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strong parallel between human and animal models, and a relatively fast government approval process, comments Mark Dainty, MPharm, director of pharmaceutical research for Citi in London. "It's a good place to invest," he says. "For a pure commercial decision, I think it's absolutely the right thing to do."

"We've got a strong pipeline in the early space," says Susan Galbraith, MD, PhD, head of AstraZeneca's oncology innovative medicines group in Alderley Park. "Eleven of 12 of our phase I trials have seen tumor shrinkage."

The company will focus its oncology research on 3 areas, Galbraith says: drugs that target tumor drivers and resistance, such as selumetinib for non–small cell lung cancer; agents that trigger cell death, such as olaparib, a small molecule for treating solid tumors, and moxetumomab pasudotox, for treating hairy cell leukemia; and immune-mediated therapies, such as the CTLA-4 monoclonal antibody tremelimumab for treating solid tumors. Olaparib, moxetumomab pasudotox, and selumetinib are all slated to enter phase III clinical trials this year.

Like many other drug companies, AstraZeneca also is working to shore up its pipeline through collaborations with start-ups and academic researchers. The company took one such step on March 21, announcing a $240 million partnership with Moderna Therapeutics, a Cambridge, MA, start-up developing RNA therapeutics for cancer and cardiometabolic diseases.

"They're going to be taking more risks on novel therapies, not just playing it safe," says Cheryl Gradziel, PhD, an oncology analyst with GlobalData in Boston. "They're pushing themselves to be working at the forefront of oncology, more so than they have done in the past." ■

TCGA Sees Heterogeneity in Head and Neck Cancers

Investigators in The Cancer Genome Atlas (TCGA) Research Network have uncovered numerous genomic aberrations involved in head and neck squamous cell carcinomas (HNSCC), which are often caused by tobacco use but have recently been increasingly associated with human papilloma virus (HPV).

"We've found that these tumors are heterogeneous across all patients," says David Neil Hayes, MD, MPH, a medical oncologist at the University of North Carolina in Chapel Hill, cochair of the TCGA head and neck cancer working group. Hayes presented these findings at the American Association for Cancer Research Annual Meeting 2013 in Washington, DC, held April 6–10.

The study examined tumor and healthy tissue samples from 279 patients with HNSCC. Among the samples from this group, 80% of tumors were associated with tobacco use and 13% were HPV-positive.

For smoking-related cancers, 60% to 70% of patients already have lymph node–positive cancer at the time of diagnosis and typically have 5-year survival rates of about 50%, says Hayes.

The outlook for people with HPV-positive tumors is more optimistic, with at least one study showing a 5-year survival rate of 90%. However, standard treatment—radiation plus chemotherapy—is aggressive and toxic. "There's an incentive to find targeted treatments that cause less toxicity," notes Hayes.

Among HPV-positive samples, the study revealed that 40% to 50% harbored alterations in *PIK3CA*. Interestingly, these were linked with very low rates of *EGFR* alterations. "EGFR has been described as universally expressed in head and neck cancer," says Hayes. "But these findings suggest there may be a subgroup that does not fit this description."

He suggested that this finding may raise questions about the efficacy of Erbitux (cetuximab; Bristol-Myers Squibb and Lilly), which has been approved by the U.S. Food and Drug Administration for the treatment of metastatic HNSCC in patients with HPV-positive tumors.

All 279 tumor samples showed 15 significantly mutated genes, among them *CDKN2A, TP53, PIK3CA, NOTCH1, HRAS*, and *NFE2L2*.

Of these, *PIK3CA* stands out because inhibitors for it are already in the works. Activated in approximately 21%

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- **The UK National Health Service (NHS) has launched its first multi-gene test for cancer patients using next-generation sequencing technology.** Researchers at the University of Oxford and Oxford University Hospitals NHS Trust said that the 46-gene test "heralds the arrival of genomic medicine, with whole-genome sequencing of patients just around the corner."
- **Almost half of U.S. parents say they won't have their teenage daughters vaccinated against the human papilloma virus** (Pediatrics 2013;131:645–51). The percentage of parents opposing the vaccine climbed from 40% in 2008 to 44% in 2010. "HPV causes essentially 100% of cervical cancer," noted senior author Robert Jacobson, MD.
- **The U.S. Food and Drug Administration (FDA) "has yet to receive an application for a biosimilar or interchangeable product, but we know there is much industry interest in them,"** FDA Director Margaret Hamburg, MD, told the Massachusetts Biotechnology Council on March 15 in Boston. "As of yesterday, FDA's drugs center had received 51 requests for meetings on 12 different biological products, it had held 38 initial meetings with potential sponsors, and had received 15 Investigational New Drug applications for biosimilar development programs."
- **If the FDA uses its Accelerated Approval process correctly, "there will be drugs that have to come off the market,"** commented Richard Pazdur, MD, director of the agency's Office of Hematology and Oncology Products, during a session about regulatory affairs at the American Association for Cancer Research Annual Meeting 2013 in Washington, DC, April 6–10.
- Around the world, **nearly 28,000 principal investigators ran clinical studies in 2012,** with 61% of them based in North America, down from 84% in 1996, said an analysis from the Tufts Center for the Study of Drug Development in Boston, MA.
- **Of the 13 anticancer drugs the FDA approved in 2012, "only 1 may extend life by more than a median of 6 months,"** noted Ezekiel Emanuel, MD, and 21 coauthors in a March commentary in the *New York Times*. "All cost more than $5,900 per month of treatment."

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of all samples, *PIK3CA* shows the highest frequency of a druggable mutation found in HNSCC. "PIK3CA inhibitors are being developed for breast cancer," says Hayes. "Let's see if these drugs work in head and neck cancer."

Additionally, roughly 5% of samples exhibited *HRAS* mutations, and those tumors might be vulnerable to farnesyltransferase inhibitors. These drugs have shown disappointing clinical results so far, "but this might be fertile ground for revival," says Hayes.

The study also revealed that the NOTCH and/or NFE2L2 pathways are altered in 30% to 40% of cases of HNSCC, suggesting that these pathways could be promising targets for new therapies.

Overall, the findings inform the development of a rational HNSCC research strategy, says Hayes. "There are many potential drugs, but only so many patients, and so much time and money," he says. "If we can design trials around the features of the tumor, that might be a more effective way to make progress." ■

Screening for Mutations in Circulating DNA

Thanks to a sophisticated technology that allows the detection and quantification of mutant DNA in a blood sample, researchers can track cancer-causing mutations associated with distinct responses to targeted drugs used to treat patients with gastrointestinal stromal tumors (GIST).

Data from a subanalysis of the phase III GRID study, designed to assess the efficacy of regorafenib (Stivarga; Bayer) in patients with GIST, indicates that the technology, called BEAMing (Beads, Emulsions, Amplification, and Magnetics), may offer physicians a real-time composite picture of the mutations across all tumors in any given patient, says George Demetri, MD, director of the Ludwig Center for Cancer Research at Dana-Farber Cancer Institute in Boston, MA, and the study's principal investigator.

Demetri presented his team's findings at the American Association for Cancer Research Annual Meeting 2013, held in Washington, DC, April 6–10.

Although sequencing tumor DNA can reveal GIST mutations in the cancer-related genes *KIT* and *PDGFRA*, "over time, tumors develop a clonal heterogeneity of resistance that makes diagnostics a challenge," Demetri explains. Patients may eventually wind up with dozens of different mutations in different tumors, or even different mutations in different parts of any single tumor, so that detecting all of those mutations in a traditional biopsy would be nearly impossible, he says.

Because tumor cells are constantly dying as well as growing, the cells release fragments of DNA into the bloodstream; Demetri's team reasoned that analyzing mutations in the circulating DNA would provide "a more sensitive and accurate assessment of everything that's going on in the whole person," he notes.

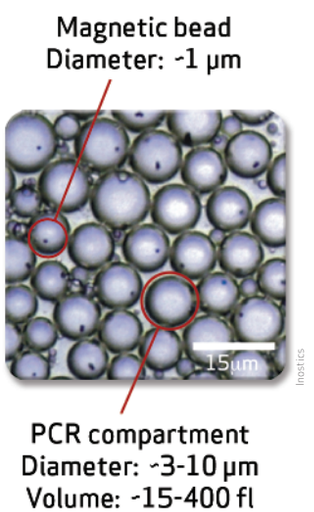
The researchers decided to analyze tumors from GIST patients who participated in the GRID study. First, they used conventional Sanger sequencing to analyze 102 archived tissue samples for mutations in *KIT* and *PDGFRA*, 2 genes that produce the cancer-driving proteins targeted by the tyrosine kinase inhibitors imatinib (Gleevec; Novartis), sunitinib (Sutent; Pfizer), and regorafenib.

Next, using the BEAMing technology, developed by Inostics (Hamburg, Germany) and customized with primers to amplify known mutations, they analyzed blood samples taken from 163 patients after the patients had developed resistance to imatinib and sunitinib.

The researchers detected *KIT* mutations in 58% of the blood samples compared with 66% of the tumor tissue samples. However, when focusing their analysis on secondary *KIT* mutations—those that drive resistance to targeted therapies such as imatinib and sunitinib—they found resistance mutations 4 times more often in the blood samples (48%) than in the tumor tissue samples (12%). Furthermore, nearly half of the blood samples that had secondary *KIT* mutations harbored multiple secondary mutations.

Compared with a placebo, regorafenib was clinically active in patients with secondary *KIT* mutations, says Demetri, showing a clear association between the presence of different cancer-driving gene mutations in circulating DNA and clinical outcomes.

"By using this technology," Demetri says, "we hope to develop the most rational drug combinations and better tests to match patients with the most effective therapies going forward." ■



Offered by Inostics of Hamburg, Germany, BEAMing performs single-molecule PCR on magnetic beads in water-in-oil emulsions (above). The core process transforms a population of DNA molecules into a population of beads, each coated with thousands of copies of an identical sequence, says the company, noting that BEAMing offers sensitivity and selectivity 100-fold higher than conventional PCR approaches. Using the technology to test circulating tumor DNA in patients with gastrointestinal stromal tumors provided a real-time composite picture of the cancer's mutations—and yielded a larger number of secondary mutations that drive resistance to targeted therapies—than probing tissue samples from the same patients.

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