**NEWS IN BRIEF**

### PEOPLE

**Peter P. Yu, MD,** a medical oncologist and hematologist and director of cancer research at Palo Alto Medical Foundation in Palo Alto, CA, began a 1-year term as president of the American Society of Clinical Oncology (ASCO) at its 2014 Annual Meeting in Chicago, IL, on June 2. Yu is well-known for his knowledge and understanding of how health information technology can advance the prevention, diagnosis, and treatment of cancer. He has served on several ASCO committees, and he is a member of two cooperative clinical trials groups.

**H.M. Pinedo, MD, PhD,** professor emeritus and former chief of the Department of Oncology at the VU University Medical Center in Amsterdam, the Netherlands, received the David A. Karnofsky Memorial Award on May 31 at the ASCO meeting. The award recognizes his outstanding contributions to cancer research, diagnosis, and treatment. During a career that spanned more than four decades, Pinedo made seminal observations in cancer biology, as well as in mechanisms of drug action and resistance. He is also a former president of the European Society of Medical Oncology.

Also at the ASCO meeting, German virologist **Harald zur Hausen, MD,** received the Science of Oncology Award on June 1. The award honors his ground-breaking research on oncoviruses, most notably on human papillomavirus (HPV) and its role in the development of cervical cancer. Zur Hausen’s work led to the development of the HPV vaccine in 2006, an achievement for which he received the Nobel Prize in Physiology or Medicine in 2008.

### Neratinib Graduates to I-SPY 3

In the phase II I-SPY 2 trial, the tyrosine kinase inhibitor neratinib (PB273; 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 predefined 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
UV Light Accelerates Melanoma Metastasis

Scientists have confirmed that melanoma cells can spread along the outside of blood vessels, and, for the first time, have found this alternative metastatic process speeds up when the cells are exposed to UV light.

The findings, published recently in *Nature*, confirm a discovery made 15 years ago by two scientists in the pathology department of the David Geffen School of Medicine at the University of California, Los Angeles (UCLA). Claire Lugassy, MD, and Raymond Barnhill, MD: Melanoma cells can crawl along the outer surface of blood vessels (*Nature* 2014;507:109-13).

The feat is accomplished through angiotropism, by which melanoma cells mimic pericytes located outside blood vessels. These creeping melanoma cells are thus able to spread to nearby or distant sites without ever entering the bloodstream or lymphatic system. Lugassy and Barnhill named the metastatic process extravascular migratory metastasis, or EVMM.

Lugassy and Barnhill collaborated with German researchers at the University of Bonn on the new study, led by Thomas Tüting, MD. In a genetically engineered mouse model of melanoma, they found that repetitive exposure to UV light caused inflammation at the primary tumor site. Inflammation triggered the mouse immune response to recruit and activate neutrophils, which in turn stimulated new blood vessel formation and the migration of melanoma cells toward endothelial cells. The result was accelerated angiotropism, increased EVMM, and more lung metastases in UV-irradiated mice than in mice not exposed to UV light.

It is well established that UV sun exposure plays a key role in causing melanoma through DNA mutations in melanocytes. However, these new findings indicate that UV light inflicts damage independent of its tumor-inducing effect, Barnhill says.

“Here we have ultraviolet light inducing inflammation, and the inflammation is inducing a mechanism of cancer spread. These very important aspects of cancer development and cancer spread are now linked,” says Barnhill.

Although scientists don’t know how frequently EVMM occurs in melanoma, Barnhill says its incidence is likely “significant and may mark a certain point in the evolution of melanomas.”

The new findings could lead to the development of novel drugs to disrupt the EVMM process, says Lugassy.

“This work led by Tüting has shown for the first time that in addition to the specific association between angiotropic tumor cells and vessels, the inflammatory response due to ultraviolet light could also be a drug target,” she says.

“Targeting UV-activated neutrophils represents a potential therapeutic opportunity to interfere with metastatic melanoma, and potentially with other cancer types.” Other studies have found angiotropism and EVMM also occur in glioblastoma and pancreatic cancer.

Of the 76,100 Americans expected to be diagnosed with melanoma in 2014, nearly 10,000 will die—most of them
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