Physicians Update

**BREAST CANCER**

**Newer Herceptin Treatment Improves Women’s Survival**

Before the targeted breast-cancer drug Herceptin (trastuzumab) was developed, breast-cancer patients with high levels of the human epidermal growth factor receptor 2-positive (HER2+) faced a bleak prognosis. Their aggressive tumors were less likely to respond to standard therapies. Now, these women have among the highest survival rates.

“The HER2+ story demonstrates that we can provide more effective and less toxic treatments by targeting therapies that are most appropriate for the genetic changes present in each patient’s tumor,” says Dennis Slamon, MD, director of UCLA’s Jonsson Comprehensive Cancer Center’s Revlon/UCLA Women’s Cancer Research Program and the Translational Oncology Research Laboratory at UCLA.

Herceptin now is standard treatment for women with HER2+ tumors.  

*continued on p. 4*
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**Immunotherapy for Advanced Melanoma**
A novel immunotherapy drug that was tested at UCLA has gained FDA approval. It is the first in a new class of immune-system modulators that are expected to dramatically improve survival in patients with unresectable or advanced disease.

**Hypertrophic Cardiomyopathy**
Offering the most advanced therapies — including myectomy and alcohol septal ablation — UCLA physicians are able to restore a more normal blood flow to patients who have become obstructed with excess muscle tissue in the septal walls.

**UCLA Cardiovascular Center**
At UCLA, a collaborative, multidisciplinary team of specialists provides coordinated consultation and treatment to offer a full range of care, including the most advanced and innovative therapies available.

**Pelvic Floor Dysfunction**
Physical therapy can be an effective, conservative treatment for pelvic floor conditions, including bladder and bowel dysfunctions and chronic pelvic pain.

**Minimally Invasive Surgery for GERD in Pediatric Patients**
Mattel Children’s Hospital UCLA pediatric surgeons employ an advanced, minimally invasive technique called laparoscopic Nissen fundoplication to treat infants and children diagnosed with severe gastroesophageal reflux disease.

**Cellular and Gene Therapy for Pediatric Diseases**
Mattel Children’s Hospital UCLA is developing and conducting several groundbreaking gene-therapy clinical trials. Therapies that use the patients own cells can avoid the graft-versus-host disease risk of bone-marrow transplantation.

**Clinical Trial for Brain Aneurysm Device**
UCLA is taking part in a study on the use of the FRED™ stenting system for wide-necked or large intracranial aneurysms. The new device holds the promise of improved clinical outcomes and fewer procedure-related complications.

**Female Athlete Triad**
Some girls and women who exercise intensely are at risk for this medical condition encompassing three interrelated components: low energy availability with or without disordered eating, menstrual dysfunction and low bone-mineral density.

**Pediatric Craniofacial Clinic**
In addition to caring for children with congenital abnormalities — such as cleft lip or palate — UCLA doctors treat pediatric patients with trauma-related injuries and vascular anomalies and reconstruct children’s faces disfigured by cancer removal or treatment.

_To download these and other clinical advances at UCLA Health, go to:_ uclahealth.org/clinicalupdates

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**News from UCLA Health**

**FDA Approves Lung-Cancer Drug**
The Food and Drug Administration has approved a new drug to treat non-small-cell lung cancer (NSCLC). The drug, ramucirumab, was tested on more than 1,200 people with NSCLC whose cancer worsened during or after first-line chemotherapy. The research was conducted as part of a multiyear, Phase 3 clinical trial at UCLA and other centers in 26 countries on six continents.

uclahealth.org/lungcancerdrug

**Protein Plays Important Role in Blood Stem Cell Replication**
UCLA scientists have identified a protein that plays a key role in regulating how blood stem cells replicate in humans. This discovery could lead to the development of more effective therapies for a wide range of blood diseases and cancers.

uclahealth.org/stemcellprotein

**Some Men Receive Prostate-Cancer Treatment Contrary to Guidelines**
National guidelines recommend that men with low- and intermediate-risk prostate cancer who have life expectancies of fewer than 10 years should not be treated with radiation or surgery, since they are unlikely to live long enough to benefit from treatment. Yet a new study by UCLA researchers found that more than half of such men are receiving these aggressive treatments, putting them at risk for potentially debilitating side effects.

uclahealth.org/prostatecancer
development
Coordinated Program Essential to Best Treat Colorectal Cancer

Advanced medical and surgical treatments coupled with a coordinated program that integrates the expertise of a multidisciplinary team of specialists is critical to ensuring that patients with colorectal cancer receive the best possible care.

“Too often, patients with these cancers have to find their own surgeon, medical oncologist and radiation oncologist,” says Kevork Kazanjian, MD, chief of Colon and Rectal Surgery at UCLA. “The specialists don’t necessarily know one another and may not communicate with each other or coordinate patient care as well as they should; as a result, the treatment by each specialist is delivered in a vacuum. Patients benefit from an environment in which everyone involved in their care collaborate.”

At the UCLA Colorectal Cancer Treatment Program, the multidisciplinary team includes medical oncologists, gastroenterologists, colorectal surgeons, geneticists, radiation oncologists and pathologists. The team meets weekly to develop and monitor each patient’s plan of care, and provides patients and their referring physicians with written and oral summaries of its recommendations, some of which may be implemented closer to the patient’s home by their local physicians.

“Our program brings together a comprehensive team of leading specialists in the field to develop a personalized treatment plan for patients in a simple and efficient manner,” Dr. Kazanjian says. “We work to make it easy for patients to see us, and we do the organizing and communicating among specialists so patients don’t have to worry about that aspect of their care.”

The UCLA Colorectal Cancer Treatment Program offers the full gamut of surgical, chemotherapeutic and radiation treatments. On the surgical side, the emphasis is on minimally invasive operations, including laparoscopic and robotic surgery, for appropriate patients. In addition, the program offers trans-anal endoscopic surgery and combined endoscopic laparoscopic surgery, turning what in the past was a major surgery for patients with large colon and rectal polyps into a minimally invasive outpatient procedure. For patients whose cancer has spread to the liver, the program works in tandem with surgeons who are part of one of the world’s leading liver-surgery centers — often enabling the liver- and colon-cancer surgeries to be performed as one procedure.

Patients with metastatic disease benefit from newer biologic agents. These include antiangiogenesis therapy, which starves tumors of the blood flow they need to thrive, and epidermal growth factor receptor (EGFR) inhibitors, which block the EGFR protein believed to contribute to the growth of colorectal cancer. Often these chemotherapeutic treatments are administered in combination with surgery to maximize outcomes, Dr. Kazanjian says. Access to clinical trials also is available to qualified patients. UCLA researchers have conducted clinical trials on experimental drug regimens and new diagnostic techniques that have helped clinicians and scientists establish new treatments for patients with the disease. The program also includes genetic-counseling resources available for patients who may have inherited syndromes or patients diagnosed younger than age 50, as well as relatives of these patients who are concerned about their risk.

The program has begun an innovative technology-based initiative, Patient Remote Interactive Medical Enterprise (PRIME), designed to reduce hospital readmissions and improve patient satisfaction after surgery. Patients are given a tablet device during their hospitalization, which they will take home so that they can be monitored remotely through questionnaires and photographic documentation during their recovery. “In looking at the national literature, we found that many readmissions were due to problems that, had they been brought to the team’s attention sooner, could have been easily addressed in the office,” says Anne Lin, MD, co-director of the UCLA Colorectal Cancer Treatment Program. “This gives patients more of a sense of control over their recovery, and it helps to avert any issues that may come up while they’re at home, before they become bigger problems.”

For more information about colorectal surgery at UCLA, go to: colorectalsurgery.ucla.edu
The earlier Herceptin is used, the more effective it is; and it has been shown to improve survival in late-stage breast cancer.

The legacy of Herceptin can be seen in the understanding that breast cancer and other cancer types can take a variety of forms, each subtype potentially requiring its own treatment options.

(continued from cover)

It has been found that when offered in combination with other therapies, including chemotherapy or surgery, Herceptin dramatically reduces breast-cancer-recurrence rates, without causing the adverse side effects such as hair loss and nausea that often accompany conventional chemotherapies.

“The earlier you use Herceptin in the disease course, the better,” Dr. Slamon says, adding that Herceptin also is one of the few drugs that can improve survival in late-stage breast cancer. And despite recent theories about the optimal period of time to use Herceptin, there is no evidence that prolonging treatment beyond one year will improve outcomes, he says.

The numbers are impressive. A study led by Dr. Slamon and published in the New England Journal of Medicine in 2011 found that treating HER2+ early stage breast-cancer patients with
a combination of chemotherapy and Herceptin significantly reduced recurrence rates by half in specific types of early HER2+ breast cancer and by one-third in metastatic HER2+ patients. It increased survival by about 35 percent and 30 percent, respectively, in those early and metastatic HER2+ breast cancers. In 2014, a large study led by researchers at the Mayo Clinic in Jacksonville, Florida, and published in the *Journal of Clinical Oncology* expanded on the results, reporting that adding a year of Herceptin to standard chemotherapy for HER2+ patients improved overall survival by 37 percent and boosted 10-year overall survival rates from 75 percent to 84 percent.

In 2010, a Jonsson Cancer Center study published in the journal *Clinical Cancer Research* found that Herceptin and the targeted-therapy drug Tykerb (lapatinib ditosylate) packed an effective one-two punch — inhibiting tumor growth in a subset of gastric cancers that had amplified levels of HER2. The work was done both on cell lines and in animal models with human HER2-amplified gastric cancers. The same year, Herceptin was approved by the FDA for use in HER2+ metastatic stomach cancer, in combination with chemotherapy.

Herceptin continues to be a fruitful area of study. One focus has involved fine-tuning the optimal amount of time the drug should be given. Thus far, in early breast cancer there is no evidence that prolonging treatment beyond one year will improve outcomes. "We believe in early breast cancer there is a finite amount of time that you need to be treated with the drug to derive benefit if used correctly," Dr. Slamon says. "By using the drug beyond that time, patients do not gain additional benefit, and by discontinuing use, they do not lose benefit. This period of time may be longer, of course, in metastatic breast cancer."

Researchers are also working on ways to make the drug more powerful — and developing new Herceptin-inspired treatments for women with other types of tumors. T-DM1 is Herceptin coupled with an experimental chemotherapy drug, emtansine, or DM-1. "It is like a smart bomb — Herceptin armed with a warhead," Dr. Slamon says. Initial studies in women with late-stage HER2 breast cancer found that T-DM1 had few side effects and increased progression-free survival (the time between the start of treatment and when the cancer gets worse) by three months, on average.

And UCLA researchers are targeting a different and larger subset of patients — women with advanced breast cancers who are estrogen-receptor positive (ER+) and HER2-negative, which accounts for 60-65 percent of breast cancers in most countries. Preliminary results show that women taking the investigational drug palbociclib in addition to letrozole, a commonly used drug for ER+ breast cancer, had significantly higher progression-free survival than women with standard treatment alone. "The benefit is the largest we’ve seen to date in this large subgroup, doubling disease-control times from 10 months to 20 months and counting with the experimental therapy,” Dr. Slamon says.

The legacy of Herceptin can be seen in the understanding that breast cancer and other cancer types can take a variety of forms, each subtype potentially requiring its own treatment options. This is a principle that will prove true in all major malignancies, Dr. Slamon believes, as the number of targeted cancer therapies hitting the market continues to grow.

"By identifying the correct targets for treatment in the right patient population," Dr. Slamon concludes, "we move forward with personalized oncology that we hope will greatly improve outcomes.”

For more information about breast-cancer treatment at UCLA, go to: breastcenter.ucla.edu

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In September, the U.S. Food and Drug Administration approved a new drug for treating advanced melanoma. The medication is the first in an exciting new class of cancer therapies known as programmed cell death inhibitors. Antoni Ribas, MD, PhD, a UCLA oncologist, was the principal investigator on the study of pembrolizumab (Keytruda) that led to its approval. Dr. Ribas describes the significance of the new medication.

What is pembrolizumab, and how does it work? It’s the first member of a new class of cancer therapeutics that works by releasing a brake to the immune system to attack malignant cells. Pembrolizumab has been shown to benefit patients whose cancer had spread anywhere in the body, and the incidence of side effects was found to be relatively low.

A Game-Changing Drug in the Fight against Melanoma

Have researchers been working on this idea for a long time? The concept of taking off the brakes to the immune system has been around for about 20 years. It led to the first antibody that was approved for treating melanoma, called ipilimumab, or Yervoy, which was licensed four years ago. That drug provided the proof of concept, but it was not that effective and there were side effects in patients. With pembrolizumab, we get better responses and fewer side effects. So the concept was started with ipilimumab, but now we have a better target.

How effective was the drug in your clinical trial? One-third of the patients with metastatic melanoma responded long term to this agent alone. Another third had some tumor shrinkage, but not enough and the disease eventually progressed. Other immunotherapies like interleukin-2 and interferon could lead...
maybe one-in-20 patients to live a normal life, but with pembrolizumab, we’ve elevated the benefit to those one-third of patients who will respond well to the treatment. Pembrolizumab benefited patients whose cancer had spread anywhere in the body. If you get an immunotherapy that works really well, it can work all over.

What about side effects?
Clinically significant side effects occurred in 12 percent of study patients. For any cancer therapy, that’s a low frequency of side effects. But there have not been any toxic deaths with this therapy, and it has been tested in more than 600 patients.

Why is an alternative to traditional cancer therapies important for patients with melanoma?
Immune modulators like pembrolizumab are being developed to treat melanoma because we’ve known for many years that melanoma doesn’t respond well to chemotherapy, radiation therapy, hormonal therapy and the standard treatments we have for cancer. Melanoma was the cancer where none of these things worked. But occasionally patients did well when they received some kind of an immune stimulant, such as a vaccine or a drug like interferon or interleukin-2. Both interferon and interleukin-2 were approved for the treatment of melanoma, but they all had low activity and a lot of side effects. The problem was that we were trying to turn on the immune system against the cancer. What we realized afterward was that we needed to take off the brakes instead of trying to turn it on. So that’s where ipilimumab and pembrolizumab come in.

Pembrolizumab was approved after completion of a Phase 1 trial. That’s unusual, isn’t it?
Yes. Drugs usually are approved after a Phase 3 trial. But the FDA saw the initial data and said, “Wow this is working in a group of patients where we have no active drugs.” These are patients with advanced melanoma whose disease had progressed on ipilimumab and other therapies. The FDA has something called Fast-Track review — meaning it’s a breakthrough therapy and the FDA looks at the Phase 1 data — that can lead to the approval in a quite restricted use. But I have no doubt that in the near future, this will become a broader approval, and it will become a front-line therapy as opposed to a salvage therapy.

Will we see other PD-1 inhibitors?
Pembrolizumab is the first one of at least eight in clinical development right now that work on the same pathway. This class of drugs is going to have a big impact on cancer care. The drugs also are being tested in about 30 types of cancers, but melanoma is the front line. It’s where the first testing is being done because it has this history of responding to immune therapies.

Is immunotherapy the direction in which cancer treatment now is heading, or is it just one avenue among many?
Immunotherapy is an avenue that had potential, but now it’s becoming a reality for some patients. Cancer therapy usually was surgery, radiation therapy, chemotherapy, and now the fourth pillar may be immunotherapy. Before, it was something many oncologists would disregard systematically. They’d say immunotherapy doesn’t work. I’ve heard that many times, that it doesn’t work or it works in a patient occasionally. But now we have higher-activity immunotherapy. So I would anticipate that this is a turning point for immunotherapy. We always knew that the immune system in some patients could fight the cancer, but it was so infrequent. And it was hard to study. Now it’s becoming a phenomenon. We can study it better, and we can develop it for more patients.”

For more information about the UCLA Melanoma Program, go to: uclahealth.org/melanoma

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(Top) White blood cells attempt to attack a deadly melanoma cancer tumor but are blocked by a protein that rises up from the cancer cell like a shield. (Middle) Pembrolizumab blocks the protein and breaks down the protective shield. (Bottom) After treatment with pembrolizumab, the immune system is able to resume its attack by the white blood cells, shrinking the tumors.

Graphics: Courtesy of UCLA Jonsson Comprehensive Cancer Center
Pediatric sarcomas are among the most challenging of childhood cancers, with five-year survival-rate estimates ranging from 59.2 percent to 68.5 percent. However, oncologists are optimistic that survival can be improved through a growing understanding of the biology of the disease and the use of targeted therapies. Already, significant gains have been made to enhance the care and quality of life of pediatric sarcoma patients through specialized services aimed at addressing all of a child’s needs.

“We see a group of much more aggressive types of sarcoma — metastatic disease, recurrent disease or refractory disease,” says Noah Federman, MD, associate clinical professor of pediatrics and director of UCLA’s Pediatric Bone & Soft Tissue Sarcoma Center. “We have a large population of those patients because we are a referral center.”

Pediatric soft-tissue sarcomas are a heterogeneous group of malignant tumors that originate from primitive mesenchymal tissue. Sarcomas are diagnosed in about 1,600 U.S. children each year. At UCLA, the pediatric sarcoma center, which is part of UCLA’s Jonsson Comprehensive Cancer Center, was established within the long-standing adult program to focus on the particular issues related to children.

Patients with sarcomas typically require multimodal therapy, including aggressive chemotherapy, high-dose radiation and surgery. To coordinate a multi-pronged and individualized treatment approach, each case is reviewed by a team, including physicians from pediatric oncology, medical oncology, orthopaedic oncology, surgical oncology, pediatric surgery, musculoskeletal radiology, radiation oncology and musculoskeletal pathology, as well as specialists in nursing, social work, psychology, physical therapy and nutrition.

“At UCLA we understand the need for a devoted pediatric sarcoma program,” explains Dr. Federman, who has joint appointments to the departments of pediatrics and orthopaedics. “Most of the sarcomas tend to predominate in the adolescent or young-adult years. These cases are very different from small children and very different from older adults. That’s what this program is about. It’s about state-of-the-art multidisciplinary care and, at the same time, state-of-the-art psychosocial care of these patients.”

An overarching philosophy of the pediatric oncology-hematology division at UCLA is to provide treatment while lessening the burden of illness, pain and disability on children and adolescents. The UCLA Daltrey/Townshend Teen & Young Adult Cancer Program — an extension of Teenage Cancer Trust, a charity dedicated to improving the lives of young people with cancer — is designed to meet the special needs of patients ages 13 to 25. UCLA’s Children’s Pain and Comfort Care Program aims to alleviate pain and other causes of distress for children and adolescents with complex illnesses and to offer support to family members. Moreover, the Pediatric Long-term Follow-up Clinic at Mattel Children’s Hospital UCLA was created to address the medical and quality-of-life issues of childhood-cancer survivors through a comprehensive health evaluation, psychosocial assessment and targeted specialty referrals.
Throughout this spectrum of care, patients also benefit from leading-edge treatments aimed at curing the disease or extending life. Patients today receive radiation therapy that targets the tumor while sparing healthy surrounding tissue. Moreover, the Musculoskeletal Oncology Program in the Department of Orthopaedics has been a pioneer in the development of limb-sparing surgical strategies for both malignant bone and soft-tissue sarcomas. The goal is to save both the life and limb while maximizing the function of the limb. The division is one of the most experienced in the nation in the use of metal implants (endoprostheses) for bone tumors and resections for soft-tissue sarcomas.

A deeper understanding of pediatric sarcoma has ushered in a new era of targeted medications aimed at addressing the underpinnings of the disease, Dr. Federman says. “I feel we’re at the cusp of new therapies because we’re learning more about the biology of this disease,” he says. “We’re going to see more targeted therapies and immune therapies. I think we’re going to start seeing a real explosion in the agents we have available to us and an improvement in outcomes.”

Cooperative clinical trials, which are comprised of researchers at cancer centers around the world who collaborate to answer important research questions, have led to better outcomes. UCLA’s Pediatric Bone & Soft Tissue Sarcoma Center participates in the Sarcoma Alliance Research through Collaboration (SARC) global network, a nonprofit organization dedicated to the development and support of clinical-trial research for the prevention, treatment and cure of sarcomas.

“We’d like every patient who walks through the door to be part of a clinical trial or registry,” Dr. Federman says. “It’s really important to move the ball forward. Because these cancers are so rare, we have to learn from each patient and provide each of them with personalized care.”

For more information about the UCLA Pediatric Bone & Soft Tissue Sarcoma Program, go to: uclahealth.edu/pediatricsarcoma

Because UCLA is a referral center, the UCLA Pediatric Bone & Soft Tissue Sarcoma Center sees much more aggressive types of sarcoma — metastatic disease, recurrent disease or refractory disease.
MRI-Guided Radiotherapy Opens Window to See Tumors in Real Time

As home to the first MRI-guided radiotherapy system in the western United States — and one of only three locations in the world — UCLA physicians in the Department of Radiation Oncology have an unparalleled ability to see and accurately target cancerous tumors, while making immediate adjustments to treatment delivery in real time. This technological advance addresses a long-standing challenge for radiation oncologists, enabling them to see the targeted tumor and the surrounding healthy tissue during treatment and to ensure that the radiation beam stays within desired margins as tumors or organs move.

Prior to this advance, imaging could only take place before or after the treatment. This meant that treatment plans were often based on images that had been captured minutes, days or even weeks beforehand; during treatment, when the beam was on, clinicians could not see exactly where the therapy target was located inside a patient’s body. Numerous studies showed that soft-tissue motion can shift the positions of the tumor and nearby organs, creating the possibility that the beam would miss the tumor’s edges or unnecessarily irradiate healthy tissue.

Known as ViewRay, this new technology combines continuous magnetic resonance imaging (MRI) with radiation therapy for cancer patients. It was approved by the U.S. Food and Drug Administration in 2012 for clinical use. “The ability to image in real time with high-quality MRI during therapy is new and a game-changer in all aspects,” says radiation oncologist Percy Lee, MD.

MRI is the preferred method for imaging soft tissue because it can produce a clearer, more detailed view of internal organs than computed tomography (CT) without the radiation exposure associated with CT. In areas of the body such as the abdomen, pelvis and breast, MRI allows physicians to more easily differentiate a tumor from healthy tissue, and it is especially useful for mobile tumors, which often change position in unpredictable ways, Dr. Lee explains. The clearer visualization potentially allows for more precise therapy.

During treatment, the technology’s integrated MRI-guided radiotherapy system captures a steady stream of soft-tissue images and, in real time, compares them to the planned treatment...
If the tumor or a critical structure moves beyond a physician-defined boundary, the ViewRay’s treatment beam automatically pauses; when the structure moves back into the target zone, treatment automatically resumes.

Real-time MRI imaging is especially useful for mobile tumors that often change position in unpredictable ways. This movement occurs for a number of reasons, including a patient’s respiration, heart beat, muscle contractions and weight changes or tumor response to treatment. A lung tumor, for example, can move an inch or more every few seconds as the patient breathes. Patients with such cancers as lung, prostate, bladder and pancreas, as well as cancers of the head and neck and central nervous system, are expected to benefit from this nonstop MRI imaging.

Since radiation oncologists traditionally have designed treatment plans based on images taken days or weeks before the treatment date, redesigning a plan if doctors suspect tumor movement from weight loss or other reasons can take several days. Using this new technology, UCLA radiation oncologists can adapt radiation on the fly by creating a customized plan of the day for each patient. In doing so, radiation that otherwise would have hit healthy tissue is redirected to hone in on malignant tissue, increasing the probability of exact delivery and improving outcomes.

MRI-guided radiation therapy expands the personalized treatment options available at UCLA and supports all available advanced and traditional radiation-delivery techniques, including image-guided radiation therapy, intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery and 3D-conformal therapy.

“We are excited to learn how real-time MRI-guided radiation can change the paradigm of how radiation therapy is delivered, with an eye toward benefiting our patients,” says Dr. Lee.

For more information about radiation oncology at UCLA, go to: radonc.ucla.edu
Continuing Medical Education: Save the Date

UCLA Primary Care Update 2015

When: April 17-18, 2015

What: This program will include such topics as cardiovascular disease; diabetes management; oncology, including melanoma and head and neck cancers; pancreatic disorders; liver disorders, including fatty liver, liver cancer and management of hepatitis C; endocrine surgery; obesity; robotic GYN surgery; and medical ethics.

Where: Wynn Las Vegas, Las Vegas, Nevada

Cost: Preregistration: $95, On-Site Registration: $125

Register: Go to www.cme.ucla.edu/courses and select “UCLA Primary Care Update 2015”