Speed SPYing: adaptive clinical trials hit the gas

The I-SPY 2 breast cancer clinical trial paves the way for multi-arm adaptive learning trials.

The multi-armed I-SPY 2 breast cancer clinical trials are starting to fulfill the promises of smarter, more efficient, biomarker-driven trials long touted by reformers (*Nat. Biotechnol.* **25**, 287–292, 2007). I-SPY 2 has now sped six drug candidates or combinations to phase 3 and has inspired a generation of Bayesian adaptive platform trials beyond breast cancer applications.

Donald Berry, a biostatistician at the University of Texas MD Anderson Cancer Center, an architect of I-SPY 2 (Investigation of Serial Studies to Predict Therapeutic Responses with Imaging and Molecular Analysis 2) and founder of the Bayesian statistical consultant group Berry Consultants, discussed trial outcomes at the 2019 Biotechnology Innovation Organization International Convention on 6 June 2019 in Philadelphia. Puma Biotechnology's Nerlynx (neratinib), AbbVie's veliparib, Genentech's Perjeta (pertuzumab), and Merck's MK-2206 and Keytruda (pembrolizumab) have moved on to phase 3 trials in breast cancer subtypes, as has a combination of Perjeta and Genentech's Kadcyla (ado-trastuzumab emtansine) (Table 1).

Berry says that I-SPY 2 launched in 2010 and received mixed enthusiasm from the community (*Nat. Biotechnol.* **28**, 383–384, 2010). But the tide began to turn in 2016 when researchers published the results of the first two arms to graduate—Nerlynx (*N. Engl. J. Med.* **375**, 11–22, 2016) and veliparib (*N. Engl. J. Med.* **375**, 23–34, 2016)—in the *New England Journal of Medicine*. "People read the papers and observed there was this strange thing going on—there were no *P* values, it was Bayesian probabilities," says Berry. "The reaction has moved from being really skeptical of these lunatics that are trying to do this to 'this is transformative.'"

I-SPY 2 uses magnetic resonance imaging and ten biomarkers to direct patients to the right trial arm, monitor their progress and identify promising results as data become available, by using Bayesian statistical modeling to learn and adapt the trial rather than assembling the data afterward. Unlike randomized controlled trials, which must be designed from scratch, I-SPY 2 can add in new experimental agents or combinations to its ongoing trial without ramping up patient accrual, by using a single control arm for all the experimental arms. Its Bayesian algorithm incorporates pre-existing and constantly accruing data into probability predictions about efficacy, thus enabling faster decisions. When the algorithm predicts that a drug candidate's efficacy is above 85% in a molecular subtype of breast cancer, the drug graduates and can move on to phase 3 studies. The result is a more nimble trial that can be started faster and can generate results more quickly: I-SPY 2 drugs can spend as few as 12 months in phase 2.

"I-SPY was truly groundbreaking," says Victoria Manax Rutson, Chief Medical Officer for Pancreatic Cancer Action Network (PanCAN), adding that master protocols allow researchers to ask multiple questions simultaneously and to carve out the right niche for new drugs.

Inspired by I-SPY 2's underpinnings, other similarly structured platform trials have since cropped up in a host of disease areas. One example is Precision Promise, a trial that PanCAN will launch this year in an attempt to accelerate development of drugs for pancreatic cancer.

An eighteenth-century theologian, Thomas Bayes, came up with a formula for determining conditional probability that is increasingly used in the life sciences. Credit: The Picture Art Collection / Alamy Stock Photo

Genentech picks three

Genentech has deepened its discovery and development efforts by forging three new collaborations in its key therapeutic areas of neurology and oncology. In each of the July deals, with Convelo Therapeutics, Skyhawk Therapeutics and Sosei Heptares, Genentech will hold exclusive worldwide marketing rights to resulting drugs.

The partnership with Convelo centers on discovering first-in-class remyelinating therapies to treat neurodegenerative diseases, including multiple sclerosis. Convelo has developed a platform to identify drug candidates capable of directly stimulating oligodendrocyte progenitor cells in the central nervous system to form new myelin. The company will receive an up-front payment and research support from Genentech, which as part of the deal gets an option to acquire the company.

The second transaction, with Skyhawk, aims to discover small molecules that correct defects in RNA splicing, for use in oncology and neurology. Genentech receives options to license and develop RNA splicing modifier drug candidates that Skyhawk may identify using its SkySTART platform, which combines structural, kinetic and computational models. In exchange Skyhawk receives up-front and milestone payments worth more than $2 billion.

The third collaboration taps Sosei Heptares' expertise in G-protein-coupled receptor (GPCR)-focused structure-based drug design. Genentech is paying $26 million up front plus milestones for Sosei Heptares to use its GPCR-oriented platform to identify biologics and small molecules against targets Genentech chooses, covering a range of diseases the parties have not disclosed. GPCRs are popular but often intractable drug targets. Sosei Heptares is already partnered with several pharmas and biotechs around GPCRs, including Astra-Zeneca (immuno-oncology), Allergan (Alzheimer's disease), Daiichi Sankyo (pain), Pfizer (multiple diseases), Kymab (immuno-oncology) and MorphoSys (monoclonal antibodies, including one against protease-activated receptor 2). Sosei, headquartered in Tokyo, acquired London-based Heptares Therapeutics in early 2015.

Published online: 4 September 2019
https://doi.org/10.1038/s41587-019-0257-1