months, compared with 10.2 months in those who took letrozole alone. The final results were published in January (Lancet Oncol 2015;16:25–35).

Common side effects of palbociclib, including low white blood cell counts and upper respiratory infections, were “predictable and manageable,” the study authors reported.

However, the authors acknowledged the trial’s limitations, such as its open-label design and reliance on investigators’ assessments of tumor progression, rather than on assessments by a central panel of independent reviewers. Furthermore, PFS is a surrogate endpoint, so it is unclear whether palbociclib extends overall survival; PALOMA-1 did not track participants long enough to answer that.

The FDA’s decision came with the caveat that continued approval of palbociclib “may be contingent upon verification and description of clinical benefit in an ongoing confirmatory trial.” Pfizer’s phase III replication trial, PALOMA-2, is now under way, with final results due in October 2016.

Sunitinib Effective for Rare Thymus Cancer

Sunitinib (Sutent; Pfizer), a tyrosine kinase inhibitor already approved for several cancers, slowed disease progression in a phase II trial of patients with advanced thymic carcinoma who failed the standard first-line chemotherapy. The drug might therefore offer the first effective second-line treatment option for patients with this rare and aggressive form of thymus cancer, whose 5-year survival rate is 30% to 50%.

The findings are exciting because there have been very little data to support any treatment options for patients whose cancers have progressed despite first-line platinum-based therapy; says Gregory Riely, MD, PhD, a medical oncologist at Memorial Sloan Kettering Cancer Center in New York, NY, who specializes in treating thymic tumors. “This is certainly the most active drug we’ve seen for patients who have had prior therapy for thymic carcinoma.”

Several observations suggested that tyrosine kinase pathways—such as those that involve VEGFR, KIT, and PDGFR, which stimulate cell survival, proliferation, and/or angiogenesis—contribute to thymic epithelial cancers. For example, overexpression of these proteins or their ligands is associated with thymic carcinoma or other thymus pathology in humans. Furthermore, several small case studies have suggested that drugs that hinder VEGF, KIT, or PDGF signaling fight thymic epithelial tumors. Giuseppe Giaccone, MD, PhD, associate director for clinical research at Georgetown Lombardi Comprehensive Cancer Center in Washington, DC, and his colleagues therefore speculated that sunitinib, which targets these pathways, might curb the cancer’s growth.

In a phase II trial, researchers found that the tyrosine kinase inhibitor sunitinib may be effective as a second-line treatment in patients with advanced thymic carcinoma.

The open-label trial enrolled two cohorts with a total of 41 patients who had advanced thymic epithelial tumors—25 with thymic carcinoma and 16 with thymoma—whose tumors had progressed after one or more rounds of platinum-based chemotherapy. After a median follow-up of 17 months, 6 of the 23 assessable patients with thymic carcinoma (26%) had partial responses; 15 (65%) achieved stable disease; and 2 (9%) had progressive disease. The thymoma cohort closed early due to insufficient drug activity. The results were published in February (Lancet Oncol 2015;16:177–86).

“The take-home message is that there is a drug that works in thymic carcinoma and it is a relatively well-tolerated, well-known drug,” says Giaccone, the study’s senior author. “This will become standard second-line treatment for patients with thymic carcinoma.”

Giaccone and colleagues attempted to identify somatic variations in genes, including those for sunitinib’s targets, that might identify individuals who would benefit from the drug. No association was found between a specific mutation and response to sunitinib. The researchers also probed the immunological effects of sunitinib administration. They documented an increase in expression of the checkpoint receptors PD-1 and CTLA4—molecular markers of regulatory T-cell activity. The result might reflect what typically would be a healthy attempt to keep inflammation in check, the authors suggest, but in this situation, a sunitinib-incited immune attack presumably shrinks the tumor and is desirable. Perhaps drugs that block checkpoint receptors would prolong sunitinib’s assault on the cancer. To explore that idea, Giaccone’s team recently opened a phase II trial of the PD-1 inhibitor pembrolizumab (Keytruda; Merck) in patients with advanced thymic carcinoma.

TCGA Releases Head and Neck Cancer Data

Researchers have published the most comprehensive genomic analysis of head and neck cancers. Their findings may lead to improved treatments for this type of cancer; current therapies are successful only about half of the time.

More than 90% of head and neck cancers are squamous cell carcinomas, and most are triggered by tobacco or alcohol use or by infection with human papillomavirus (HPV). To clarify how these tumors develop and identify potential new treatment targets, researchers with The Cancer Genome Atlas (TCGA) analyzed squamous cell carcinomas from 528 patients, three times as many as in any comparable study. Instead of relying on one technique, as most genome profiling projects for this type of cancer have done, the team used several methods, including whole-exome sequencing, microarray analysis, and copy-number analysis.

“We think of this project as an atlas or encyclopedia” of these tumors, says co-author D. Neil Hayes, MD, of the University of North Carolina Lineberger Comprehensive Cancer Center in Chapel Hill. Hayes and more than 300 colleagues recently reported results for the first 279 patients (Nature 2015;517:576–82).
Researchers have uncovered genomic abnormalities that drive some head and neck cancers. For example, some tumors that tested positive for human papillomavirus (illustrated above) had recurrent deletions and truncating mutations in TRAF3.

The researchers uncovered genomic abnormalities that help explain the origin and progression of the cancers. For instance, they discovered that some HPV-positive tumors had recurrent deletions and truncating mutations in TRAF3. This gene is crucial for defense against several viruses, and its absence might impair the immune system’s ability to clear HPV.

The study also suggests new treatment avenues and ways to pinpoint patients likely to benefit from therapy. Among HPV-negative patients, Hayes and colleagues found a subset that showed a three-gene signature: normal TP53, mutations that inactivate the cell-death gene CASP8, and mutations that activate HRAS, which promotes cell division. Clinical records indicate that these patients have more favorable outcomes, and the signature could enable doctors to identify those who could be treated successfully with less-aggressive therapy.

In addition, one third of head and neck cancers have amplifications of the cell cycle regulator CCND1, the team discovered. CDK4/6 inhibitors, such as the recently approved drug palbociclib (Ibrance; Pfizer), disrupt this pathway. The paper supports testing these inhibitors in head and neck cancer, Hayes says.

“This study is important because it’s laying the foundation for the genomic and molecular characterization of the disease,” says Thomas Ow, MD, of the Montefiore Einstein Center for Cancer Care in New York, NY, who wasn’t involved in the study. “It’s a great example of how understanding the molecular consequences of specific mutations can inform the use of standard chemotherapy.”

Kim and Fillmore hope their findings will also guide patient selection for EZH2 inhibitors in development—but there are several in clinical trials, although none is yet approved. “We still have to consider the tumor genotype, even with epigenetic therapy,” Kim says.

A Potential Epigenetic Therapy for NSCLC

Beyond targeted treatments for non–small cell lung cancer (NSCLC), researchers are increasingly exploring the potential of therapies that influence DNA methylation and histone modification—two epigenetic processes frequently disrupted in cancer—against this disease.

One such epigenetic target is EZH2, a protein that silences various genes by adding methyl groups to histone H3, causing chromatin compaction. “High EZH2 expression correlates with a poor prognosis for NSCLC, which is why we decided to investigate the therapeutic possibilities of drugs that inhibit this enzyme,” says Carla Kim, PhD, an associate professor at Boston Children’s Hospital in Boston, MA. She recently showed that EZH2 suppression may boost the sensitivity of two NSCLC subsets to etoposide, a standard chemotherapy that works in only a minority of patients (Nature 28 Jan 2015 [Epub ahead of print]).

When Kim and her team blocked EZH2 in NSCLC cells, they observed two distinct phenotypes: Some cells became more sensitive to etoposide, while others became more resistant to the drug’s effects. The researchers found that the majority of sensitized cells harbored inactivating mutations in BRG1 or activating mutations in EGFR. On the other hand, cells resistant to etoposide in the wake of EZH2 inhibition were nearly all wild-type for both genes. In an EGFR-mutant mouse model of NSCLC, combining etoposide with EZH2 suppression significantly impeded tumor growth; however, this dual therapy was ineffective in mice with wild-type EGFR and BRG1.

Unlike EZH2, BRG1 remodels chromatin into a more open structure and helps topoisomerase II (TopoII)—the target of etoposide—ensure that DNA daughter strands separate completely during replication. “Without BRG1, TopoII can’t do its job,” says Christine Fillmore, PhD, a postdoctoral fellow in the Kim laboratory and the study’s first author.

The researchers noted that in BRG1-mutant NSCLC cells—rendered still more vulnerable to etoposide by EZH2 inhibition—the number of anaphase bridges, or entangled DNA daughter strands, increased, as did the rate of programmed cell death. EGFR-mutant NSCLC cells, also acutely sensitive to combined EZH2 suppression and etoposide, behaved similarly despite having wild-type BRG1. “For reasons we don’t yet understand, EGFR-mutant cells aren’t able to fully utilize BRG1, even though it’s present,” Fillmore says.

“The clinical implications of our research are exciting,” Kim says, “because there are no specific drugs for BRG1-mutant NSCLC, and the EGFR-mutant subset inevitably becomes resistant to targeted therapy.”

“This study opens the door to a closer investigation of dual EZH2 and TopoII inhibition in certain disease settings,” agrees Katerina Politi, PhD, an assistant professor at Yale Cancer Center in New Haven, CT, who wasn’t involved in the research. “It’s a great example of how understanding the molecular consequences of specific mutations can inform the use of standard chemotherapy.”

Kim and Fillmore hope their findings will also guide patient selection for EZH2 inhibitors in development—there are several in clinical trials, although none is yet approved. “We still have to consider the tumor genotype, even with epigenetic therapy,” Kim says.

Nanostars Amplify Ability to Image Cancer

Most cancer imaging techniques rely on probes linked to tumor-specific targets. New research has shown that one nanoparticle without ligands can detect five different cancers in mice. These “nanostars” boost surface-enhanced resonance Raman scattering signals enough to visualize tumor margins, microscopic metastases, and even precancerous cells.

“With this ultra-bright probe, we can now really see cancer, no matter how small, no matter what type,” says Moritz F. Kircher, MD, PhD, a radiologist at Memorial Sloan Kettering Cancer Center in New York, NY, and senior investigator in the study (Sci Transl Med 2015;7:271ra7).
TCGA Releases Head and Neck Cancer Data


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