

PEOPLE



Napoleone Ferrara, MD, a professor of pathology and senior deputy director for basic sciences at the University of California, San Diego, Moores Cancer

Center, was named editor-in-chief of *Molecular Cancer Therapeutics*, effective September 1. He replaces John C. Reed, MD, PhD.

Before joining Moores Cancer Center in 2012, Ferrara held various scientific positions over 24 years at Genentech in South San Francisco, CA. Prior to that, he served as a postdoctoral research fellow at the Cancer Research Institute at the University of California, San Francisco.

Ferrara's research focuses on the mechanisms of angiogenesis. His pioneering work led to the identification of VEGF and the development and approval of two drugs: the anti-VEGF monoclonal antibody bevacizumab (Avastin) for the treatment of multiple cancers and the anti-VEGF monoclonal antibody fragment ranibizumab (Lucentis) for the treatment of age-related macular degeneration. He has received numerous awards, including the Lasker-DeBakey Clinical Medical Research Award.



Bruce G. Haffty, MD, professor and chair of radiation oncology at Rutgers' Robert Wood Johnson Medical School, New Jersey Medical School, and

Cancer Institute of New Jersey in New Brunswick, began a 1-year term as president of the American Society for Radiation Oncology in September.

A graduate of Yale School of Medicine in New Haven, CT, Haffty completed his training at Yale-New Haven Hospital. Later a professor of therapeutic radiology at Yale, he served in multiple leadership roles there before moving to New Jersey in 2005.

Haffty's areas of expertise include breast cancer and head and neck cancer. His research aims to identify molecular markers of sensitivity and resistance to radiation.

Olaparib Enters Phase III Clinical Testing

AstraZeneca announced in September the launch of two phase III studies for its PARP inhibitor olaparib in patients with *BRCA*-mutated ovarian cancer. The initiative comes nearly 2 years after an interim analysis of a phase II trial of olaparib in a broader population of ovarian cancer patients showed no overall survival benefit, which led AstraZeneca to discontinue the drug's development in 2011.

The drug maker decided to forge ahead with phase III trials of olaparib after a retrospective analysis of the phase II data showed a marked effect in ovarian cancer patients with a *BRCA* mutation, says Jane Robertson, MD, executive global clinical director at AstraZeneca. "We were getting a lot of pleas from the investigators who had worked on it in the early part of the program to carry on the development," she says.

Median progression-free survival in patients with a *BRCA* mutation reached 11.2 months with olaparib maintenance therapy compared with 4.3 months with placebo, according to the subgroup analysis presented at the American Society of Clinical Oncology (ASCO) 2013 Annual Meeting in June. Median overall survival for patients with a *BRCA* mutation was 3 months longer among those who received olaparib compared with placebo, a finding potentially confounded by 22.6% of placebo patients later receiving another PARP inhibitor.

Difficulty identifying the right dose and schedule for a new oral tablet formulation also necessitated the drug's nearly 2-year hiatus, Robertson explains. "We didn't give up on olaparib," she says. "Now, we're confident we have the right dose and schedule, and we have a clear patient population we know benefits that we can focus our phase III studies on."

The two phase III studies are investigating the PARP inhibitor as maintenance monotherapy. The U.S.-based SOLO 1 study will test olaparib in *BRCA*-mutated ovarian cancer patients who have a complete or partial response to platinum-based chemotherapy in the first-line setting.

The Europe-based SOLO 2 trial will test the drug in patients who have a complete or partial response to platinum-based chemotherapy for *BRCA*-mutated ovarian cancer that has relapsed. Results from both studies are expected by 2016.

Susan Domchek, MD, director of the Basser Research Center at the University of Pennsylvania's Abramson Cancer Center in Philadelphia, has conducted research with olaparib in *BRCA*-mutation carriers with ovarian, breast, pancreatic, and prostate cancers. "The resurgence of interest in these drugs is very exciting," she says of PARP inhibitors.

"These new studies emphasize that we must target the group of patients who are most likely to respond based on the cancer's underlying biology," says Domchek, who presented a separate phase II olaparib study at the ASCO meeting. "For olaparib, that's *BRCA1*- and *BRCA2*-mutation carriers."

BRCA1/2 mutations, which are present in about 15% of ovarian cancers, disable the cancer cell's ability to repair double-strand DNA breaks through homologous recombination. Treatment with olaparib blocks PARP, an enzyme involved in the repair of single-strand DNA breaks. Without these pathways it is thought that cells are unable to repair their DNA, and may die.

AstraZeneca recently launched a study in Asia to test olaparib in advanced gastric cancer. The company also plans to assess its effectiveness in *BRCA*-mutated breast cancer and lung cancer. ■

Targeting and Retargeting in Lung Cancer

Clinical studies show that epidermal growth factor receptor (EGFR)-directed treatment is better than chemotherapy in first-line treatment of non-small cell lung cancer (NSCLC) with EGFR mutations. That result holds up consistently in terms of response rate, quality of life, and progression-free survival (PFS) across eight trials, according to a recent *Journal of Clinical Oncology* editorial written by Corey Langer, MD, a professor of medicine at the University of Pennsylvania and director of thoracic

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