Researchers develop newly redefined breast cancer response subtypes

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Research scientists and statisticians from UC San Francisco have developed improved biomarker classifications as part of their research results in the I-SPY 2 trial for high-risk breast cancer patients. The new

cancer response subtypes reflect responsiveness to drug treatments and are intended to help clinicians be more precise in how they target therapies.

Using the I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis) trial's comprehensive multi-omic molecular characterization of all tumors and the diverse array of drugs targeting different molecular pathways, the I-SPY 2 researchers were able to access the associated datasets to create breast cancer subtypes to match modern treatments.

The researchers, whose findings were recently published online in *Cancer Cell*, show that by combining predictive biomarkers to create response predicting breast cancer subtypes, these subtypes can then be matched to the most effective modern treatments. The best subtyping schemas incorporate Immune, DNA repair, Luminal, and HER2 phenotypes, Treatment assignment using these response predictive subtypes may improve the efficacy of the treatment and patient outcomes.

I-SPY 2, sponsored by Quantum Leap Healthcare Collaborative (QLHC) who manages all of the collaborations among academic and industry partners, announced that these new subtypes will move forward in the next iteration of the trial I-SPY 2.2.

Using the I-SPY2-990 mRNA/phospho-protein Data Resource from nearly 1000 patients who participated in 10 arms of the I-SPY 2 TRIAL, researchers evaluated 27 predictive I-SPY 2 qualifying biomarkers which led to the development of a response-predictive subtyping schema for prioritizing therapies. First authors Denise Wolf, Ph.D., and Christina Yau, Ph.D., both of UCSF, used gene expression, protein levels and response data from 10 drug-arms of the I-SPY2 neoadjuvant trial to create new breast cancer subtypes that incorporate tumor biology

beyond clinical hormone-receptor (HR) and HER2 status.

"Use of these response predictive subtypes can be used to guide treatment prioritization, will increase response, and will revolutionize the way in which physicians treat their patients" said Laura van 't Veer, Ph.D., Co-Director of the UCSF Breast Oncology Program and lead scientist for the I-SPY 2 biomarker studies.

The triple negative, as well as the HER2 negative hormone receptor positive high-risk groups, are divided into 3 different response predictive subtypes; the HER2 positive groups is divided into 2 response predictive subtypes. The researchers demonstrate that use of the subtype schema representing several drug targetable pathways allows more appropriate classification of tumors and is an improvement over current standard methods.

The I-SPY 2 trial is considered the archetype of a new approach to clinical trials. Rather than the traditional 'one drug, one disease' model for [drug development](#), it is a 'platform' trial. I-SPY 2 evaluates multiple drugs (or combination of drugs) in parallel with the goal of determining which drugs work best in various types of breast cancer. I-SPY 2 is also designed for efficiency and speed, by employing an 'adaptive' statistical model. The results of each patient are used to refine how the investigational drugs are assigned to new patients. Because of its approach, I-SPY 2 can achieve similar results in a fraction of the time with fewer patients than traditional trials. The goal is to get the right drug to the right patient. These new response predictive subtypes help to better characterize a person's tumor and from that determine if they are likely to respond to specific treatments such as immune checkpoint blockade.

"The past ten years of treating patients within the I-SPY program has taught us that the standard biomarker tests that we use today do not allow

us to optimize treatment for our patients, said Laura Esserman, MD, Co-Director of the UCSF Breast Oncology Program and Director of the UCSF Breast Care Center as well as I-SPY 2 principal investigator. "The whole I-SPY team is truly excited to see these results and improve the way we target our therapies. It is an important advance for patients, and a clear demonstration that the I-SPY model can not only accelerate the development of new cancer treatments, it can also target treatment to the patients who will benefit most. That means increasing the chance a drug will lead to a cure and minimizing the use of other therapies that may not be useful or add toxicity."

The I-SPY 2 network will prospectively test the response-predictive subtyping schema in I-SPY2.2, an upcoming version of the I-SPY2 trial that incorporates a sequential multiple assignment randomize trial (SMART) scheme and adapts treatment within individual patients based on biology and response.

The I-SPY2-990 mRNA/RPPA Data Resource is now publicly available. "This dataset will be an invaluable resource to the breast cancer research and drug development community, and ultimately to patients," said Esserman.

More information: Denise M. Wolf et al, Redefining breast cancer subtypes to guide treatment prioritization and maximize response: Predictive biomarkers across 10 cancer therapies, *Cancer Cell* (2022). DOI: 10.1016/j.ccell.2022.05.005

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