oncology at the Abramson Cancer Center, both in Philadelphia (J Clin Oncol 2013;31:3303–6).

However, the findings about targeted therapies still leave clinicians pondering which one to choose, Langer says.

For years, the go-to drug for treatment-naïve NSCLC patients has been erlotinib (Tarceva; Astellas Pharma). The first-generation tyrosine kinase inhibitor (TKI) was used off-label until it was approved for first-line therapy by the U.S. Food and Drug Administration (FDA) in May 2013. In July, the FDA approved afatinib (Gilotrif; Boehringer Ingelheim), a second-generation TKI, for the same indication.

Afatinib is called a second-generation drug because it covalently binds to the receptor itself, as opposed to erlotinib, which is ATP-competitive at the binding site. Afatinib is also a pan-HER inhibitor, whereas erlotinib is specific for EGFR.

These two drugs have never been compared head to head, and investigators say that published results don't point to a clear advantage for afatinib over its predecessor.

Separate trials indicate that afatinib offers 11.1 months of PFS in this population (increasing to 13.6 months among patients who don't acquire TKI-resistance mutations) compared with 10.4 months with erlotinib.

However, clinical experience shows that afatinib can be more toxic. Side effects are manageable, but afatinib-treated patients are more likely to suffer from skin rashes, diarrhea, and mouth sores, says Alice Shaw, MD, PhD, a thoracic oncologist at Massachusetts General Hospital in Boston. "Choosing one or the other," she says, "boils down to what you think your patients can tolerate."

Roy Herbst, MD, PhD, chief of medical oncology at the Yale Cancer Center in New Haven, CT, raises another consideration—afatinib could be less susceptible to acquired resistance, potentially justifying second-line uses for which it is currently not approved. Preclinical studies have shown that when combined with cetuximab chemotherapy, afatinib remains effective in TKI-resistant mice.

Lecia Sequist, MD, an associate professor at Harvard Medical School in Boston, MA, comments, though, that evidence in humans doesn't support these preclinical findings. "Afatinib doesn't appear to have a lot of activity in human patients with acquired TKI resistance," she says.

Moreover, Sequist says, "it would be difficult to get the combination treatment outside of a clinical trial—afatinib isn't approved in combination with cetuximab, and cetuximab isn't approved in lung cancer. This would also be a very expensive regimen."

The four oncologists agree that third-generation TKIs now in phase I trials, such as Clovis Oncology's CO-1686, might offer greater benefits in TKI-resistant, EGFR-mutant–positive cancers. Unlike their first- and second-generation predecessors, these drugs are thought to bind only to mutated EGFR and not to the wild-type receptor in normal cells. "First- and second-generation TKIs are about the same," Langer concludes, "but this story is by no means over." ■

Project to Mesh Genomic, Patient Data

A new integrated database may offer a powerful resource for cancer genomics analysis by merging whole-genome sequencing data with clinical information.

Current efforts such as The Cancer Genome Atlas (TCGA) typically offer few details about the patients' responses to treatments, notes Anthony Tolcher, MD, director of clinical research for South Texas Accelerated Research Therapeutics (START) in San Antonio. For maximal use, genomic data need to be closely linked to detailed clinical treatment and outcome data, he says.

In September, START and BGI Tech Solutions of Shenzhen, China, announced that BGI will handle sequencing and analysis of genomic data that will be integrated with clinical data in the San Antonio 1000 Cancer Genome Project. Launched last year, the project is generating and studying sequences from 10 cancer types, using frozen tissue samples.

In addition to its focus on integrating clinical data, the initiative differs from most cancer genome efforts in the type of patients it is enrolling, Tolcher says. Patients come mainly from community-based hospitals in the San Antonio area, not from academic medical centers, and thus may be more representative of cancer patients in the general population. Software created by START gathers a variety of information from the participants' files, including tumor staging, treatments, survival, and lab results.

So far, about 1,200 patients have signed on. "Ideally, we want to get up to 10,000 patients," says Tolcher.

All of the genomic and patient information will be housed in a database that will be publicly accessible to researchers worldwide, and should be online next year, Tolcher says.

More than 200 San Antonio–area cancer surgeons, pathologists, researchers, and oncologists have joined the effort. Drawing heavily on time donated by these medical professionals, the project is projected to cost $5 million, all raised from donations.

"It is important to link the genomic data with clinical information," says Lynda Chin, MD, chair of the department of genomic medicine and scientific director of The University of Texas MD Anderson Cancer Center in Houston, who isn't involved in the project. "It's great that they are going to target community physicians, and it's great that they will use frozen tissues."

However, Chin is concerned that the project's small budget—just over 1% of the price tag for TCGA—might not support the careful specimen collection and meticulous quality control necessary to ensure the data's accuracy and usefulness. "I think they have underestimated the challenge of getting the samples," she suggests. ■

Oral Bacteria May Cause Colorectal Cancer

Scientists have long known that the oral microbe *Fusobacterium nucleatum* plays a role in plaque formation and various periodontal diseases, but it isn't confined to the mouth. The bacterium is prevalent in intrauterine infections that can cause complications during pregnancy. In addition, separate research teams reported in 2012 that levels of *F. nucleatum* and other *Fusobacterium* species were

NOTED

- **The number of US cancer survivors rose to 13.7 million as of January 2012,** noted the *Cancer Progress Report 2013* (www.cancerprogressreport.org), released in September by the American Association for Cancer Research (AACR). Continued progress "will only be possible if we make funding for cancer research and biomedical science a national priority," emphasized Charles Sawyers, MD, AACR president and chair of the human oncology and pathogenesis program at Memorial Sloan-Kettering Cancer Center in New York, NY.
- **The U.S. Food and Drug Administration granted accelerated approval to Genentech's Perjeta (pertuzumab) for neoadjuvant treatment of early-stage breast cancer,** the first drug to receive such approval. "We are seeing a significant shift in the treatment paradigm for early-stage breast cancer," said Richard Pazdur, MD, director of the agency's Office of Oncology Drug Products.
- **Merck is cutting about one fifth of its global workforce,** with a new round of about 8,500 layoffs in addition to an earlier reduction of about 7,500 employees.
- **In a phase III trial of 602 women with advanced HER2-positive breast cancer whose cancer recurred or progressed despite previous treatments, those given Genentech's Kadcyla (T-DM1, ado-trastuzumab emtansine) achieved median progression-free survival (PFS) of 6.2 months,** compared with PFS of 3.3 months for those who received their physician's choice of treatment. Patients given Kadcyla also experienced fewer serious adverse side effects than those in the control group. The study was reported at the European Cancer Congress (ECC) 2013, held in Amsterdam, the Netherlands, from September 27 through October 1.
- **During the next 50 years, the dominant contributions to the global cancer burden will be from India, China, and Nigeria,** predicted the *State of Oncology 2013* report (www.i-pri.org/oncology 2013), presented at the ECC.
- **Nike cofounder Phil Knight pledged to give Oregon Health and Science University (OHSU) a $500 million award for cancer research**, but with an important footnote: For the award to be delivered, OHSU must raise an equivalent sum within 2 years.

higher in malignant colorectal tumors than in surrounding tissues. What wasn't clear, however, was whether the microbe was a cause or a consequence of cancer.

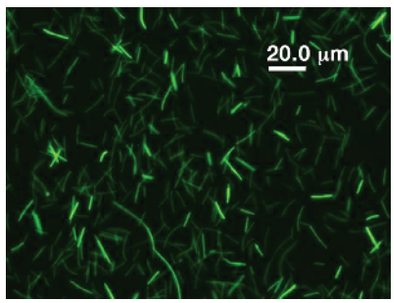
Now, two studies published in *Cell Host & Microbe* suggest that *F. nucleatum* creates a proinflammatory microenvironment and promotes colorectal carcinogenesis through E-cadherin and β-catenin signaling.

"*Fusobacteria* may provide not only a new way to group or describe colon cancers, but also, more importantly, a new perspective on how to target pathways to halt tumor growth and spread," says Wendy Garrett, MD, PhD. Garrett is an assistant professor of immunology and infectious disease and medicine at Harvard School of Public Health, Harvard Medical School, and Dana-Farber Cancer Institute, all in Boston, MA, and senior author of one of the studies (Cell Host Microbe 2013;14:207–15).

Building on the earlier research, Garrett's team examined colonic adenomas and normal tissue from 29 patients. They found an increased abundance of *Fusobacteria* sp. in adenomas compared with normal tissue, suggesting that the microorganism is involved in the initiation or progression of neoplasms. They also examined stool samples from healthy controls as well as patients with colorectal adenomas and carcinomas and found that levels of the bacteria increased as disease progressed.

Additionally, in a mouse model of intestinal tumorigenesis, the researchers found that *F. nucleatum* potentiated tumor development and recruited differentiated myeloid cells—including dendritic cells, myeloid-derived suppressor cells, and macrophages—that promote angiogenesis and tumor progression.

In the other study, a team led by Yiping Han, PhD, a microbiologist who has studied *F. nucleatum* for more than a decade and a professor of periodontics at Case Western Reserve University School of Dental Medicine in Cleveland, OH, showed that a small molecule called FadA on the surface of *F. nucleatum* binds to and modulates E-cadherin, a tumor suppressor, on colorectal epithelial cells (Cell Host Microbe 2013;14:195–206). β-catenin signaling is then activated, leading to the increased expression of transcription factors, oncogenes, *Wnt* genes, and inflammatory genes, and stimulating the growth of cancer cells.



Yiping Han

Abundant in the mouth, *Fusobacterium nucleatum* may cause colorectal cancer. Researchers don't know for certain whether the microbe plays a role in other cancers of the gastrointestinal tract.

Han's team also found specific *fadA* gene copy levels in normal colorectal tissue, adenomas, and carcinomas, with a 10-fold jump between each tissue type. "The differences were very clear," she says. "There was very little overlap between the three groups, and no overlap between normal and carcinoma."

Because *fadA* is unique to *F. nucleatum,* its expression could be used to diagnose colorectal cancer and identify people at risk for the disease, Han suggests. It could also be used to guide and assess possible treatments. "If FadA levels are reduced after treatment, perhaps it is an effective treatment," she says. "If it doesn't reduce the levels, perhaps the danger is still there."

As part of the research, Han's lab derived a synthetic peptide from a region of E-cadherin. Tested in mice, the peptide prevented *F. nucleatum* from binding to and invading cells, inhibiting tumor growth and inflammatory responses. Although the researchers didn't test the compound against other disorders related to *F. nucleatum,* she says there could be value in doing so.

"If we could block systemic proliferation of *Fusobacterium nucleatum,*" Han suggests, "we could kill many birds with one stone." ■

For more news on cancer research, visit *Cancer Discovery* online at http://CDnews.aacrjournals.org.