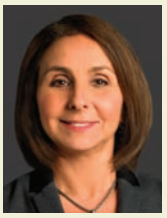
PEOPLE


Penn Medicine

Chi Van Dang, MD, PhD, began his role as editor-in-chief of *Cancer Research*, a journal of the American Association for Cancer Research (AACR), on January 1. Dang is the scientific director of the Ludwig Institute for Cancer Research and a professor in the Molecular and Cellular Oncogenesis Program at The Wistar Institute in Philadelphia, PA. He also serves on the Blue Ribbon Panel of the National Cancer Moonshot Initiative, is a fellow of the American Academy of Arts and Sciences, and chairs the NCI's Board of Scientific Advisors, and he previously served on the editorial board of the AACR's *Cancer Discovery*. Dang's lab established a link between *MYC* and energy metabolism in cancer cells, and his current research focuses on developing cancer therapies that exploit metabolic vulnerabilities of cancer cells.



Elizabeth Barrett, MBA, was named CEO of Novartis Oncology and a member of the Executive Committee of Novartis, effective February 1. She succeeds Bruno Strigini, MBA, PharmD, who retired. Most recently, Barrett was the global president and general manager of Oncology at Pfizer, where she had worked since 2009. Previously, Barrett spent 3 years as vice president and general manager of Oncology at Cephalon and 13 years as vice president, Oncology Franchise, at Johnson & Johnson. She earned her business degree in marketing from Saint Joseph's University in Philadelphia, PA.

Advancing Cancer Screening with Liquid Biopsies

A new blood test for tumor-specific mutations and proteins may bring cancer screening with liquid biopsies closer to reality (Science 2018 Jan 18 [Epub ahead of print]). The procedure can identify 70% of patients who have any of eight common tumors, including five tumors for which no screening test is currently available.

Researchers have been trying to develop liquid biopsies to spot cancers early, but to date the techniques have had several shortcomings. For early-stage cancers, when detection is more likely to benefit patients, the blood levels of tumor DNA may be insufficient for tumor detection. Furthermore, the tests' specificity has remained unclear because researchers haven't tested them in large populations of healthy volunteers.

To overcome these limitations, Nickolas Papadopoulos, PhD, of Johns Hopkins School of Medicine in Baltimore, MD, and colleagues developed CancerSEEK, a blood test that combines sequencing with analysis of protein biomarkers. The test searches for tumor-specific mutations in 16 genes and, to improve detection, uses approaches such as barcoding the DNA fragments isolated from the blood.

Because many early-stage tumors release minuscule amounts of DNA, CancerSEEK then evaluates the levels of eight proteins produced in large quantities by cancer cells, including CA-125 and carcinoembryonic antigen. Papadopoulos and colleagues designed an algorithm that weighs the protein and DNA data to determine whether a patient is likely to have a tumor.

To evaluate their approach, the researchers applied CancerSEEK to blood samples from 1,005 patients with one of eight cancers—breast, colorectal, lung, esophagus, pancreas, ovarian, stomach, or liver—the last five of which don't have screening tests. The scientists also analyzed samples from 812 healthy subjects.

CancerSEEK identified 70% of the patients with cancer. It worked best for ovarian cancer, detecting tumors in 98% of the patients with the disease, and worst for breast cancer, where the detection rate was 33%. The false-positive rate for all cancers was less than 1%.

Because liquid biopsy techniques that rely only on genomic information usually cannot determine a tumor's location, the researchers asked whether CancerSEEK could do that. In the 626 patients who tested positive, CancerSEEK narrowed the tumor's location to either of two organs in 83% of patients and pinpointed the site in 68%.

Papadopoulos and his colleagues estimate that the test would cost about $500.

"I would say it's a step on the way" to a feasible liquid biopsy screening test, says Ian Cree, MBChB, PhD, of the World Health Organization's International Agency for Research on Cancer in Lyon, France. Cloud Paweletz, PhD, of Dana-Farber Cancer Institute in Boston, MA, agrees, saying the researchers "have done a really good job to maximize the information that they get at a reasonable price."

Both scientists also agree that the approach requires refinement before it could be clinically useful. Cree notes that the sensitivity declined from 73% for stage II cancers to 43% for stage I. "We do need something that will do even better in low-stage disease," he says.

The authors should strive for even higher specificity, says Paweletz, because the control group isn't likely to be representative of the patients who would undergo cancer screening. "We need to get the specificity higher to use it in a broader population." *–Mitch Leslie* ■

First PARP Inhibitor OK'd for Breast Cancer

The FDA has approved the oral drug olaparib (Lynparza; AstraZeneca) for patients with metastatic breast cancer who also bear germline *BRCA1* or *BRCA2* mutations. The January 12 approval marks the first targeted therapy approved for this indication as well as the first PARP inhibitor approved for breast cancer.

Olaparib was initially approved in late 2014 for *BRCA*-mutated advanced ovarian cancer, the first PARP inhibitor approved for any cancer. Expanding its indication to another population of patients is "a plus for science," says Lori J. Goldstein, MD, director of The Naomi and Phil Lippincott Breast Evaluation Center at Fox Chase Cancer Center in Philadelphia, PA. "It's a plus for patients, especially for triple-negative *BRCA*-mutated cancer patients, for

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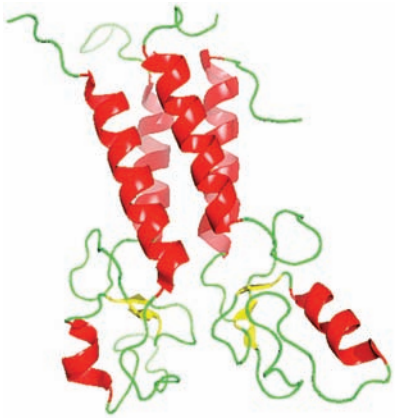

Structure of BRCA1

whom there is no previous targeted therapy approved."

The drug's approval was based on the phase III OlympiAD trial, which enrolled 302 patients with HER2-negative, metastatic breast cancer and germline *BRCA* mutations (N Engl J Med 2017;377:523–33). Patients were randomly assigned to receive olaparib or the physician's chemotherapy of choice in a 2:1 ratio. Median progression-free survival was significantly longer among those treated with olaparib compared with chemotherapy (7 months vs. 4.2 months, respectively). In addition, the response rate for the PARP inhibitor was more than double that for chemotherapy: 59.9% versus 28.8%, respectively.

Patients also tolerated olaparib better than chemotherapy and reported a higher quality of life, says Mark Robson, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, and OlympiAD's lead investigator. Although previous studies found that olaparib could, in rare cases, lead to hematologic malignancies such as myelodysplastic syndrome, Robson says, that didn't occur in the OlympiAD trial.

However, the drug didn't show an overall survival (OS) benefit. Median OS was slightly more than 19 months in both groups.

Assessing OS was difficult in this trial partly "because we don't control what treatment people get after they progress on the study," Robson says. In fact, patients in the chemotherapy group were more likely to be later treated with a PARP inhibitor or platinum-based chemotherapy than those in the olaparib group. That could partially explain the lack of difference in OS, Robson says.

Patients with breast cancer who have germline *BRCA1* or *BRCA2* mutations represent only about 5% of all breast cancer cases, and those with metastatic disease are an even more limited group. Despite the small numbers, Robson is hopeful that olaparib's approval lays the groundwork for further expanding its use. A clinical trial testing olaparib in patients with early-stage *BRCA*-mutated breast cancer is under way, Robson says, adding that olaparib could also prove to be effective even in those without inherited *BRCA* mutations but whose tumors have acquired a BRCA1 or BRCA2 deficiency. *–Rachel Tompa* ■

Celgene Targets Blood Cancers with Major Buys

Celgene inked two multibillion dollar deals in January, buying Seattle, WA–based Juno Therapeutics, a developer of chimeric antigen receptor (CAR) T-cell therapies, and Impact Biomedicines of San Diego, CA, which is testing a JAK2 inhibitor.

One impetus for the acquisitions is the pending arrival of generic competition for Celgene's most profitable drug, lenalidomide (Revlimid). Usually prescribed for the treatment of multiple myeloma, lenalidomide generated global revenue of nearly $7 billion in 2016. To drive new growth, Celgene announced on January 7 that it will buy Impact for $1.1 billion up front and another $5.9 billion in potential milestone payments. Two weeks later, plans to take over Juno for approximately $9 billion were announced.

"They're staring down Revlimid's patent expiry in a couple of years," says David Nierengarten, PhD, head of health-care equity research at Wedbush Securities in San Francisco, CA. The acquisition of Impact in particular "shows that they were really looking for potential near-term revenue opportunities that can fill that hole."

Impact's JAK2 inhibitor fedratinib will likely be the first financial stopgap. Phase III trial data showed that 35% to 40% of patients with previously untreated myelofibrosis taking the drug experienced a reduction in spleen volume, compared with 1% of those taking a placebo (JAMA Oncol 2015;1:643–51). A phase II single-arm trial of patients with the rare bone marrow cancer who did not respond to the JAK1/2 inhibitor ruxolitinib (Jakafi; Incyte) had even better outcomes, with 55% displaying a splenic response (Lancet Haematol 2017;4:e317–24).

A regulatory filing for fedratinib is anticipated later this year. If approved, analysts believe the drug could generate sales of up to $1 to $2 billion annually. The real moneymaker, though, could be Juno's pipeline of CAR T and T-cell receptor therapies now in early-stage trials.

Gilead Sciences, of Foster City, CA, made a similar bet on CAR T-cell therapies last August when it spent nearly $12 billion for Kite Pharma in Santa Monica, CA. Then, on January 23, the company helped bankroll Tmunity Therapeutics, spun off from the University of Pennsylvania in Philadelphia, which counts CAR T-cell pioneer Carl June, MD, among its founders.

The Kite buyout started to pay off in October when the anti-CD19 CAR T-cell therapy axicabtagene ciloleucel (Yescarta) earned FDA approval for patients with refractory or relapsed large B-cell lymphoma.

None of Juno's candidates are as far along, but the company does have a variety of promising agents, at least eight of which are in clinical development for a range of hematologic and solid cancers. These include an anti-BCMA CAR T-cell therapy for multiple myeloma that supplements Celgene's only prior CAR T agent, bb2121, under development with bluebird bio.

However, the lead asset in Juno's collection is JCAR017 (lisocabtagene maraleucel), an anti-CD19 CAR T-cell therapy that the company pushed forward after halting the development of JCAR015 following five deaths in 2016. With that setback, Juno fell behind Kite/Gilead and Novartis, the other company with an approved CAR T-cell therapy. However, Nierengarten says that might not be detrimental.

Nierengarten cites the difficulties Kite/Gilead has faced in securing reimbursement for axicabtagene ciloleucel, and he suggests Celgene could benefit from having a rival address regulatory hurdles first—especially if, as many observers suspect based on phase I data, JCAR017 proves to be best-in-class.

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