomarkers and in basing their validity on tumor type alone. Glioblastoma multiforme (GBM) is characterized by gene overexpression, mutation, and rearrangement of EGFR. The most common variant, EGFRvIII, is characterized by a 267 amino acid deletion in the extracellular domain, thereby leading to a receptor that doesn’t bind ligand but remains constantly turned on.

Theoretically this makes GBM an ideal candidate for kinase inhibitors. **Researchers say, however, that such targeted therapies remain extraordinarily challenging. This is partly because tumor responsiveness is determined not only by the presence of the relevant mutant kinases but also by other changes in the molecular circuitry of cancer cells, including loss of key tumor suppressor proteins, the selection for kinase-resistant mutants, and the deregulation of feedback loops.**

Exemplifying the complexity of identifying reliable, consistent tumor biomarkers is a 2005 study by Paul Mischel, M.D., of the [David Geffen School of Medicine](#) and [Jonsson Comprehensive Cancer Center at UCLA](#). Dr. Mischel and his colleagues performed genetic analyses on tissue from recurrent malignant glioblastoma patients, 26 of whom responded either very well or very poorly to Tarceva and Iressa. The scientists found that glioblastomas producing both EGFRvIII and PTEN, an enzyme that functions as part of a complex intracellular signaling pathway involved in programmed cell death, were 51 times more likely to shrink when treated with EGFR inhibitors than tumors without this combination of proteins.

Patients with tumors that expressed these proteins and who received an EGFR inhibitor went almost five times longer on average before their tumors progressed (243 days vs. 50 days) than those whose tumors did not express both of the proteins. EGFR and HER2/neu activity did not influence tumor response to these drugs.

“The term ‘biomarker’ can mean many different things from a pharmacodynamic endpoint that is used to demonstrate a drug effect to a genomic signature that is used to select an appropriate patient population,” points out Pfizer’s Dr. Spinella. “Like most pharma and biotech companies, Pfizer is committed to the discovery and use of biomarkers throughout its R&D process. The real key to effectively using them is in qualifying and validating them early enough in the process so that they can be employed to make rational decisions during the later stages of clinical development.”

◆◆◆

Patricia F. Dimond, Ph.D., is a principal at BioInsight Consulting. Email: drpdimond@comcast.net.