Florida’s famous sunshine comes with a dark side: skin cancer, melanoma in particular. The state is second only to California in the number of new melanoma cases in the United States annually. Despite progress that has been made in understanding the biology, genetics and immunology of melanoma, the outlook for patients with metastatic melanoma and recurrent non-melanoma skin cancers remains poor.

Several unique clinical trials at Moffitt Cancer Center are exploring innovative approaches to skin cancer treatment aimed at improving the outlook for late-stage melanoma patients. The studies tap into the Cancer Center’s culture of teamwork and adaptability to bring quickly – new science discoveries from the laboratory to patient clinical trials.

Some pioneering melanoma clinical trials at Moffitt are made possible by a newly awarded National Cancer Institute (NCI) Specialized Programs of Research Excellence (SPORE) grant for melanoma research. The SPORE grant, which is being overseen by principal investigator Jeffrey S. Weber, MD, PhD, director of the Donald A. Adam Comprehensive Melanoma Research Center of Excellence, totals $8,829,020 over five years. This is Moffitt’s second SPORE grant. The first, for lung cancer research, was awarded in 2008. Moffitt is the only cancer center based in Florida that has received this prestigious grant.

“SPORE grants were established to promote interdisciplinary research and to move basic research findings from the laboratory to a clinical setting. This collaborative bench-to-bedside approach to medicine is ingrained at Moffitt,” says Dr. Weber. “The addition of a melanoma SPORE acknowledges the translational research being done by our Comprehensive Melanoma Research Center.”

Moffitt’s clinical services are organized into disease-oriented interdisciplinary programs with a full complement of services. Our specialized clinical research unit is dedicated to phase I and early-phase II clinical trials and supports projects with intensive pharmacokinetics and correlative laboratory studies. To view clinical trials that are accruing patients, visit MOFFITT.org/ClinicalTrials. Physicians interested in referring patients to Moffitt for clinical trials may call 813-745-4106.
SPORE Advances  Continued from front

Center of Excellence. We are honored to be recognized by the NCI, and this SPORE grant will allow us to significantly enhance our efforts to contribute to the prevention and cure of skin cancer.”

This melanoma SPORE has been several years in the making. In 2007, Moffitt was awarded a melanoma SPORE planning grant from Florida’s Bankhead-Coley Cancer Research Program spearheaded by Vernon K. Sondak, MD, chair of the Department of Cutaneous Oncology, to help recruit a team of interdisciplinary skin cancer researchers. That same year, Donald A. Adam, a melanoma survivor and banker, donated $20.4 million to Moffitt to expand expertise in the area of melanoma research. The gift led to the development of the Donald A. Adam Comprehensive Melanoma Research Center of Excellence and facilitated the recruitment of Dr. Weber.

Improving Melanoma Treatment And Outcomes

Skin cancer is the most common form of cancer in the United States. Although melanoma accounts for less than 5 percent of all skin cancer cases, it is the deadliest form of the disease, responsible for 75 percent of all skin cancer-related deaths. This new SPORE grant will fund three melanoma research projects that have a common thematic approach designed to promote progress in skin cancer treatment based on novel and promising research. All three projects deal with stage IV disease with the goal of keeping patients alive longer with a better quality of life.

Project 1: Potentiating the effects of targeted and cytotoxic agents on cell-based immunotherapy in melanoma

Investigators: Jeffrey S. Weber, MD, PhD, and Dmitry I. Gabrilovich, MD, PhD, of The Wistar Institute in Philadelphia

This unique project studies targeted therapy with adoptive transfer of T cells with the goal of boosting the immune system’s response against melanoma cells.

“This project includes a clinical trial that explores a novel notion that targeted therapy and chemotherapies depend on the immune system for their activity,” says Dr. Weber. “Moffitt is conducting one of only two such trials in the U.S.”

The clinical trial tests the combined effect of adoptive T-cell transfer and drug therapy to inhibit the BRAF mutation in patients with melanoma. It is based on an observation by Moffitt researchers that targeted therapy may prime the immune system and add to the effects of adoptive therapy with therapeutic tumor infiltrating lymphocytes (TIL) - a preparation of immune cells cultured in the laboratory that when infused into a patient can help break down tumors.

Moffitt is one of three centers in the country combining adoptive cell therapy with TIL for melanoma.

Project 2: Abrogation of therapeutic escape pathways in BRAF mutant melanoma

Investigators: Vernon K. Sondak, MD, and Keiran S. Smalley, PhD

This project seeks to determine why some patients develop resistance to BRAF inhibitors like vemurafenib, a drug approved by the Food and Drug Administration for treatment of BRAF mutation-positive metastatic melanoma. The investigators aim to find whether the resistance can be overcome or if different treatment options are necessary.

Resistance to vemurafenib can develop as early as six months after treatment begins. This clinical trial combines previously used agents that show promise of improving results for BRAF V600-mutated melanoma patients.

The study goal is to overcome pathway resistance in melanoma by determining the best and safest dose of an experimental drug, XL888, when administered orally with vemurafenib.

Phase I of this study opened in August 2012 and will continue through the end of 2013. Currently, six patients are enrolled and receiving treatment. Four of those participants have had an antitumor response.

Another facet of this project is to determine whether resistance to BRAF inhibition can be overcome using heat shock protein inhibitors. The researchers will perform correlative studies in tumor specimens to determine if XL888 can inhibit a heat shock protein known as Hsp90 and assess
how changes in the expression of this key signaling protein relates to a patient’s response.

“The clinical trial will potentially support the use of heat shock inhibitors to overcome resistance to BRAF inhibition in phase II and III trials, redefining how we look at resistance to targeted therapies,” Dr. Weber says.

Project 3: Augmenting the immunogenicity of melanoma through manipulation of histone deacetylases (HDACs)

Investigators: Eduardo Sotomayor, MD; Ed Seto, PhD; and Jeffrey S. Weber, MD, PhD

This innovative research looks at specific histone deacetylases (HDACs), enzymes that regulate gene expression, to determine if they can be manipulated by an inhibitor drug to stimulate the immune system’s response against melanoma cells.

HDAC inhibitors represent a promising new class of compounds for the treatment of cancer. In this project, HDAC inhibitor LBH-589 will be used in combination with other drugs to treat solid melanoma tumors.

The hope is that the LBH-589 will augment the immune system’s response against melanoma cells through suppression of HDAC 6 and 11, enzymes needed for cancer cells to grow and survive.

“The project is new, because to date nobody has used an HDAC inhibitor in a clinical trial to show that it can function as an immune stimulant,” Dr. Weber says. “Additionally, it is a new concept that LBH-589 has immunological effects. Drugs whose effectiveness was thought to lie elsewhere are turning out to work with the immune system.”

It is hoped that knowledge in this area to be generated by the team effort will lead to novel epigenetic-based immunotherapy that will overcome the substantial barrier of melanoma-induced T-cell tolerance.

New Clinical Trials: Not Just For The Hopeless

“Previously, people thought of clinical trials as only for people who had no hope. That’s not true in this day and age,” says Ragini Kudchadkar, MD, a co-director of the Administration and Clinical Trials Core of the SPORE grant. “Today, clinical trials are all about finding better therapies and drugs. It gives patients the opportunity to gain access to drugs they normally couldn’t obtain, and many of the participating patients say they feel good about helping develop therapies for the future.”

Dr. Kudchadkar is the principal investigator on a number of clinical trials for patients with advanced-stage BRAF-mutated melanoma, including a phase I study of XL888 with vemurafenib, a phase Ib/II study of LGX818 combined with MEK162 and a phase I/II study of PI3K inhibition with PX-866 combined with vemurafenib.

“People are positive and feel rewarded about enrolling in a clinical trial, even if the outcome is unknown, because they realize that they might help someone in the future. Today, the standard of care for most melanoma patients is to participate in a clinical trial,” Dr. Weber says.

Select Melanoma Clinical Trials At Moffitt Cancer Center

Clinical trials, such as those highlighted in this publication, are essential in the search for new and better cancer treatments. We encourage physicians to refer their patients to participate in clinical trials offered through Moffitt Cancer Center. We will make every effort to provide the information and services you request and return your patients to you for continued care. For a complete listing of active clinical trials at Moffitt, visit MOFFITT.org/ClinicalTrials. Physicians interested in referring patients to Moffitt for clinical trials may call 813-745-4106.

The mission of the H. Lee Moffitt Cancer Center & Research Institute is to contribute to the prevention and cure of cancer.

MCC#16545: A randomized phase II study to assess the safety and immunogenicity of recMAGE-A3+AS15 ASCI with or without Poly IC:LC in patients with resected MAGE-A3-positive stage IV melanoma.

Summary: The purpose is to find a better way to treat melanoma. Study goals are to measure the side effects of and find out how well patients tolerate the recMAGE-A3 + AS15 ASCI (MAGE-A3 ASCI) treatment with or without the Poly IC:LC; to see how well the patient’s immune system responds to the MAGE-A3 ASCI treatment with or without the Poly IC:LC; to measure the rate of return of the patient’s tumor after the MAGE-A3 ASCI treatment with or without the Poly IC:LC; and to measure the rate of return of the patient’s tumor in two groups of patients: one group positive for the gene signature and the other group not positive for the gene signature in their tumor after the MAGE-A3 ASCI treatment with or without the Poly IC:LC.

Contact: Erica Royster, 813-745-4279.

MCC#16733: A phase III randomized study of adjuvant ipilimumab anti-CTLA4 therapy versus high-dose interferon α2b for resected high-risk melanoma.

Summary: The purpose of this study is to compare the effects, good and/or bad, of ipilimumab with interferon α2b on patients and their melanoma to find out which is better. In this study, participants will receive either ipilimumab or the interferon α2b. We plan to determine whether ipilimumab stops or delays their cancer from returning in comparison to interferon α2b.

Clinical Trials continued next page
Contact: Denise Dorman, 813-745-7631.

MCC#16755: A phase Ib study of Yervoy with Sylatron for patients with unresectable stages IIIB/C/IV melanoma.

Summary: The purpose is to see how much of the drug Yervoy can be safely tolerated when given to people who are also receiving the drug Sylatron. Investigators also wish to find out whether the addition of Yervoy increases the chance that Sylatron will cause a rise in the level of antibodies in the patient’s blood that recognize their own tissues, known as “autoimmune” antibodies. Investigators also want to find out how likely it is that patient’s tumor will shrink.

Contact: Denise Dorman, 813-745-7631.

MCC#16992: A phase II clinical trial of vemurafenib with lymphodepletion plus adoptive cell transfer and high-dose IL-2 in patients with metastatic melanoma.

Summary: The investigators want to find out more about the effects of an investigational combination of medicines, which includes special T cells (lymphocytes), a kind of white blood cell that protects the body from viral infections, helps other cells fight bacterial and fungal infections, produces antibodies, fights cancers, and coordinates the activities of other cells in the immune system. The co-primary objectives of this study are to improve the drop-out rate in patients undergoing adoptive cell transfer and to improve the 12 month PR + CR rate based upon RECIST 1.1 criteria on an intention-to-treat basis. A secondary objective is an evaluation of progression-free survival.

Contact: Erica Royster, 813-745-4279.

MCC#17013: A phase I study of escalating doses of XL888 with vemurafenib for patients with unresectable BRAF-mutated stage III/IV melanoma.

Summary: This is a multi-cohort, dose-escalation study of XL888 with a fixed dose of vemurafenib. New dose escalation or de-escalation cohorts will be assigned by the principal investigator with discussion with appropriate coinvestigators once safety and tolerability are known for a given cohort in accordance to dose escalation rules. Participants will be defined to be enrolled within a cohort upon receipt of first dose of XL888/vemurafenib.

Contact: Leticia Tetteh, 813-745-4617.

MCC#17057: A pilot feasibility trial of ipilimumab with lymphodepletion plus adoptive cell transfer and high-dose IL-2 in patients with metastatic melanoma.

Summary: The investigators want to study the safety, side effects, and benefits of therapeutic tumor infiltrating lymphocytes (TILs) when they are given with the drug ipilimumab. Ipilimumab is a type of immunotherapy – a drug used to boost the ability of the immune system to fight cancer, infection and other diseases.

Contact: Cabel Eysmans, 813-745-3007; Erica Royster, 813-745-4279.

MCC#17204: An open-label, expanded access study of melphalan with the percutaneous hepatic perfusion system in patients with ocular and cutaneous melanoma metastatic to the liver.

Summary: The main purpose of this study is to provide this experimental treatment to participants before it has been approved for use by the United States government (specifically the US Food and Drug Administration [FDA]). The study will also gather information about the side effects of this study treatment, determine whether the treatment reduced the size of the tumor in the liver, and (in some patients) measure the amount of melphalan that is in patients’ liver and in the rest of their body.

Contact: Kira Hulse, 813-745-2493; Mira Lacevic, 813-745-6042.

MCC#17318: A phase Ib/II, multicenter, open-label, dose-escalation study of LGX818 in combination with MEK162 in adult patients with BRAF V600-dependent advanced solid tumors.

Summary: This is a multicenter, open-label, dose-finding phase Ib dose-escalation study to estimate the maximum tolerated dose(s) and/or recommended phase II dose(s) (MTD/RP2D) for the dual combination of LGX818 and MEK162 and the triple combination of LGX818 and MEK162 and LEE011, followed each independently by a phase II part to assess the clinical efficacy and to further assess the safety of the combinations in selected patient populations. The dose escalation parts of the trial will be conducted in adult patients with BRAF V600-dependent advanced solid tumors. Following MTD/RP2D declaration, patients will be enrolled in three phase II arms for the dual combination and one phase II arm for the triple combination.

Contact: Denise Dorman, 813-745-7631.

MCC#17365: An open-label, randomized, phase II study of nivolumab given sequentially with ipilimumab in subjects with advanced or metastatic melanoma.

Summary: The purpose of this study is to evaluate the safety and efficacy of a sequential combination therapy of nivolumab and ipilimumab. Cohort A: nivolumab followed by ipilimumab. Cohort B: ipilimumab followed by nivolumab.

Contact: Donna Kay Gallenstein, 813-745-4960.
More Novel Immunotherapeutic Melanoma Treatment Studies

In other clinical research projects, surgical oncologist Amod A. Sarnaik, MD, received an NCI K-23 award funded at $937,865 for five years to study adoptive cell therapy for metastatic melanoma. His project is a phase I clinical trial that combines costimulatory antibodies and adoptive cell therapy with TIL for stage IV melanoma patients.

Additionally, Dr. Sarnaik is studying the feasibility and safety of minimally invasive inguinal lymph node dissection in patients with melanoma.

Dr. Sarnaik also is the principal investigator of a feasibility study to determine the ability to detect immune cell infiltration into melanomas treated by PV-10, a solution developed from Rose Bengal, a water-soluble dye commonly used to stain damaged cells in the eye. Early clinical trials show PV-10 can boost immune response in melanoma tumors as well as the blood stream.

In the initial study, researchers injected a single dose of PV-10 into mice with melanoma. The results were a significant reduction in the skin cancer lesions and a sizable reduction in melanoma tumors that had spread to the lungs. The researchers said the dye solution appeared to produce a robust antitumor immune response and may be safer than existing immunological agents.

“We are conducting our first human clinical trial of PV-10 for advanced melanoma patients. In addition to monitoring the response of injected melanoma tumors, we are also measuring the boost in the antitumor immune cells of patients after injection,” says Dr. Sarnaik.

The October 2013 issue of Moffitt’s Cancer Control Journal is dedicated to recent advances in the treatment of melanoma. With the approval of four new therapies (ipilimumab, vemurafenib, dabrafenib and trametinib) for stage IV disease, more FDA-approved therapies for metastatic melanoma have emerged in the last three years than have been available in the previous 20 to 30 years combined. This issue details the research behind these promising new discoveries. To view the publication, visit www.MOFFITT.org and select “Cancer Control: Journal of the Moffitt Cancer Center” under the “For Physicians & Healthcare Professionals” tab located at the bottom of the webpage.
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