ACC Celebrates AZEDRA FDA Approval

It’s become a tradition: what’s an Abramson Cancer Center FDA approval without a virtual flash mob?

On Thursday, August 9, the ACC assembled to celebrate the green-lighting of AZEDRA for the treatment of rare neuroendocrine cancers pheochromocytoma and paraganglioma. Penn Medicine CEO Ralph Muller and Perelman School of Medicine Dean Larry Jameson, along with ACC director Bob Vonderheide and deputy director Kate Nathanson, led the flash mob for this FDA approval and to celebrate this accomplishment with lead investigator Dan Pryma.

This celebration marks the ACC’s fourth FDA approval in the past year. Kymriah® CAR T cell therapy was authorized for children and young adults with relapsed or refractory B-cell ALL in August 2017, and for relapsed or refractory DLBCL in May 2018. In addition, Kymriah® was approved in August 2018 for use in the EU to treat both cancers (see article on page 2). Finally, olaparib was approved for patients with BRCA mutant advanced breast cancer in January 2018.

AZEDRA (iobenguane I131) is the first ever non-surgical treatment for the rare neuroendocrine cancers pheochromocytoma and paraganglioma. The July 31 FDA approval was based on a multi-center trial led by researchers in the Abramson Cancer Center of the University of Pennsylvania and was granted to Progenics Pharmaceuticals.

“This is a true breakthrough. Until today, there were no anti-tumor therapies available for patients with these tumors who were not candidates for surgery,” said the trial’s principal investigator Daniel A. Pryma, MD, an associate professor of Radiology and Radiation Oncology, chief of Nuclear Medicine and Clinical Molecular Imaging at Penn’s Perelman School of Medicine, and a member of the ACC’s Radiobiology and Imaging Program.

AZEDRA is a targeted, high-specific-activity radiotherapeutic, indicated for the treatment of adult and pediatric patients (12 years and older) with a positive iobenguane scan, and unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy. AZEDRA is the first and only approved therapy for this indication.

Pheochromocytoma and paraganglioma are neuroendocrine tumors that form from the same type of tissue. Pheochromocytoma forms in the adrenal gland, while paraganglioma forms outside of the gland. There are an estimated 650 to 2,600 new cases in the United States each year, with between 10 and 35 percent of cases metastatic or locally invasive at diagnosis. In addition, when the disease returns, it may not be resectable surgically. The five-year survival rate of unresectable cases can be as low as 12 percent.

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AZEDRA Receives FDA Approval for Rare Cancers

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AZEDRA is a radiotherapy drug that attacks these tumors with a high, specifically targeted dose. The FDA gave it an Orphan Drug designation, Fast Track status, and Breakthrough Therapy designation in the U.S.

In the Penn-led trial, 68 patients received at least one therapeutic dose of AZEDRA. Twenty-five percent of patients who received at least one dose met the trial clinical benefit endpoint, and the number jumped to 32 percent in patients who received two doses. That clinical benefit was measured by a 50 percent or greater reduction in the amount of hypertensive medications these patients took for at least 6 months, as high blood pressure and associated cardiovascular side effects are a major cause of harm from these cancers. Additionally, 92 percent of evaluable patients who received at least one dose achieved a partial response or stable disease.

“This therapy not only controls the tumor, but also the debilitating symptoms caused by their excess hormone production, meaning it provides a dual benefit to patients,” Pryma said.

Pryma noted that Penn is one of the few academic medical centers in the country that has a dedicated tumor board for these rare cancers, making it an ideal institution to lead the multi-center trial. In fact, this is the second FDA approval in which the center has played a role this year.

In January, the FDA approved Lutathera (lutetium Lu 177 dotate) for the treatment of gastroentero-pancreatic neuroendocrine tumors which originate in the pancreas or gastrointestinal tract.

“Penn’s multidisciplinary approach draws on our physicians’ extensive experience in dealing with rare tumors and brings multiple experts from varying backgrounds together to offer cutting-edge treatments,” said David C. Metz, MD, the co-director, with Debbie Cohen, MD, of the Neuroendocrine Tumor Center at Penn.

“This is a very exciting step in bringing a much needed treatment to patients with metastatic pheochromocytomas and paragangliomas where limited treatment options exist,” Cohen said.

Source: Penn Medicine Communications

CAR T Cell Therapy Receives Approval for Use Across European Union

The European Commission (EC) has approved a personalized cellular therapy developed at the Abramson Cancer Center, making it the first chimeric antigen receptor (CAR) T cell therapy permitted for use in the European Union in two distinct indications. The EC granted the approval today to Novartis for Kymriah® (tisagenlecleucel, formerly CTL019) for the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia (ALL) in pediatric and young adult patients up to 25 years of age, as well as relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in patients over 18. The decision follows approval from the U.S. FDA approval for Kymriah in B-cell ALL and DLBCL in the United States.

“This is another milestone in the fight against cancer, allowing patients across the European Union to benefit from these potentially lifesaving therapies,” said Carl June, MD, the Richard W. Vague Professor in Immunotherapy in the department of Pathology and Laboratory Medicine in the Perelman School of Medicine at the University of Pennsylvania and director of the ACC’s Center for Cellular Immunotherapies. “This approval demonstrates the global impact of the therapies we developed in Philadelphia, and the far-reaching potential of these therapies to change the way cancer is treated across the world.”

Investigators at Penn’s Perelman School of Medicine led research, development, and clinical trials of CAR T therapy in collaboration with Novartis and Children’s Hospital of Philadelphia (CHOP). In August 2017, Kymriah became the first therapy based on gene transfer ever approved by the FDA when it was authorized for children and young adults with relapsed or refractory B-cell
CAR T Cell Therapy Receives Approval for EU Use

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ALL: Approval for relapsed or refractory DLBCL followed in May 2018.

The treatment modifies patients’ own immune T cells, which are collected and reprogrammed at the Novartis manufacturing facility to potentially seek and destroy the patients’ cancer cells. Once they are infused back into patients’ bodies, these newly built cells both multiply and attack, targeting cells that express a protein called CD19. Tests reveal the army of hunter cells can grow to more than 10,000 new cells for each single engineered cell patients receive – producing durable remission rates in refractory ALL and DLBCL – and can survive in the body for years.

The approval in the EU is the latest accomplishment in the alliance between Penn and Novartis, which entered into a global collaboration in 2012. Specifically, the action of the European Commission is based on two global CAR T cell trials.

The first global trial, known as ELIANA, evaluated patients in 25 centers in the US, Canada, Australia, Japan, and in Europe in Austria, Belgium, France, Germany, Italy, Norway and Spain. The trial involved 75 children and young adults with relapsed or refractory B-cell ALL and showed 81 percent of patients achieved a complete remission at three months follow up, with 80 percent of responders still in remission at six months. Overall survival at six months was 90 percent.

The second trial, called JULIET, is the largest study examining CAR T therapy in DLBCL, enrolling patients from 27 sites in 10 countries across the US, Canada, Australia, Japan, and Europe in Austria, France, Germany, Italy, Norway and the Netherlands. The trial showed an overall response of 52 percent, with 40 percent of patients achieving a complete response, among the 93 infused patients with three or more months of follow-up or earlier discontinuation.

Many patients in both trials experienced a side effect called cytokine release syndrome (CRS). CRS is a toxicity associated with CAR T therapy, which includes varying degrees of flu-like symptoms, with fevers, nausea, and muscle pain, and can require ICU-level care. In the ELIANA trial, 47 percent of patients experienced grade 3 or grade 4 CRS. In the JULIET trial, the number was 22 percent, using a CRS grading scale developed at the University of Pennsylvania. Patients with severe CRS required treatment with tocilizumab, a therapy initially implemented at Penn and CHOP, and now FDA-approved for CAR T cell-induced severe or life-threatening CRS, or corticosteroids. All of those patients recovered from their CRS. Other toxicities included infections, cytopenias or low blood count, neurologic events such as confusion, febrile neutropenia, and a metabolic abnormality called tumor lysis syndrome. All of those issues resolved on their own or with treatment, and there were no treatment-related deaths.

Source: Penn Medicine Communications

Cancer Cells Send Out “Drones” to Battle Immune System from Afar

Cancer cells are more than a lump of cells growing out of control; they participate in active combat with the immune system for their own survival. Being able to evade the immune system is a hallmark of cancer. Cancer cells release biological “drones” to assist in that fight—small vesicles called exosomes circulating in the blood and armed with proteins called PD-L1 that cause T cells to tire before they have a chance to reach the tumor and do battle, according to researchers from the University of Pennsylvania.

The work, published in the journal Nature, is a collaboration between Wei Guo, PhD, a professor of Biology in the School of Arts and Sciences and member of the ACC’s Tumor Biology Program, and Xiaowei Xu, MD, PhD, a professor of Pathology and Laboratory Medicine in the Perelman School of Medicine. While primarily focused on metastatic melanoma, the team found that breast and lung cancer also release the PD-L1-carrying exosomes.

The research offers a paradigm-shifting picture of how cancers take a systemic approach to suppressing the immune system. In addition, it also points to a new way to predict which cancer patients will respond to anti-PD1 therapy that disrupts immune suppression to fight tumors and a means of tracking the effectiveness of such therapies.

“Immunotherapies are life-saving for many patients with metastatic melanoma, but about 70 percent of these patients don’t respond,” said Guo. “These treatments are costly and have toxic side effects so it would be very helpful to know which patients are going to respond. Identi-
Cancer Cells Send Out “Drones” to Battle Immune System from Afar

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Identification of a biomarker in the bloodstream could potentially help make early predictions about which patients will respond, and, later on, could offer patients and their doctors a way to monitor how well their treatment is working.”

“Exosomes are tiny lipid-encapsulated vesicles with a diameter less than 1/100 of a red blood cell. What we have found with these circulating exosomes, is truly remarkable,” said Xu. “We collected blood samples from melanoma patients treated with anti-PD1 therapy. This type of liquid biopsy assay allows us to monitor tumor-related immune suppression with time.”

One of the most successful innovations in cancer therapy has been the use of checkpoint inhibitor drugs, which are designed to block attempts by cancer cells to suppress the immune system to allow tumors to thrive and spread. One of the primary targets for this class of drugs is PD-1, a protein on the surface of T cells. On tumor cells, they express a counterpart molecule called PD-L1, which interacts with the PD-1 protein on T cells, effectively turning off that cell’s anti-cancer response. Blocking that interaction using checkpoint inhibitors reinvigorates T cells, allowing them to unleash their cancer-killing power on the tumor.

While it was known that cancer cells carried PD-L1 on their surface, in this new work, the team found that exosomes from human melanoma cells also carried PD-L1 on their surface. Exosomal PD-L1 can directly bind to and inhibit T cell functions. Identification of the exosomal PD-L1 secreted by tumor cells provides a major update to the immune checkpoint mechanism, and offers novel insight into tumor immune evasion.

“Essentially exosomes secreted by melanoma cells are immunosuppressive.” Guo said. “We propose a model in which these exosomes act like drones to fight against T cells in circulation, even before the T cells get near to the tumor.”

Since a single tumor cell is able to secrete many copies of exosomes, the interaction between the PD-L1 exosomes and T cells provides a systemic and highly effective means to suppress anti-tumor immunity in the whole body. This may explain why cancer patients might have weakened immune systems.

Because exosomes circulate in the bloodstream, they present an accessible way of monitoring the cancer/T cell battle through a blood test, compared to the traditional more-invasive biopsy of tumors. After an acute phase of treatment, the researchers envision such a test as a way to monitor how well the drugs are keeping cancer cells in check.

By measuring pre-treatment levels of PD-L1, oncologists may be able to predict the extent of tumor burden in a patient and associate that with treatment outcome. In addition, a blood test could measure the effectiveness of a treatment, for example, levels of exosomal PD-L1 could indicate the level of T cell invigoration by immune checkpoint inhibitors.

“In the future, I think we will begin to think about cancers as a chronic disease, like diabetes,” says Guo. “And just as diabetes patients use glucometers to measure their sugar levels, it’s possible that monitoring PD-L1 and other biomarkers on the circulating exosomes could be a way for clinicians and cancer patients to keep tabs on the treatments. It’s another step toward precision and personalized medicine.”

The study was funded in part by an NCI SPORE grant in melanoma.


Source: Penn Medicine Communications

Additional Inhibitor Can Help Anti-VEGF Therapy Overcome Resistance in Glioblastoma

Adding another inhibitor to therapies that cut off a tumor’s access to blood vessels could be the key to helping those therapies overcome resistance in glioblastoma, a deadly form of brain cancer. Drugs that target the vascular endothelial growth factor (VEGF) – a signaling protein that stimulates the formation of blood vessels – are available but have yet to show an overall survival benefit in many malignant cancers. Now researchers from the Perelman School of Medicine at the University of Pennsylvania have shown the key may lie in adding an additional inhibitor that blocks the platelet-derived growth factor (PDGF), which regulates cell growth and division. The study not only identifies PDGF as a combination target for anti-VEGF therapies, but it also shows that pairing makes tumors more sensitive to anti-VEGF therapies in mice. Nature Communications published the findings last month.

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Seminars and So Forth

Monday 9/10/18 12:00 pm
SPATT Seminar Series
“Observational Data for Discovery Science.” Nicholas P. Tatonetti, PhD, Herbert Irving Assistant Professor of Biomedical Informatics; Director of Clinical Informatics, Herbert Irving Comprehensive Cancer Center, Columbia University
SCTR 10-146AB

Tuesday 9/11/18 12:00 pm
Distinguished Lecture in Cancer Research
“Dissecting tumor metabolism from immunometabolism.” Jonathan Powell, MD, PhD, Professor of Oncology; Associate Director, Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins Medicine
Wistar Institute, Caplan Auditorium

Tuesday 9/11/18 4:00 pm
Immunology Colloquium
“Engineering tolerance in autoimmunity and transplantation.” Megan Levings, PhD, Professor, Dpt. of Surgery, University of British Columbia
CRB Austrian Auditorium

Tuesday 9/11/18 4:00 pm
CVI/IDOM Joint Seminar
“Regulation of Energy Homeostasis: Basic Biology and New Therapeutic Opportunities.” Bruce Spiegelman, PhD, Stanley J. Korsmeyer Professor of Cell Biology and Medicine, Dana-Farber Cancer Institute, Department of Cancer Biology/Department of Cell Biology, Harvard Medical School
SCTR Rubenstein Auditorium

Thursday 9/13/18 12:00 pm
ACC Radiobiology & Imaging Program Seminar Series
Ling Qin, PhD, Associate Professor Of Orthopaedic Surgery, PSOM
SCTR 10-146AB

Thursday 9/13/18 12:00 pm
Gastroenterology Seminar Series
“De-regulation of the Hippo pathway resets the clock in sarcoma.” T.S. Karin Eisinger, PhD, Ann B. Young Assistant Professor, Department of Pathology & Laboratory Medicine, PSOM
901 BRB II/III

Monday 9/17/18 12:00 pm
SPATT Seminar Series
“Increasing the Cancer-Specificity and Persistence of CAR-T Cells.” Avery D. Posey, Jr., PhD, CCI Clinical Instructor and Associate Laboratory Director, Carl June Lab, PSOM
SCTR 10-146AB

Monday 9/17/18 2:00 pm
Penn Muscle Institute Seminar Series
“Building anti-cancer therapy out of the basic science of the actin cytoskeleton.” Peter Gunning, PhD, Head of the School of Medical Sciences, University of South Wales Sydney, Australia
CRB Austrian Auditorium

Tuesday 9/18/18 10:00 am—3:00 pm
Scientific Innovation In Oncology Drug Development: An ACC Pharma Collaboration Forum
Learn about oncology pipelines/R&D priorities directly from industry leaders, and network with pharma scientists. Participating companies include BMS, Boehringer-Ingelheim, Celgene, Incyte, and GlaxoSmithKline. Register here.
SCTR Rubenstein Auditorium

Tuesday 9/18/18 12:00 pm
Distinguished Lecture in Cancer Research
“IMP-licating post-transcriptional regulons in intestinal homeostasis and tumor growth.” Kathryn E. Hamilton, Assistant Professor of Pediatrics, Division of GI, Hepatology, and Nutrition, CHOP
BRB II/III Gaulton Auditorium

Wednesday 9/19/18 10:00 am—7:00 pm
IFI Systems Immunology Symposium
A day of scientific talks followed by a panel discussion with editors from Cell, Immunity, and Nature Immunology. Details here.
SCTR Rubenstein Auditorium

Thursday 9/20/18 12:00 pm
Gastroenterology Seminar Series
“The Epigenetic basis of myeloid cell fate decisions.” M. Andres Blanco, PhD, Assistant Professor, Biomedical Sciences, Penn Vet
901 BRB II/III

COMING SOON

Wednesday 10/3/18 8:00 am—6:00 pm
Penn IRM Animals in Translation Symposium
Featuring speakers across the veterinary and regenerative medicine fields. Registration deadlines: posters/trainee talks 9/20; general registration 9/28.
SCTR Rubenstein Auditorium
Funding Opportunities

PAR-18-887/PAR-18-888 NCI Research Specialist Award (R50)

LOI Due Date: 30 days before application due date
Application Due Date: January 11, 2019

The Research Specialist Award is designed to encourage the development of stable research career opportunities for exceptional scientists who want to continue to pursue research within the context of an existing NCI-funded basic, translational, clinical, or population science cancer research program, but not serve as independent investigators.


PAR-18-893/PAR-18-892 Physical Activity and Weight Control Interventions Among Cancer Survivors: Effects on Biomarkers of Prognosis and Survival (R01/R21)

Application Due Dates: Standard dates apply

These RFAs encourage transdisciplinary and translational research that will identify the specific biological or biobehavioral pathways through which physical activity and/or weight control (either weight loss or avoidance of weight gain) may affect cancer prognosis and survival.


Resistance in Glioblastoma

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The American Cancer Society estimates there will be almost 24,000 diagnoses of malignant glioblastoma in the United States in 2018. It is the most common and most aggressive primary brain tumor, and patients have a median survival of about 14 months. One treatment approach involves targeting VEGF – most commonly with the drug bevacizumab – with the idea being that cutting the tumor’s access to blood vessels will cut off its supply of oxygen and nutrients it needs to survive.

A team led by senior author Yi Fan, MD, PhD, an assistant professor of Radiation Oncology at Penn and a member of the ACC’s Radiobiology and Imaging Program, analyzed human glioblastoma specimens and found VEGF receptor expression was reduced in tumor-associated endothelial cells – the cells that line the interior surface of the blood vessels. In other words, the tumors are transforming the endothelial cells to make these cells resistant to anti-VEGF therapies.

That’s where the second inhibitor comes in. Researchers identified a PDGF pathway to knock out called PDGF/NF-κB/Snail. Blocking that pathway prevented the tumor endothelial cells from transforming, leaving the cancer vulnerable.

“This could be the key to solving the biggest problem in the field of anti-vascular cancer therapies,” Fan said. “Tumors are highly resistant to anti-VEGF therapies alone, but our study shows the flaw is in the current treatment, not the concept itself.”

Since drugs already exist that can target both pathways, researchers put the combination to the test and showed that blocking both VEGF and PDGF improved overall survival in mice.

“These findings point the way toward a next generation of anti-VEGF therapies, opening the door to version 2.0,” Fan said.

Fan noted that further research is needed to evaluate this combination in humans, as well as to look for other potential targets.


Source: Penn Medicine Communications