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Hurvitz Looks Back and Ahead at Advances in Treating HER2-Positive Breast Cancer

Sara A. Hurvitz, MD

From the 1998 FDA approval of trastuzumab (Herceptin) to the novel agents currently under exploration, significant advances have been made in the treatment of HER2-positive breast cancer.

Trastuzumab made history as the first therapy HER2-targeted therapy, following the discovery of the HER2 gene, which encodes a tyrosine kinase receptor that is a potent mediator of cellular growth and proliferation.

The addition of trastuzumab to chemotherapy in patients with previously untreated metastatic breast cancer led to a significantly higher objective response rate, prolonged time to progression (TTP, 7.4 vs 4.6 months; P <.001), and improved overall survival (OS; 25 vs 20 months; P = .01) compared with chemotherapy alone.

Lapatinib, a dual TKI of HER2 and EGFR, gained FDA approval in 2007. The therapy was the first to show that continuing HER2-targeted therapy after progression on a HER2-targeted regimen improves outcomes. Patients who had already progressed on regimens that included trastuzumab, an anthracycline, and a taxane had a better TTP (8.4 vs 4.4 months; P <.001) when they received lapatinib in combination with capecitabine compared with those who received capecitabine alone.

Pertuzumab, approved in 2012, also furthered the treatment of the disease. Two phase II trials evaluated a pertuzumab-plus-trastuzumab–based therapy in the neoadjuvant setting. In the randomized, multicenter phase II NeoSphere trial, pertuzumab and/or trastuzumab with or without docetaxel were administered for four cycles prior to surgery. In this trial, the use of dual HER2-targeted therapy with pertuzumab and trastuzumab combined with docetaxel had a 45.8% progression-free survival (PFS) rate compared with pertuzumab or trastuzumab plus docetaxel (24% and 29%, respectively).

The Antibody-drug conjugate T-DM1 has also made strides in anti-HER2 therapy. In the TH3RESA trial, a heavily pretreated patient population with advanced HER2-positive breast cancer was randomized to receive T-DM1 compared with physician's choice therapy. The PFS was significantly improved with T-DM1 compared with physician's choice (median PFS, 6.2 months vs 3.3 months; P <.001).

Several emerging agents have are also being explored in HER2-positive breast cancer. These include neratinib, a potent pan-TKI that

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Florida Doctors Trade Independence for Security in Epicenter of Merger Wave

Raul Storey, MD

Just 2 years after oncologist Raul Storey, MD, finished his training and joined a private practice in Vero Beach, Florida, he was already eager to make another change.

He and his partner Noor Merchant, MD, who founded the practice 30 years ago, found themselves battling a familiar set of confounding problems: patients who had to be turned away over insurance issues, limited access to new drugs, narrowing profit margins, and the demands of office administration.

So last October they took the plunge and merged with Florida Cancer Specialists, the nation's largest independent, physician-owned medical oncology practice. Now they have relationships with 6 times as many insurers, a centralized business office, and access to more than 100 clinical trials, which Storey called "a dream come true for hematology-oncology."

"We are able to basically focus on the clinical part of the treatment of patients with hematological diseases and cancer, instead of all the administrative business and work you have when you run a practice on your own," he said.

The array of services and opportunities with which Florida Cancer Specialists provides its physicians, while still allowing them a high degree of autonomy, has proved a powerful draw since the group was founded as a solo practice by William Harwin, MD, in 1984.

The organization now boasts 180 doctors, most of whom are or will become partners, and 120 nurse practitioners, at more than 85 locations around the state. The total staff numbers more than 2000 across a variety of professions. The firm treats 50,000 new patients and takes in more than $1 billion in fees each year, more than 3 times the amount it collected in 2012.[1]

The company has a practicewide electronic medical record (EMR) system, a central pathology laboratory, an oral oncolytics pharmacy, and on-site radiation facilities at many locations, as well as access to clinical trials through its partnership with Sarah Cannon Research Institute in Tennessee. Thanks to its size, the company can negotiate better drug prices and guarantee patients access to all FDA-approved chemotherapy and immunotherapy treatment options, Harwin said.

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Hurvitz Looks Back and Ahead at Advances in Treating HER2-Positive Breast Cancer (Continued from page 1)

irreversibly inhibits HER2; MM-302, a novel antibody-drug conjugate; and ONT-380, a small-molecule selective inhibitor of HER2, also known as ARRY-380.

In a recent interview with *The American Journal of Hematology/Oncology (AJHO)*, Sara A. Hurvitz, MD, director of the Hematology/Oncology Breast Cancer Program and an associate professor in the Department of Medicine at UCLA, discusses the evolving treatment paradigm of HER2-positive breast cancer and what the future might hold.

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Mark D. Pegram, MD, director, Breast Cancer Oncology Program, Stanford Cancer Institute, discusses contemporary sequencing of therapies for HER2-positive breast cancer.
http://goo.gl/bI29b5

Q: *AJHO*: How has the treatment of HER2-positive breast cancer evolved over the years?

Dr Hurvitz: The discovery of the HER2 alteration literally transformed the landscape for women diagnosed with HER2-positive breast cancer. Previously, it was understood that HER2-positive breast cancer was associated with a more aggressive disease biology and a worse disease-related outcome. However, since the advent of HER2-targeted therapy, there has been a shift in the natural history of this disease.

Now, women can expect a much more positive outcome. First, trastuzumab was developed, a clinical antibody that targets the outside of the HER2 receptor. It was FDA approved in 1998 for metastatic HER2-positive breast cancer because it was associated with improved survival and reduced progression when combined with chemotherapy.

In 2006, trastuzumab was FDA approved for early-stage breast cancer in combination with chemotherapy because it showed improved survival and disease-free survival compared to patients who received only chemotherapy in that setting.

In the past decade, however, three more HER2 targeted therapies have been developed and approved. The first was lapatinib, approved in combination with capecitabine, for patients whose disease was resistant to trastuzumab. This therapy demonstrated an improved time to progression compared to use of capecitabine alone.

Then in 2012, pertuzumab was approved in combination with trastuzumab and taxane. Pertuzumab, a monoclonal antibody that also targets HER2, appeared to synergize with trastuzumab and significantly improve the OS and PFS compared to trastuzumab and taxane alone. In 2013, TDM-1 was FDA approved for the treatment of trastuzumab-resistant metastatic breast cancer that is HER2 positive.

Q: What makes TDM-1 different than other therapies approved in this space?

This is the first antibody-drug conjugant FDA approved for breast cancer. It really is a "smart bomb" type of therapy where the antibody is connected to the cytotoxic chemotherapy, and does not release the chemotherapy until the antibody has bound to the HER2 receptor on the malignant cell and has been taken up inside the malignant cell.

Q: How have these advancements shaped today's treatment paradigm?

Now, first-line therapy for patients newly diagnosed with HER2-positive breast cancer is taxane plus trastuzumab and pertuzumab. The second-line standard approach is TDM-1. We will continue to treat patients with HER2-targeted therapy in the advanced disease setting, alternating the chemotherapy partner. Patients are now expecting a medium OS of 5 years or even greater at the time of their diagnosis, owing to the HER2-targeted therapies that are available.

Changes have also been made in the neoadjuvant setting, which include the use of pertuzumab and trastuzumab with chemotherapy in the early-disease setting. A number of new exciting molecules are also being evaluated that target this disease, making it a very exciting time to be involved in the treatment of women diagnosed with this type of breast cancer. ■

Florida Doctors Trade Independence for Security in Epicenter of Merger Wave (Continued from page 1)

William Harwin, MD

Building a Trendsetter

Harwin said he did not originally intend to turn his solo practice into a "great entity." Initially it grew slowly, to just 48 doctors in 17 offices as of 2008. Over time, however, mounting economic pressures on small practices,the advantages of size, and a reputation for good management allowed Florida Cancer Specialists to become a merger machine and a poster child for the consolidation trend of recent years. By 2011 it had doubled in size to 40 sites and close to 100 doctors, and since then it has nearly doubled again.

Another factor contributing to FCS's growth may be the state's size and its large elderly population. Florida's cancer rates are among the highest in the nation and it has the second-greatest number of people with cancer after California, according to National Cancer Institute data.[2] The state has the fifth-highest number of oncologists after New York, California, Texas, and Pennsylvania, according to the Kaiser Family Foundation.[3]

Florida also has seen the most mergers and acquisitions: from 2008 to 2014, at least 30 oncology practices have been acquired by hospitals and 46 by group practices and other non-hospital entities like Florida Cancer Specialists, according to the Community Oncology Alliance's most recent Practice Impact Report.

Harwin, who practices in Fort Myers and serves as the company's president, described its initial expansion as serendipitous. A radiation therapy group in adjacent Charlotte County told him the area needed better oncologists, so his practice started consulting there and eventually hired 2 doctors out of training to staff a new office, he said. Then a staff physician who wanted to be closer to family opened an office in Bonita Springs, a struggling practice in Naples asked for help and was acquired, and many others followed.

"In the early '90s, there was a lot of concern about managed care and how that was going, and the thought was, well, if we were a little bit larger we'd be in a better position to compete in what appeared to be a new healthcare environment," Harwin said.

Unlike some other large groups, the business had a head start on the merger trend because it was already growing and benefiting from its billing efficiencies and economies of scale when the Medicare Modernization Act, passed in 2003, began slashing the profit from drug margins on which small oncology offices had survived. Florida Cancer Specialists was poised to start absorbing such practices as the financial pressures tightened.

The partners made the key decision to turn down acquisition offers from 2 companies that were precursors of US Oncology in favor of remaining independent, Harwin said. Florida Cancer Specialists also started making merger deals with larger groups of several doctors each,

and growth further accelerated after CEO Brad Prechtl, a CPA who previously worked at US Oncology, joined the company in 2009.

"We're enamored with the idea of still being a private practice group that's physician-centric and patient-centric. We were never interested in becoming a publicly traded company," Harwin said. "It doesn't matter if it's US Oncology or a hospital-based system; we just really like being in charge of our own business."

And the growth continues. Among other projects, in December the group launched construction of an $11-million cancer center in Brandon, near Tampa, that will house a linear accelerator, PET/CT, and high dynamic range imaging equipment.[4] The company is also spending $2.5 million to expand its corporate headquarters in Fort Myers, adding 21,000 square feet for administration and its Rx to Go specialty pharmacy.

An Abundance of Caution

Harwin said he's much prouder of his work as an oncologist than his success as a businessman. He maintains a busy practice, dedicating just a day a week to his managing partner duties, and said that for 4 years he's led the company in the number of patients participating in clinical trials.

But he said that all the back office support and infrastructure the company has built up over the years has helped Florida Cancer Specialists stand out in the field and prosper despite the headwinds the profession is facing.

Working on behalf of 180 doctors, specialized staffers handle contract negotiations, purchasing, drug regulations, purchasing, human resources, and the whole range of regulatory and compliance issues, he said.

"We have to be so careful with healthcare compliance. We feel like because we're big there's a target on our back. So we're just so ultra-careful about everything," he said. "Every bill that goes out for an office visit, there's someone measuring and checking to make sure there's a documentation that goes with that. If somebody billed an office visit and forgot to dictate or forgot to document, we'll catch it. We have people really checking every little thing."

Despite that vigilance, the firm was singled out in a Wall Street Journal article last year for its oncologists' frequent use of the anemia drug Procrit, which increases red blood cell levels but carries significant health risks.[5]

Use of the drug declined nationally after 2007, when the FDA warned it was linked to increased stroke risk, tumor growth, and early death in cancer patients. Yet a number of Florida Cancer Specialists doctors continued using it frequently, and in 2012 one-sixth of Medicare payments to oncologists to administer the drug went to the company, according to the article.

Harwin responded that the group's use of the drug was medically correct, FCS doctors were using it less often since 2007, and doctors had no financial incentive to choose a drug based on its margin. The firm also described the cited data as skewed because FCS's high volume of patients in various stages of cancer and with multiple conditions made use of Procrit necessary.[1]

The company got in the news for a different reason when insurer Humana announced it would drop the group from its network in March 2014. Harwin said the insurer gave little explanation and didn't respond to requests to discuss the decision. He noted that Humana CEO Bruce Broussard formerly headed US Oncology, a competitor that has lost 3 groups to Florida Cancer Specialists over the years.

Further Expansion Planned

The firm plans to keep growing and is currently talking to more doctors who are likely to join up, Harwin said. It recently came close to acquiring some groups in North Carolina, but big hospitals in the Charlotte area threatened to start hiring their own oncologists rather than work with Florida Cancer Specialists, scotching the deal, he said.

Expanding to another state is also tricky because, for regulatory reasons, practices in other states could not use the central laboratory in Florida, and the company would not immediately have a large enough presence in the new state to justify building another lab, he said.

While growth has many advantages, he admitted that he misses recruiting and knowing all his colleagues personally. "It's impossible to have as personal a relationship with every doctor as I once had," Harwin said. But he said that does not affect patients' perspectives on their own doctors.

"The small, homey, close to home approach, that doesn't change," he said.

Storey said that when he and his partner were contemplating a merger, they weighed the potential downsides of being swallowed up by a large health provider. They considered joining a hospital but rejected that option.

"You are coming from having an independent practice, where you are your own boss and you make your own decisions, and then you become part of a big monster, you know?" he said. "We were worried about the potential of losing our autonomy and then having someone try to rule what you do or what you don't. But that was not the case at all with Florida Cancer Specialists."

Storey said he believes that in the near future small independent practices will no longer be able to survive, and that large groups like his company, offering many community oncology offices scattered throughout a multitude of towns, are the best solution to serve Florida's population. The state's handful of giant cancer centers are far from many people's homes, he said, and on their own they cannot provide the access patients require. ■

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PER Acquires, Expands Chemotherapy Foundation Symposium

Phil Talamo

The Chemotherapy Foundation Symposium, one of the largest oncology/hematology-focused conferences in the United States, was acquired last week by Physicians' Education Resource (PER) Events, LLC, an affiliate of the accredited medical education provider PER.

The late Ezra Greenspan, MD, a pioneer and trailblazer in medical oncology, founded the Chemotherapy Foundation Symposium in 1972. The conference, which is attended by nearly 2000 healthcare professionals, will continue to be co-chaired by Edward Ambinder, MD, and Franco Muggia, MD. Prior to the acquisitions, PER's largest event was the Miami Breast Can-

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PER Acquires, Expands Chemotherapy Foundation Symposium (Continued from page 3)

cer Conference, which is attended by over 1000 medical, surgical, and radiation oncologists.

For insight into how this acquisition could impact the agenda and focus of the Chemotherapy Foundation Symposium and other PER conferences, *OncLive* interviewed Phil Talamo, PER's vice president of Independent Medical Education & Operations.

Q: *OncLive*: What will be the focus of the 2015 Chemotherapy Foundation Symposium?

Talamo: This year's symposium, to be held November 4 to 6 in New York City, will retain its educational focus on new developments in cancer therapeutics and state-of-the-art care. In fact, the full name itself is *Chemotherapy Foundation Symposium: Innovative Cancer Therapy for Tomorrow*.

This year's meeting will continue to provide oncology professionals with the opportunity to learn about new compounds, novel approaches to diagnosis and treatment with currently available agents, ongoing clinical trials, and emerging developments that define current progress aimed at the goal of control and cure of cancer.

Q: What are some of the anticipated hot topics at this year's meeting?

When chemotherapy was invented in the 1940s and 1950s, this was the pinnacle of innovative therapy. The first chemotherapy was actually derived from mustard gas. And it was a game-changer for patients with cancer. It is with this spirit of "innovative cancer therapy for tomorrow" that is the cornerstone of the annual *Chemotherapy Foundation Symposium*.

These days there are so many therapeutic options available, and many more in late-stage clinical trials. Some of them are unbelievably innovative, like immunotherapies, which actually stimulate the patients' immune system to fight cancer. This type of "innovative cancer therapy for tomorrow" is what we will discuss at this year's chemotherapy foundation symposium, and of course how we can best use these innovations to provide patients with state-of-the-art care.

More specifically, this year we will see expanded information on novel immuno-oncology strategies for the treatment of solid tumors and a look at the "next generation" of anti-cancer agents that address resistance mechanisms. There will be a number of sessions focused on state-of-the-art care for hematologic malignancies. The conference will provide updates on almost every type of cancer, including ovarian cancer, soft tissue sarcoma, colorectal cancer, and more.

Outside of specific cancer types, there will be sessions on predictive and prognostic markers, the potential of next-generation sequencing in the clinic, oncology informatics, EHRs [electronic health records], shared decision-making, patient access to trials, epigenetic mutations, and much more. The goal is to provide a comprehensive agenda that expands nearly all corners of 'modern' oncology.

Q: What major changes or additions were made to the agenda with the acquisition?

We will retain the original format of the agenda–concise rapid-fire trial updates and interpretation that oncologists and hematologists can use in their practice immediately. This will include the treatment and management of disease across virtually every tumor type and subtype.

There will be some shifts in the agenda that reflect the "state of new data," meaning that areas of vast data will be given more time than in previous years. This holds true to examples such as lung cancer, where we might see a historic ASCO with all the new lung data emerging. And then in multi-tumor components like immunotherapies, which will be a theme throughout the agenda as they are being studied in many different solid and liquid tumors.

Q: What type of things do you plan to keep and continue?

We will certainly keep the spirit of the meeting and how it addresses the latest emerging developments in a comprehensive multi-tumor format. There really has never been a more exciting or more challenging time to practice oncology than there is today. We know that cancer is no longer one disease, but numerous different diseases each that can be identified with various molecular markers and other predictive and prognostic indicators. The diverse content at this year's chemo foundation meeting will speak about the best way to personalize care for all of these different areas by using the latest information on novel and emerging therapies.

We also know these days in oncology there is unprecedented excitement regarding the use and potential use of novel targeted therapies and immuno-oncology agents. We will touch on all of this game-changing data across all tumors, and that is what makes this meeting so unique and exciting.

Q: How do you plan to incorporate any late-breaking news out of the ASCO or ESMO annual meetings?

As we develop the agenda, the focus will be to include the most impactful data that will impact clinician practice. We are going to work with the chairs and steering committee to ensure that we cover and address all of the latest-breaking data from ASCO and ESMO, just like we do with all of our PER legacy national meetings.

Q: This has now become the biggest PER meeting; will this impact other PER conferences, like the Miami Breast Cancer Conference?

This meeting will positively impact all of our PER meetings, including Miami Breast. *The Chemotherapy Foundation Symposium: Innovative Cancer Therapy for Tomorrow* meeting is one of the largest gatherings of oncologists for CME in the country, spread over virtually every tumor type.

As loyal attendees join us for this meeting and experience what it is like to attend a first-class PER CME conference, it will literally wet their appetite to make them also want to attend the more extensive and intensive tumor-focused meetings that we offer throughout the year, including Miami Breast and our other conferences. I see positive growth for all of our meetings, and this acquisition positively aligns with our educational strategy to be the "go-to" source of oncology continuing medical education.

Q: What will happen with the New York Lung Cancer Symposium, which PER generally conducts the day after the Chemotherapy Foundation Symposium?

As with all of our PER meetings, I see the Annual New York Lung Cancer Symposium to continue to grow due to the acquisition of the Chemo Foundation Symposium. The NY Lung meeting is unique in that it has always been specifically scheduled at the conclusion of the Chemo Foundation meeting to draw cross-attendance. It is a good example of how a physician can learn at a super high level about the most pressing emerging data at the Chemo Foundation Meeting in the multi-tumor setting, and then stay an extra day to attend NY Lung to learn the about in-depth interpretation and practical application of the content through engaging expert discussion and sample cases.

Now that both meetings of these are PER meetings, we see deeper efficiencies for increased attendance, more local cases, and further in-depth discussion for both the Chemo Foundation Symposium and Annual New York Lung Cancer Symposium. It will truly be an exciting time for cancer education. ■