rating means they believe “there is a moderate or high certainty that the service has no net benefit, or the harms outweigh the benefits.”

Other major international health organizations have similar reservations or recommend no PSA screening. Most groups indicate that screening to determine who should undergo prostate biopsy typically includes both a serum PSA and digital rectal examination, with the latest American Cancer Society publications noting that the rectal exam is optional. All groups recommend an informed discussion with patients and state that screening does not increase the number of men diagnosed with non-metastatic, early disease that may not prove lethal.

Gomella said this latest study led by Loeb could work in favor of PSA screening, partially because the researchers looked at a large group of men while focusing on multiple changes in PSA level. That this latest study resolves the PSA controversy and satisfies USPSTF is unlikely, however. “It’s going to take a lot more data sets to confirm these findings,” said Carter, adding that the PSA is a great test that has been used incorrectly. “There is strong evidence that PSA testing has saved lives, but too often we screen the wrong age groups. We’d be much better off if we screened the younger men who are more likely to benefit, rather than just older men.”

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Outsourcing Clinical Trials

By Joanne Nicholas

The high costs of conducting clinical trials in the U.S., the difficulty in recruiting patients, and bureaucratic delays are causing small biotechnology and large pharmaceutical companies to seek clinical trials partnerships outside the U.S.

“Over the past few years, there has been an absolute increase in the number of patients enrolled in countries outside of the U.S. and Western Europe,” said Pablo Cagnoni, M.D., senior vice president and global head of clinical development at Novartis Oncology, by e-mail. The reasons, he added, include faster regulatory timelines for approval of a clinical trial, improvement in quality of the investigators, and regulations stipulating that local patients must be enrolled in clinical trials for drug approval. He also noted that developing targeted therapies requires screening many patients to identify the small group with the molecular abnormality of interest.

Numbers of patients enrolled in Asia and Eastern Europe have increased especially, said Cagnoni. “In Japan, for example, the government has taken steps to align their requirements with those of other countries. We have increased Russian participation due to the need to include local patients for [drug] approval in Russia.”

The Chinese Example

The boom in clinical trials has perhaps been the biggest in China, owing to improvements in the medical infrastructure there. “China’s health care market is now $50 billion USD and growing at a rate of 30% a year, which will be $600 billion in 2020,” according to Lan Huang, Ph.D., CEO of Dalian Wanchun Biotechnology in China. “As of November 2010, 57 global phase III trials were being conducted in China, with companies such as GlaxoSmithKline, Bristol-Myers Squibb, and OSI Pharmaceuticals testing cancer drugs. A large amount of private investment also supports innovative drug development.”

A cancer researcher trained at the University of California, Berkeley, with a postdoctoral fellowship at Memorial Sloan-Kettering Cancer Center, Huang returned part-time to her native China 10 years ago to do drug research and development and cofounded several pharmaceutical companies. She began her China–U.S. partnership when the cost for an early phase I/II clinical trial of her drug for brain cancer was $100,000 per patient in the U.S., compared with $10,000 in China under the same protocol.

“The U.S. has very good drug discovery powerhouses that know clinical trial design,” said Huang. “In China, we can use clinical protocols from the U.S. to study a drug by looking at many indications in parallel rather than sequentially. Drug development costs are reduced by China’s lower medical costs: 20%–30% of those in the U.S. The time to trial completion is faster because the large clinical population speeds enrollment.” She said that patients have the incentive of free clinical trial drugs, which China’s universal health care coverage, capping at $300 per year, does not reimburse.

Huang said their advantage begins at the preclinical level with a molecular diagnostic analysis of each person’s tumor. “Our highly trained researchers have access to large numbers of tissue samples, many from untreated patients, that we use to identify the right people to test for a drug. With higher success rates in early phase I/II trials, we then do trials on promising drugs in the U.S.,” said Huang, who received the Thousand Talent Innovator Award from the Chinese president. But, she warns, not every pharmaceutical company can expect a welcome in China. “The Chinese government does not like companies to use Chinese patients as testing subjects, and China is very serious about patent protection.” Her company is partnering with Nereus Pharmaceutical, a California company focused on developing anticancer
of quality information” required to submit the results to government regulatory agencies.

**U.S.-Based Trials Expand Horizons**

“For any pharmaceutical company with a new product beginning clinical development, informative clinical trials, with each one informing the next, are critical,” said Howard I. Scher, M.D., chief of the genitourinary oncology service at Memorial Sloan–Kettering and principal investigator of the Prostate Cancer Clinical Trials Consortium (PCCTC). “If the drug is showing promise, progress should be rapid. If it does not, it may be that it is simply inactive, that the dose is incorrect, or that it is not being studied in the right patients.”

Established in 2006 by the Prostate Cancer Foundation and the Department of Defense Prostate Cancer Research Program, the PCCTC is a clinical trial network of leading prostate cancer experts from 13 academic medical centers in the U.S. “Members of the PCCTC developed new standards for clinical trials conducted in this disease,” said Scher. “We take an active role in trial design at the preclinical stage to maximize what is learned about a drug’s effect on the disease and the patient so that development can proceed expeditiously. Our members have a lot of regulatory and research experience. We understand the biology, know the targets, and can provide input on biomarkers. With our members being from 13 of the leading prostate cancer centers, we can accrue patients rapidly and ensure that an adequate number are treated at each site,” he said. “All the trials are facilitated by a common infrastructure that includes standard contracts, patient consents; shared legal, financial, database, and regulatory document management; and dedicated personnel at each site.”

Scher recently led the successful international trials for abiraterone (Zytiga) and enzalutamide (formerly known as MDV3100) in men with castration-resistant prostate cancer. The U.S. Food and Drug Administration approved abiraterone in September 2011. The study, co-led with Johann de Bono, M.D., Ph.D., at the Royal Marsden Hospital, also evaluated “the clinical relevance of circulating tumor cells as a potential new biomarker for measuring a drug’s effectiveness in prostate cancer,” said Scher. This achievement was followed by the completion of the large phase III AFFIRM trial of enzalutamide for castration-resistant prostate cancer (developed in the laboratories of Charles Sawyers, M.D., and Michael Jung, Ph.D., at the University of California, Los Angeles) studied in 15 countries, including the U.S.

Scher presented results of its phase III trial at an American Society of Clinical Oncology Genitourinary Symposium in 2012. FDA review of enzalutamide is expected this year.

Scher points to enzalutamide as the example of PCCTC’s new paradigm. “The collaboration with Medivation [the company developing enzalutamide] is the poster child of how this all works,” he said. “We aligned the infrastructure with the sponsor and were able to select the optimum dose to move forward into phase III testing after completing the phase I/II trial in 18 months. If you look at time from the first patient enrolled in July 2007 to the announcement of the phase III trial’s success, it was under 4.5 years. I am not sure too many cancer drugs have gone through that fast. Time is critical for our patients and has significant financial implications. Industry sponsors like Medivation appreciate the abbreviated timelines our unique drug codevelopment strategies enable,” said Scher. This approach has enabled the PCCTC to advance eight therapeutic candidates to phase III studies. “With its commitment to collaborative drug development, endpoint and biomarker codeveloped strategies, and centralized management of research, the PCCTC is poised to keep the drug pipeline primed with promising new agents,” Scher said.

In addition to the financial boost for countries, clinical trials can offer a medical benefit for patients. Ironically, some patients can access a drug during a clinical trial only if their national health plan considers it too expensive. Abiraterone
Researchers Hope New Database Becomes Universal Cancer Genomics Tool

By Mike Martin

Swiss scientists hope that a new online database called “arrayMap” will bring cancer genomics to the desktop, laptop, and tablet computers of pathologists and researchers everywhere.

The database combines genomic information from three sources: large repositories such as the NCBI Gene Expression Omnibus (GEO) and Cancer Genome Atlas (CGA); journal literature; and submissions from individual investigators. It incorporates more than 42,000 genomic copy number arrays—normal and abnormal DNA comparisons—from 195 cancer types.

“arrayMap includes a wider range of human cancer copy number samples than any single repository,” said principal investigator Michael Baudis, M.D. Ease of access, visualization, and data manipulation, he added, are top priorities in its ongoing development.

A product of the University of Zurich Institute for Molecular Life Sciences, where Baudis researches bioinformatics and oncogenomics, arrayMap illustrates the importance of copy number abnormalities (CNA)—dysfunctional DNA gains or losses that visibly lengthen or shorten certain chromosomes—in the diagnosis, staging, and treatment of various malignancies.

“I have this particular tumor type—are there any CNAs in it that can tell me anything about prognosis or treatment?” said Michael Rossi, Ph.D., director of the Winship Cancer Institute cancer genomics program at the Emory University School of Medicine in Atlanta. “Data mining tools like arrayMap are incredibly useful to help answer such questions.”

Diagnosis, Staging, Treatment

CNAs are often cancer specific, corresponding to deleted tumor-suppressor genes or duplicated oncogenes that characterize certain tumor types. HER2+ breast carcinomas, for instance, show CNAs on chromosome 17 corresponding to the gene ERBB2, which encodes the HER2 protein.

Cancer-specific CNA profiles can aid in the identification, staging, and prognosis of certain cancers. A CNA in a distant metastasis from an unknown tumor may help identify the type of primary malignancy. And in other tumors, such as glioma and renal cell carcinoma, CNA profiles “are very appropriate grading tools,” Rossi explained.

Where histology fails to find subtle distinctions, “CNAs can help a pathologist say, ‘This tumor is going to be much more aggressive,’ or ‘We have an array that shows a lower-grade tumor,’” he explained.

For example, two powerful prognostic markers have emerged in a well-defined region of chromosome 8 called 8q22–24. One, an amplified CCNE2 gene, predicts “distant metastasis–free survival in lymph node-negative breast cancer patients,” a group from the Netherlands Cancer...