Neratinib Graduates to I-SPY 3

In the phase II I-SPY 2 trial, the tyrosine kinase inhibitor neratinib (PB272; Puma) produced a significantly improved pathological complete response in the breast and lymph nodes at the time of surgery, compared with a control group, among women with HER2+/HR− breast cancer. Researchers announced the findings on April 7 at the American Association for Cancer Research 2014 Annual Meeting in San Diego, CA.

Given the strength of the results, neratinib has become the second experimental drug to “graduate” from the adaptive I-SPY 2 trial, making it eligible for a phase III trial that could lead to accelerated approval by the FDA.

“This trial shows that neratinib is a highly effective agent in the HER2+ subset, especially the HER2+/HR−tumors,” said Laura Esserman, MD, MBA, overall co-principal investigator for I-SPY 2, a professor of surgery and radiology, and director of the Carol Frank Buck Breast Care Center at the University of California, San Francisco (UCSF). “The mechanism of action of this drug, which is a small-molecule tyrosine kinase inhibitor, is different from and may be complementary to an antibody-based therapy, such as trastuzumab [Herceptin; Roche/Genentech].”

In the trial, led by John Park, MD, director of novel therapeutics, breast oncology, at UCSF, 115 patients with newly diagnosed stage 2 or 3 breast cancer were randomly assigned to the arm of the trial that received neratinib plus paclitaxel while a 78-patient control group received trastuzumab plus paclitaxel or paclitaxel alone.

The primary endpoint of the trial was pathological complete response (pCR) in the breast and lymph nodes at the time of surgery. The estimated pCR rate was higher in the neratinib group than in the control group (55% vs. 32%), and researchers estimated a 78% Bayesian predictive probability of success in phase III trials for women with the HER2+/HR− signature. In addition, researchers estimated a 73% probability of success in phase III for all women with the HER2+ signature, regardless of hormone status.

“It’s significant that neratinib graduated in an arm without trastuzumab, suggesting that paclitaxel with neratinib is better than paclitaxel plus trastuzumab,” said Esserman. “In the future, we want to test the addition of neratinib to the standard therapy of paclitaxel plus trastuzumab.”

Neratinib is one of seven investigational arms of I-SPY 2, a randomized phase II trial for women with high-risk breast cancer that compares the effectiveness of adding novel agents to standard chemotherapy with standard treatment alone in the neoadjuvant setting. The goal is to match investigational regimens to subsets of patients based on biomarker signatures.

Investigational drugs progress to phase III if they have a higher estimated pCR rate than the control group and meet the Bayesian predictive probability threshold for success in a 300-patient phase III trial in at least one of 10 pre-defined biomarker signatures.

The adaptive design of I-SPY 2 speeds the drug development because agents can be dropped or added without obtaining FDA approval for a new protocol.

In December, I-SPY 2 researchers reported that, in another arm of the trial, veliparib (ABT-888; AbbVie) plus carboplatin added to standard chemotherapy was estimated to have a 92% Bayesian predictive probability of success in a phase III trial for women with triple-negative breast cancer.

Investigators are now working to set up I-SPY 3 confirmatory trials as soon as the end of this year, said Esserman. “We’re working to set up a network of standing phase III trials that would allow us to enroll enough patients to confirm an event-free survival endpoint,” explained Esserman. “Once we’ve accrued enough patients, we can apply for accelerated approval from the FDA.”

Palbociclib Ups PFS in HER2-/ER+ Breast Cancer

In postmenopausal women with locally advanced or metastatic HER2-/+ ER+ breast cancer, treatment with the experimental drug palbociclib and the aromatase inhibitor letrozole nearly
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