Q&A: George Sledge on Trends in Clinical Trials

As the diversity of breast cancer becomes clearer, clinical studies face new complexities

"Breast cancer is becoming a series of orphan diseases, which will make it intensely more complicated to study," notes George Sledge, MD. A longtime leader in basic and clinical research on breast cancer, he was president of the American Society for Clinical Oncology in 2010–2011. After many years as professor of oncology at Indiana University and codirector of the breast cancer program at Indiana University's Simon Cancer Center in Indianapolis, in January Sledge will become director of the Division of Oncology in the Department of Medicine at Stanford University. He talked with *Cancer Discovery*'s Eric Bender about challenges and opportunities in breast cancer clinical trials.

What are the main themes today in breast cancer research?

The biggest theme of course is that breast cancer isn't a single disease but a collection of diseases, and we're learning from genomics how incredibly complicated it is.

Once we get by the kind of simple stuff that we've known for a long time, like estrogen receptors and HER2, you get into dark waters in a hurry. If you look at triple-negative breast cancer, work by Jennifer Pietenpol and her colleagues at Vanderbilt suggests that there are at least 6 subtypes (J Clin Invest 2011;121:2750–67). If triple-negative accounts for 10% to 15% of breast cancer, and you're breaking that into 6 different subtypes, you are now talking about breast cancer as devolved into a series of orphan diseases.

How are these types of findings changing clinical trials?

In trying to treat such subtypes, the era of 5,000- or 7,000-patient clinical trials that try to answer broad questions in large populations will be a thing of the past. You can't do 5,000-patient studies on 2% of breast cancer.

Are the clinical trial networks making this shift to more focused trials?

We're starting to see those trials. Some results that I find very encouraging from one ACOSOG [The American College of Surgeons Oncology Group] trial were recently published. (J Clin Oncol 2011;29:2342–9). This was a fairly simple neoadjuvant hormonal therapy trial where researchers treated patients with an aromatase inhibitor, got a baseline biopsy, looked at patients who had a response as measured in KI67 levels, and then looked at how genomics informed what was going on in responders versus nonresponders. It was done with less than 100 patients, but it gave us a wealth of information.

Such as?

First, it suggests the extent to which drug resistance is a quantitative as well as a qualitative problem. Those who have drug resistance, on average, have about twice as many mutations as the patients who don't. Second, if you look at the drivers, once you get past a few high-flyers such as *PI3-kinase*, everything is rare. Everything represents rare subtypes.

These kinds of findings will require us to rethink how we do these trials. Collecting tissues and doing biomarker analysis may be the primary purpose of many of these trials, whereas in the past we thought of that as a secondary purpose.

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Will clinical research teams need much more sophisticated computational skills?

In the country of the blind, the one-eyed man is king. In the country of the oncologist, the bioinformatician will be king because most of us are blind when it comes to data analysis. By and large the bioinformatician is still the one-eyed man because in many cases he or she is not in the clinic or deeply invested in the underlying biology. But bioinformaticians will be the kings going forward.

What are the ongoing issues in clinical trials?

The national clinical trials program is massively underfunded. The trial process itself has been slow and cumbersome. As the science has gotten more exciting, the clinical trials process has gotten slower and slower. (NCI has been trying very hard to improve that.) The informed consent process is dysfunctional; it's based on a 1960s model of how Institutional Review Boards should run.

The bigger challenge is that we have not yet learned how to integrate our understanding of modern genomics and indeed of modern biology into the clinical trials process. Let me give an example. There's a wonderful paper, "The landscape of cancer genes and mutational processes in breast cancer," that looked at 100 breast cancers and did deep sequencing (Nature 2012;486:400–4). The authors found 40 different mutational drivers of growth expressed in those 100 cancers. Those 40 drivers were present in as many as 73 different combinations in those 100 patients. The number of drivers per tumor ranged from 1 driver in up to 28% of patients to a grand total of 6 drivers.

Hear those numbers and you have some sense of the issues that we face. If three quarters of every 100 patients has some different combination of mutational drivers, wow. Think about what that means in terms of how we have to combine agents!

What are the biggest challenges ahead?

Again, it's incorporating this great new knowledge into clinical trials. How do we obtain data quickly, do the bioinformatics that informs the treatment, design the trials that allow us the flexibility to attack different targets within the same trial, get collaboration from the companies and from the NCI that allows us to use multiple agents simultaneously in patients, get better informed consents, and deal with the very real toxicities that we'll get from combining these agents? These are the challenges. ■