thousands of false-positive findings and strain health care resources.

Though reluctant to rule out that a protein biomarker could reveal new pancreatic tumors, Goggins questions whether proteins in general are selective enough to avoid diagnostic overlap with other, noncancerous problems. Such proteins include the initial 28 in the M. D. Anderson study, he said, most of which are elevated under multiple settings. Goggins’s views on biomarker candidates lean more toward circulating tumor DNA snippets in blood, or circulating tumor cells, which he said could be more specific to pancreatic cancer.

However, Firpo maintains that protein-based panels can be continually improved.

“Each biomarker is individually a weak classifier, so our goal is to combine them into stronger classifier panels,” he said. “That approach has mathematical validity, and this latest study shows that we’re making progress, even though we’re not there yet.”

According to Taguchi, the next step will be to validate current results and then investigate the panel in prediagnostic blood samples, which will help ensure its predictive value. David Tuveson, M.D., Ph.D., a professor and pancreatic cancer specialist at Cold Spring Harbor Laboratory in New York, and a program chair at the American Association for Cancer Research conference, agrees that’s the right approach.

Emphasizing optimism over pessimism is important, he said. “However, we now need to substantiate the panel on retrospective cases, and perhaps also with a new prospective series from the general population or from patients who are at high risk.”

Sources for this story all agreed that the panel is not ready for the clinic. Screening high-risk individuals is now performed exclusively with imaging, as described in guidelines from the International Cancer of the Pancreas Consortium, published in Gut in January 2014.

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Cell Cycle Inhibitors Make Progress

By Vicki Brower

Palbociclib, the first in a new class of drugs to complete phase II testing, doubled progression-free survival (PFS) in women with metastatic estrogen receptor-positive (ER+) and HER2-negative (HER2-) breast cancer when given with standard hormone therapy, compared with hormone therapy alone.

In the 47-patient randomized study, those taking palbociclib and the aromatase inhibitor letrozole had a median PFS of 20.2 months, compared with 10.2 months for those taking letrozole alone. Women taking the combination lived a mean of 4 months longer (37.5 vs. 33.3 months). But increased survival did not reach statistical significance, said Richard Finn, M.D., assistant professor of medicine at the University of California, Los Angeles, at April’s American Association of Cancer Research meeting in San Diego. The Food and Drug Administration designated palbociclib a breakthrough therapy in April 2013.

Palbociclib targets two cell cycle enzymes, cyclin-dependent kinases 4 and 6 (CDK4/6), which normally facilitate cell cycle progression to DNA synthesis. In certain cancers, these enzymes are abnormally activated. Inhibiting CDK4/6 restores normal cell cycle function and stops uncontrolled cell growth.

“As well as increasing PFS, what is encouraging is that the drug does not appear terribly toxic,” said Eric Winer, M.D., director of breast oncology at the Dana-Farber Cancer Institute in Boston, who was not involved with the study. In the trial, known as PALOMA-1, side effects included decreased white cell count in about 75% of patients, which did not increase infection rate. Dose reductions were common, and 13% left the trial because of side effects.

Until recently, development of CDK inhibitors for cancer was a quiet endeavor. Reports on this drug, developed by Pfizer, and on two others by Novartis and Eli Lilly, started garnering attention last fall. New data from the American Association of Cancer Research in April and the American Society of Clinical Oncology meeting in May show that this new drug class is advancing rapidly through the clinic and showing efficacy. Reports show evidence of single-agent efficacy in one drug and synergy of combination treatments in others in which several pathways are targeted simultaneously. As cell cycle inhibitors, all three compounds are cytostatic and cause tumor apoptosis.

But whether CDK4/6 inhibitors can stop cancer from spreading is another question, said Larry Norton, M.D., deputy physician in chief for breast cancer programs at Memorial Sloan–Kettering Cancer Center in New York. If these drugs are effective, even in combination, a substantial market exists because they can be used in multiple cancer types, analysts say.

“Cancer involves abnormal cell development and growth, and migration, or metastasis,” Norton said. “Attaining tumor regression by slowing down cancer cell development does not touch metastasis,” he added. Stopping uncontrolled cell division will probably only modestly improve response rates of tumor regression and PFS. “That may have only a small effect on overall survival,” Norton said.

Cell cycle inhibition does not address the problem of metastasis, and combining CDK4/6 inhibitors with antimetastasis agents will be necessary, Norton said. The PFS endpoint in this and other trials should be replaced by overall survival, which reflects preventing new metastases, he said.

Winer disagrees: “PFS can be a worthwhile endpoint if toxicity is modest and quality of life is maintained. Ultimately, however, we’d like to see an increase in PFS and overall survival,” he said.
New Compounds
Why the sudden boom of CDK4/6 inhibitors?

“We have known for a long time that CDK4/6 is involved in many cancer pathways such as the KRAS, BRAF, PIK3CA, and retinoblastoma (Rb) pathways,” Finn said.

Inhibitors have been in development for many years, but candidate drugs had toxic effects and a lack of activity. Only relatively recently has the chemistry been worked out for these enzymes, he said.

Another key challenge has been to create a molecule with high specificity for CDK4/6 and cyclin D1, a regulator of cell cycle progression, which would not affect other phases of the cell cycle, said William Sellers, M.D. Sellers is global head of oncology at the Novartis Institutes for Biomedical Research in Cambridge, Mass.

“If the molecule is nonspecific, it will be toxic to many cells, such as those in the gastrointestinal tract, which would increase side effects,” Sellers said.

Drug companies are interested in the CDK4/6 pathway because if they can inhibit these enzymes, they may have a drug with broad anticancer activity in many cancers, such as head and neck, mantle cell lymphomas, breast cancers, and melanoma. Such a drug will not affect cancers due to mutations or deletions, such as pediatric retinoblastoma, small-cell lung cancer, and about 11% of glioblastomas, Sellers said.

First in Class
Researchers and analysts have been watching palbociclib as first in class. In late 2013, researchers presented even better interim results at the San Antonio Breast Cancer Symposium. Combining the drug with letrozole increased PFS to 26.1 months, compared with 7.5 months with letrozole alone. In breast cancer cell lines, palbociclib increased levels of cyclin D1; increased expression of the tumor-suppressing Rb gene; and reduced expression of p16, another tumor suppressor. These studies had also indicated that suppressing estrogen would increase cell death.

Researchers first tested palbociclib in 66 postmenopausal women with ER+ breast cancer with and without letrozole, with an endpoint of PFS. Next, patients whose tumors had amplified cyclin D1 and/or loss of p16 function were randomized to receive letrozole with or without palbociclib. Only ER+ status determined outcome.

Palbociclib is in four phase III trials in advanced ER+, HER2– breast cancer:
- PALOMA-2 tests palbociclib and letrozole against letrozole alone as first-line treatment.
- PALOMA-3 compares palbociclib plus the estrogen receptor antagonist fulvestrant with fulvestrant alone in women who have progressed despite hormone therapy.
- PEARL combines palbociclib with the aromatase inhibitor exemestane or with capcitabine in metastatic breast cancer for which letrozole or anastrozole, another aromatase inhibitor, did not work.
- PENELOPE-B, a randomized, double-blind study, compares palbociclib plus standard endocrine therapy with endocrine therapy alone in 800 women with early-stage breast cancer who are at increased risk for recurrence after surgery and chemotherapy.

“As well as increasing PFS, what is encouraging is that the drug does not appear terribly toxic.”

In May, a phase III trial began comparing palbociclib combined with letrozole with letrozole alone as first-line treatment for postmenopausal women with locally advanced or metastatic breast cancer. Researchers are also studying palbociclib in KRAS-mutated non–small-cell lung cancer (NSCLC) and squamous cell lung cancer patients.

Two Other Inhibitors
Gaining Ground
In late November 2013, after completing a previously undisclosed phase II trial, CDK4/6 inhibitor LEE011 entered a phase III trial with letrozole in 500 women with advanced or metastatic breast cancer. Because of its selectivity, some researchers believe that LEE011 will work best with certain other drugs to prevent resistance. Research now emphasizes combining drugs to inhibit more than one or two pathways.

LEE011 is in phase III testing with letrozole in women with ER+, HER2– breast cancer.
Researchers plan to combine the two drugs with a PI3K inhibitor, BYL719, which is also active in breast cancer and is now in phase III testing. The PI3K–AKT–MTOR intracellular signaling pathway is important in apoptosis.

Abemaciclib, formerly LY2835210, is another CDK4/6 inhibitor with nearly a dozen studies under way. Researchers selected CDK4/6 to target the important but elusive cancer pathway, KRAS, one of the most commonly altered pathways across cancer. The goal was to design a drug that was specific, that could be dosed to hit the cell cycle continuously to prevent developing cells from escaping drug exposure, and that could penetrate the blood–brain barrier to treat metastases.

A phase I dose-escalation study with abemaciclib in advanced cancer is complete, and tumor-specific expansions are under way in NSCLC, glioblastoma, melanoma, colorectal cancer, and breast cancer alone and with fulvestrant. Researchers at the recent American Society of Clinical Oncology presented results of the phase I study, which involved 132 patients with five tumor types. The single agent was active in patients after multiple treatments with other drugs, especially in 36 with hormone receptor–positive (HR+) disease. Among those 36 patients were nine partial responses, stable disease at 6 months in 18 patients, and an overall response rate of 19%. The median PFS was 5.8 months for all patients and 9.1 months for HR+ patients, with 18 HR+ patients still in treatment.
Also in May, phase I researchers reported at ASCO with abemaciclib in patients with advanced KRAS-mutated NSCLC, which showed single-agent activity. NSCLC patients with KRAS mutations, which are common, do poorly, but preclinical studies with the drug indicated that animal models with the mutation showed greater sensitivity to the drug. Phase I enrolled 57 patients with pretreated advanced disease, 29 with KRAS mutations, and 24 with wild-type KRAS. Those taking the CDK4/6 inhibitor demonstrated a 49% control rate; 55% of patients with the KRAS mutation responded, compared with 38% of patients with wild-type KRAS. As each drug moves through phase III combination studies, more data should reveal which is most selective, has the fewest side effects, and works best in a range of cancers alone and with other treatments.

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**Shared Mutation for Two Childhood Diseases**

By Cathryn M. Delude

The rare genetic disease fibrodysplasia ossificans progressiva (FOP) turns a child's muscle tissue into bone, forming a second skeleton that is eventually fatal. Frederick Kaplan, M.D., a leading FOP researcher at the University of Pennsylvania’s Perelman School of Medicine, helped identify the mutation responsible and searched for inhibitors. Eight years later, he learned about a bizarre coincidence: Four research teams independently found the same mutation in a rare, inoperable, and incurable pediatric brain-stem tumor called diffuse intrinsic pontine glioma (DIPG).

The mutated gene, ACVR1 (also called ALK2), has no previous association with cancer. Researchers found this gene in almost 25% of DIPGs but in no other brain tumors. Despite having the mutation in every cell, FOP patients do not get DIPG.

ACVR1 encodes a cell surface receptor for bone morphogenetic proteins (BMPs).

“We were especially excited because that’s a druggable target, and we can benefit from the work on an inhibitor [LDN-193189] already under way in the FOP field,” said Chris Jones, Ph.D., a DIPG researcher at the Institute of Cancer Research in London, who led one of four studies in *Nature Genetics* (Nat. Genet. 2014;46:457–61).

“All of a sudden, we have an explosion of insight that occurs when the cancer world and the developmental world meet,” Kaplan said. “There’s nothing worse than horrible diseases that affect children, and here are two horrible childhood diseases linked by a connection to the same mutation. We now have the best scientists in the pediatric cancer field consulting with scientists in the FOP field to gain insights into mechanisms and treatments that will help children with both diseases.”

**Blackest of Black Holes**

Each year, about 200–300 U.S. children with a median age of 6–7 years are diagnosed with DIPG. DIPGs belong to a group of pediatric high-grade gliomas (HGGs) that look identical to glioblastoma. Traditionally, biopsies are not performed, since results would not change therapy, which for lack of better understanding is based on adult gliomas. Of all the dismal pediatric outcomes for HGGs, DIPGs have the most devastating.

“Median survival for the kids is 9 months. Everyone is dead within 2 years,” said Mark Kieran, M.D., Ph.D., of Boston's Dana–Farber Cancer Institute, a coinvestigator of one of the studies (Nat. Genet. 2014;46:451–6). “We’ve made no progress in those tumors because we literally knew nothing about them.”

“It wasn’t clear whether DIPGs have such devastating outcomes because they cannot be removed surgically from the brainstem, or because they have a distinct biology,” said Suzanne Baker, Ph.D., who led a study conducted by St. Jude Children’s Research Hospital–Washington University Pediatric Cancer Genome Project in Memphis, Tenn. (*Nat. Genet.* 2014;46:444–50).

The four new studies jointly analyzed almost 200 DIPG tumors, using both autopsy and newly available biopsy tissues. Two studies also analyzed other pediatric HGGs. Except for ACVR1 and several other genes involved in developmental pathways or epigenetic regulation, even advanced tumors had few other known brain cancer genes such as BRAF or IDH1 or -2.

“This may mean that very few mutations are needed to initiate and drive the cancer,” said Cynthia Hawkins, M.D., Ph.D., who led the study from the Hospital for Sick Kids in Toronto (*Nat. Genet.* 2014;46:451–6).

“It’s an outstanding example of team science addressing a critical limitation in our knowledge of childhood malignant brain tumors,” said neurooncologist John Kuttetsch, M.D., Ph.D., chief of pediatric oncology at the University of New Mexico. “The investigators have now identified the genetic background that contributes to the development of DIPG and other midline HGGs in children. Now we have the opportunity to think about targeting those genes.”

**Weakly Activating ACVR1 Mutation**

FOP researchers had learned that when BMPs bind to the receptor that ACVR1 encodes, they activate a pathway that ultimately affects cells in different locations and stages of development. The DIPG