NSCLCs, Rizvi's team showed that anti–PD-1 therapy statistically correlated with and enhanced neoantigen-specific T-cell reactivity, as well as the presence in patients of a molecular signature that reflects his or her smoking history, and DNA repair pathway mutations. "Mutations that change the resultant amino acid [structure] correlated better than total mutation number. Because the mechanism [of action of the drug] should be immune monitoring of abnormalities, such as mutations, this makes sense, as the immune system wouldn't 'see' a mutation that doesn't alter the protein," Garon said.

Although not a perfect biomarker for efficacy because some patients who do not meet the PD-L1 threshold still experience activity of the drug, PD-L1 will be helpful in guiding treatment, said Roy Herbst, M.D., Ph.D., Ensign Professor of Medicine, Medical Oncology at the Yale Cancer Center in New Haven, Conn., who was not involved in this study. "The trial is encouraging, and the results will be used to guide testing the drug in untreated patients, and in the adjuvant and neoadjuvant settings," Herbst said.

Also discussed at the meeting was the CheckMate-057 trial, which tested the checkpoint inhibitor nivolumab against the chemotherapy docetaxel in advanced, treated nonsquamous NSCLC. This study was halted early, it was announced, because the trial met its endpoint, overall survival. The pivotal phase III randomized, open-label trial included 582 patients. Those who had not taken nivolumab are being offered the immunotherapy and final results will be reported at a future meeting.

Other Cancers

To deal with mesothelioma and other hard-to-treat cancers, researchers are turning to mesothelin, an antigen expressed at higher levels in mesothelioma, ovarian, and pancreatic tumors. For mesothelioma, no second-line treatment is available, and prognosis for patients is always grim.

Janos Tanyi, M.D., Ph.D., assistant professor of obstetrics and gynecology at the University of Pennsylvania's Abramson Cancer Center, and colleagues conducted a phase I trial in six patients: two with mesothelioma, two with ovarian, and two with pancreatic cancer by using mesothelin-targeting chimeric antigen receptor T, or CAR T, cells. Previously tested in blood cancers, in which the genetically modified T cells easily target blood-borne cancer cells, CART T cells in search of solid tumors have a higher bar to reach, Tanyi said. After infusion, the CAR T cells first expand, and then by day 28 they start disappearing from the bloodstream and begin migrating to the target cancer cells. Because mesothelin is also expressed on some normal cells, there was concern for off-target events, said Tanyi. However, no toxic effects were seen, and four of the six patients developed stable disease by day 28. The treatment is now considered safe and will move to a phase II study.

The goal is to accrue 50–100 patients for a trial in these three cancers that should begin in the summer. The phase II study will test low and high doses of T cells, with and without lymphodepleting cyclosporine. Patients will be monitored long term, for 15 years, Tanyi said.

Some of the first results in breast cancer using a checkpoint inhibitor were presented by Leisha A. Emens, M.D., Ph.D., member of the tumor immunology research program and associate professor of oncology at Johns Hopkins. In a phase Ia multisite trial, 54 patients with metastatic triple-negative breast cancer received the PD-L1 inhibitor, MPDL3280A, which prevents activation of PD-1.

Her team measured PD-L1 expression on tumor-infiltrating lymphocytes and found that 69% tested positive for PD-L1 expression. Her team found that of the 21 evaluable PD-L1–positive patients, the overall response rate was 19%, which included 9.5% complete responses and 9.5% partial responses. Seventy-five percent of responses were ongoing, with a median not yet reached. Six-month progression-free survival was 27%, and median duration of survival was 40 weeks.PD-L1 will not be a selection criterion for future trials in triple negative breast cancer, Emens said. She said that she thinks that the greater numbers of tumor-infiltrating lymphocytes that aggregate at these tumors indicate that these cancers have more mutations and make multiple novel tumor antigens, which this drug targets.

Notably, the trial used RECIST criteria, but three patients who were seen to have disease progression according to RECIST guidelines later showed tumor shrinkage, and the seeming progression was deemed to be "pseudoprogression," enlarged tumors that are due to inflammation from immune activation, not tumor growth. Questions remain about the best criteria to assess immunotherapies.

How long CAR T cells must live to have lasting effects, and how long should immunotherapies be used remain open questions as well. Other issues researchers seek to address are whether to test immunotherapies with chemotherapy, or targeted therapies. Endocrine toxic effects seen with the use of immunotherapies are also a topic of concern, said Richard Joseph, M.D., a medical oncologist at the Mayo Clinic in Jacksonville, Fla. Whether a way exists to avoid these effects, which may be permanent, is an issue that needs to be addressed by researchers, he said.

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Mammography Screening Still Brings Mixed Advice

By Susan Jenks

False-positive mammograms and overtreatment of screen-detected tumors that may lie dormant for years cost the United States an estimated $4 billion annually, a new analysis suggests.

Mei-Sing Ong, Ph.D., and Kenneth D. Mandl, M.D., M.P.H., both of Harvard University in Cambridge, Mass., led the study. Its findings come when several organizations, including the American Cancer Society and the U.S. Preventive Services Task Force, are updating recommendations for when and how often average-risk women should be screened. The revised recommendations are expected before next year.

Using claim data filed with a major U.S. insurance plan, the researchers found that costs ran higher than previously documented, with false-positive readings accounting for most of the

expense at $2.8 billion. The study, published in the April 15 *Health Affairs*, involved 702,154 women diagnosed and treated for breast cancer between 2011 and 2013. Roughly half the women screened were aged 40–49 years.

"I don't think we've solved any problems in terms of what the screening process should be," Mandl said, referring to the cancer community's decades-old disagreement over the best preventive strategy. "But [the study] gives us a sense of the magnitude of harm when the benefits are controversial, at best." Mandl is director of informatics at Boston Children's Hospital and a professor of pediatrics at Harvard Medical School. Ong is a postdoctoral research fellow at Boston Children's Hospital.

Controversy remains high regarding mammography's net benefit to women in their 40s who have no known family history or other risk factors for disease.

The cancer society currently recommends that annual screening begin at age 40 years and continue throughout a woman's lifetime, if she's healthy. However, the 16-member task force of independent experts, which advises the government, recommends that average-risk women aged 50–74 years begin screening every other year.

Screening at an earlier age, the group said, should be left to a woman's choice with her health care provider, whereas women older than 74 years should consult their physicians, as well, with the lack of useful data for or against screening. Similar advice is part of the task force's updated guidelines, now under review, after a public comment period.

"Women may want to begin screening in their 40s," said Kirsten Bibbins-Domingo, M.D., Ph.D., vice chair of the task force and a professor of medicine, epidemiology, and biostatistics at the University of California, San Francisco. "It's an important tool. But in this age group, the benefits are closer to the harms."Among the harms: false-positive mammograms that cause at least temporary emotional anxiety and distress, according to Bibbins-Domingo and others. These false alarms occur often in women in their 40s, whose dense breast tissue can make tumors harder to see. A risk factor for breast cancer, breast density occurs in at least half of women, and doctors still don't know which patterns carry the greatest risk, Bibbins-Domingo said.

Investigators in the Harvard study estimated that false positives occur during mammography screening in roughly 11% of women overall. The figure rose to 13% when the algorithm incorporated ultrasound and magnetic resonance imaging, with women aged 40–49 years more likely to have these diagnostic workups than older women. And, from earlier studies, researchers cited a 61% cumulative probability of a false-positive recall in a woman aged 40–50 years after a decade of screening.

"I don't think we've solved any problems in terms of what the screening process should be. But [the study] gives us a sense of the magnitude of harm when the benefits are controversial, at best."

Mandl said he and Ong measured false-positive rates directly, examining claim data for follow-up tests that lacked a cancer diagnosis. Not so, however, for overdiagnosis—generically defined as the diagnosis of breast lesions unlikely to threaten a women's health during her lifetime, yet treated all the same. To arrive at the study's $1 billion annual cost estimate, according to Mandl, they relied on published overdiagnosis rates gleaned from several randomized trials. One trial included a 25-year follow-up of the Canadian National Breast Screening Study, which appeared in the *British Medical Journal* (*BMJ* 2014;348:g366). Twenty-two percent of women in the study's screened cohort arm were diagnosed with breast cancers that never progressed but resulted in treatment anyway.

"It's a convincing piece of possible overdiagnosis," Mandl said. He attributed overdiagnosis primarily to interpreting mammographic images "based on a conceptual basis of cancer that might not be accurate," as well as ductal carcinoma in situ. Such diagnoses jump after the introduction of screening mammography, Mandl said. "Some of it is clearly a disease of mammography, although that's not to say every lesion is nonthreatening. Some are."

Real Value

As the American Cancer Society grapples with how, or whether, to change its own screening recommendations, Richard Wender, M.D., the society's chief cancer control officer, said his main criticism of the Harvard study is the implication that mammography carries cost without benefit to women in their 40s. "[Screening has] real value, particularly in preventing the death of otherwise healthy women in this age group," he said. Some 17.7%, or nearly one in five women who die of breast cancer, receive a diagnosis of breast cancer in their 40s, according to Wender.

Wender also questioned the analytical approach used. "If you do modeling, there's an obligation to publish a range of values," he said. "But they took the high side of overdiagnosis (22%) to estimate cost."

Although many cancer researchers agree that overdiagnosis does occur during screening mammography, Wender said, "we don't know how much there is" or how many women undergo unneeded treatment. According to his own estimates, overdiagnosis happens in 3% of invasive breast cancers, 20%–30% of ductal carcinoma in situ, and 10% overall.

Kenneth D. Mandl, M.D., M.P.H.

Moreover, not all false-positive mammograms are alike, Wender said. Most can be resolved through additional screening views or a 6-month follow-up, whereas perhaps 15% require biopsy, he said. "I don't mean to diminish the impact of living through the emotional anxiety of a biopsy, but that's just the nature of looking for cancer. Eventually, you need tissue to confirm it."

Finding Common Ground

Will the cancer community come together with uniform guidelines for mammography screening? Mandl said the economic impact of mammography needs to be part of any future discussions involving appropriate populations for screening. And, Wender said, he hopes 2015 will be the year that a clearer message emerges. "We need to emphasize areas of commonality," he said. "We want the health message to be the predominant one."

But before that happens, few would dispute the need for further improvements

in assessing individual risk—possibly through molecular profiling—and better communicating those risks to women.

"There's still so much we don't know," said Nancy Keating, M.D. M.P.H., professor of health care policy at Harvard Medical School. "In all women who have deadly tumors, mammography screening helps only a small percentage." Women in their 40s, for example, have a low risk for breast cancer numerically, but mammography screening reduces mortality from these more aggressive cancers by only 15%. That means 85% will die, even with mammography, she said.

Still, Keating added, "I don't think in America we are ready to stop screening women in their 40s. It's not that there's no benefit; it's just quite small." She called the recommendations of the task force reasonable, adding, "there are definitely women who are happy having mammograms every 2 years; others still want it every year."

About the study by her Harvard colleagues, Keating said: Though others may quibble with its findings, or the final cost estimates, "society needs to know the cost is real."

Meanwhile, the task force determined that existing evidence for newer digital mammography cannot yet balance benefits against harms or risk. Keating agreed. "The technique is so much better" than film-based mammography, she said. "But so is the treatment for breast cancer. Even when tumors are detected a little later, women are doing much better against this disease."

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PDQ (Physician Data Query) *is the National Cancer Institute's source of comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:*

Finn RS, Crown JP, Lang I, et al.: The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 16 (1): 25–35, 2015. PMID:25524798

Turner NC, Ro J, André F, et al.: Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med 373 (3): 209–19, 2015. PMID:26030518

The **PDQ Breast Cancer Treatment** summary was recently updated to include a subsection on palbociclib, an orally available CDK4/6 inhibitor that has been shown in two trials to enhance the efficacy of endocrine therapy.

PALOMA-1/TRIO-18 (NCT00721409) is an open-label, randomized, phase II trial that compared letrozole alone to palbociclib plus letrozole as the initial therapy for estrogen receptor–positive postmenopausal patients with advanced disease. Patients were enrolled in two cohorts, the first selected on the basis of ER positivity, the second on the basis of a potentially predictive molecular abnormality (CCND1 amplification or p16 loss). Results from the two cohorts were combined when no difference in efficacy of palbociclib plus letrozole in the biomarker subgroups was found. Over 2.5 years, 165 patients were enrolled in the trial. At the time of the final analysis of investigator-assessed PFS, the median PFS in the letrozole-alone group was 10.2 months, versus 20.2 months in the letrozole-plus-palbociclib group (HR 0.488; 95% CI, 0.319–0.748; one-sided $P = .0004$). Mature OS data are not available. Patients receiving palbociclib experienced more frequent cytopenias, fatigue, and nausea, but grade 3 adverse events aside from cytopenias were uncommon, and there were no episodes of febrile neutropenia. However, more patients on the palbociclib-letrozole arm discontinued treatment for adverse events (13%) than did those on the letrozole-alone arm (2%). The U.S. Food and Drug Administration granted accelerated approval to palbociclib on the basis of these results.

PALOMA3 (NCT01942135) is a double-blind, phase III trial that randomly assigned 521 patients with HR-positive, HER2/neu–negative, advanced breast cancer who had relapsed from or progressed on prior endocrine therapy to receive fulvestrant or fulvestrant plus palbociclib. Pre- and postmenopausal patients were eligible. Premenopausal patients received goserelin. The preplanned stopping boundary was crossed at the time of the first interim analysis of investigator-assessed PFS. This analysis showed a median PFS of 9.2 months on the palbociclib-fulvestrant arm versus 3.8 months on the placebo-fulvestrant arm (HR 0.42; 95% CI, 0.32–0.56; $P < .001$). Cytopenias, particularly neutropenia, were much more frequent on the palbociclib-containing arm, but febrile neutropenia was very uncommon (0.6%) on both arms. Patients receiving palbociclib had more frequent fatigue, nausea, and headache. Global quality of life as assessed by the European Organisation for Research and Treatment of Cancer questionnaire QLQ-C30 was better maintained on the palbociclib-fulvestrant arm (mean change, -0.9 points vs. -4.0 points; $P = 0.03$). Patients are continuing on blinded therapy; OS results are not yet available. To review the summary, please use the following link:
http://www.cancer.gov/types/breast/hp/breast-treatment-pdq/#link/_1408

The **PDQ Melanoma Treatment** summary was recently updated to include information on nivolumab, a checkpoint inhibitor used to treat patients with unresectable or metastatic melanoma following treatment with ipilimumab.
http://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq/#link/_896
A new subsection on duel checkpoint inhibition was also added, which includes the results of an international, randomized, double-blind trial of 945 previously untreated patients with unresectable stage III or IV melanoma who were randomly assigned in a 1:1:1 ratio to receive ipilimumab alone, nivolumab alone, or a combination of the two. Treatment with nivolumab alone or in combination with ipilimumab resulted in significantly longer PFS than with ipilimumab alone.
http://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq/#link/_1005
Text was also added on cobimetinib, a small-molecule, selective *MEK* inhibitor being developed in combination with the *BRAF* inhibitor, vemurafenib, but noted that the drug is currently not commercially available and that randomized data from the coBRIM (NCT01689519) study have been submitted to the FDA for review for approval.
http://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq/#link/_956

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