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AN AUDIENCE WITH…

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When the I-SPY 2 trial was launched in 2010, it was welcomed as a first test of an adaptive trial strategy that would simultaneously collect data on multiple drugs from different pharmaceutical partners. The Phase II signal-finding trial has now enrolled more than 1,000 patients, testing 12 different experimental regimens from 9 different pharmaceutical partners in neoadjuvant breast cancer. I-SPY2 has 'graduated' five drugs that are considered to have a high likelihood of succeeding in confirmatory Phase III trials, and last year investigators amended its protocol so that it can run indefinitely. For Melissa Paoloni, director of advanced trials at QuantumLeap Healthcare Collaborative, the charity that is sponsoring the trial, it has been a resounding success. But the 6-year-old trial has also had to evolve with the times to stay relevant, she tells **Asher Mullard**.

What lessons have you learned with I-SPY 2?

This sounds like a no-brainer, but it can be challenging to work with a platform trial that you designed 6 years ago. Imagine if you had the same smart phone now that you had 6 years ago; the technology has improved since then and this poses problems.

So, we've made several changes to the trial. We've had to rethink our timeline for running drugs through the trial, for example. One of our goals is to move drugs through the trial in a rapid manner. We've learned that doing this might mean running fewer arms at any one time. Originally we had talked about running seven or eight arms at one time, and now we think a more appropriate number is about five.

Another thing that has become evident is that designing adaptive trials, as challenging as it is, is still 'the easy part'. It's making them operational that is even harder. The difficulty of adopting adaptive design at a more mainstream level is the challenge of operationalization.

Another lesson has been in terms of how to think about the patients who do not respond to their randomized therapy. Because we are a very biomarker-driven trial — relying on multiple imaging end points and genetic analyses to enrol patients and track progress — we've learned a lot about how we might be able to recognize those patients who are not going to achieve a pathologic complete response (pCR) earlier on. At a minimum, this is the population that we would now like to re-randomize back into the trial. By looking at imaging end points to determine who those patients are, and by doing further mining with different genetic and biochemical assays, we hope to be able to introduce a second element of true precision medicine that can inform what that subsequent re-randomization step should look like.

We can do this for several reasons. One of these is just because of the large number of patients that have moved through our trial. We are also doing everything in a standardized fashion, so we don't have to piece together data from different trials to unearth signals.

You've yet to 'fail' a drug. Is that a problem?

It's true that not only do we want to define regimens that we think are the most interesting to move forward, but we also want to find the drugs that we think either shouldn't move forward in the combos that we have tested or that shouldn't move forward in the neoadjuvant setting at all. However, this is challenging to assess. Even AMG386, a drug that did not 'graduate', showed compelling data in terms of having a high predictive probability of subsequent success in one signature. So, one of the questions that we are evaluating is how do we best examine data for agents that don't graduate?

What are your plans for a Phase III follow-on to I-SPY 2?

We are still looking for the first partners for this trial, which we call I-SPY 3. Puma Biotechnology's neratinib, an inhibitor of human epidermal growth factor receptor 2 (HER2; also known as ERBB2) and epidermal growth factor receptor (EGFR), is still an option. And Merck & Co.'s MK-2206, an AKT inhibitor, is also still an option.

How would the adaptive, platform trial work in a Phase III setting?

Although the trial would still be adaptive, it would be so in a different way, adapting sample size based on interim analyses.

Obviously Phase III trials are of the highest strategic and investment importance for drug companies. They provide different hurdles from Phase II trials, and it can therefore be challenging for them to think about I-SPY 3.

But we think it makes sense. We think that our approach, using a Bayesian adaptive design to determine the exact number of patients to answer both pCR and event-free survival co-primary end points, is the best way to design the smallest trial possible to generate data that can support accelerated and full approval simultaneously. We also think that our trials are not just animals of statistical and biomarker richness, but also animals of operational efficiency. We are always thinking about how we could do this better, less expensively and more thoughtfully. We've constructed ways to improve data collection, for example, actually writing a data plan to submit these to the FDA so that we can get their upfront perspective on an appropriate data set.

We may be able to layer in other efficiencies as well. Because there is the opportunity to test more than one drug simultaneously, we could share control arms in Phase III trials, reducing the number of patients we'd need to answer a question.

We think that our mindset is paradigm shifting from how a Phase III trial can run.

Do you have plans to expand beyond cancer indications?

We would like to launch 'I-SPY more', which would be I-SPY-like trials in other therapeutic areas. There is potential interest in this from various groups.