THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

Melanoma HORIZONS

ISSUE 21

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

FEBRUARY 2016

Pittsburgh 'Health Care Hero' now Houston's asset

Pittsburgh's loss was Houston's gain when **Dr. Hussein Tawbi**, designated a 2015 "Health Care Hero" by the Pittsburgh Business Times, moved to Houston last fall to join MD Anderson's Melanoma Medical Oncology faculty ranks.

On Sept. 9, 2015, two months before his move to Houston, the Pittsburgh publication honored Dr. Tawbi among a select number of "Health Care Heroes for 2015" in an event dubbed "an annual celebration of the people and organizations who are making an impact on the Pittsburgh region." Dr. Tawbi and Dr. Kurt Weiss, then a colleague at the University of Pittsburgh Medical Center, shared the honor in the category "Health Care Provider Physician."

Dr. Hussein Tawbi

When he joined MD Anderson in November 2015, Dr. Tawbi brought an outstanding record of clinical and translational research achievements in melanoma, brain metastases and sarcoma. Dr. Tawbi, who holds an M.D. from the American University of Beirut and a Ph.D. in clinical/translational science from the University of Pittsburgh, has held myriad leadership roles in academia as well as national melanoma organizations.

Previously, he served as Associate Professor of Medicine at the University of Pittsburgh School of Medicine and Associate Professor of Clinical and Translational Science at the University of Pittsburgh Clinical Translational Science Institute. During that time, he was a collaborator on a Melanoma Research Alliance Team Science Award grant led by **Michael A. Davies, M.D., Ph.D.**, MD Anderson Melanoma Medical Oncology Deputy Chair and Associate Professor. Upon joining MD Anderson, Dr. Tawbi was appointed to the position of Associate Professor in the Department of Melanoma Medical Oncology, with the administrative title of Director of Personalized Cancer Therapy Research.

"This is an exciting time to be a clinician and a researcher in the field of melanoma," Dr. Tawbi observed shortly after his arrival. "We have managed to harness the knowledge acquired in basic science and translate it into huge progress for many patients with melanoma utilizing immunotherapy, targeted therapy, and a number of combination therapies. In the next frontier, we need to think about how to personalize therapy to maximize benefits and minimize toxicity."

His focus here is threefold: first, to choose the right therapy for the right patient; second, to advance the care of patients with brain metastases; third, to find novel therapies for patients with resistance or those who are not receiving full benefits from their primary therapy. His third objective integrates seamlessly with the Phase 1 Clinical Trials Program in the Department of Investigational Cancer Therapeutics, in which he holds a secondary appointment, he noted.

"Practicing oncology in today's world is, by definition, personalizing care in the clinic," said Dr. Tawbi. He said when an oncologist walks into a clinic room, he/she needs to be thinking about the characteristics of the patient; the characteristics of the tumor being targeted; and the molecular mechanisms of potential therapies. He/she then will be in a position to synthesize those elements to choose the best possible therapeutic approaches ranging from the current standard of care to suitable and promising clinical trials, said Dr. Tawbi.

"What matters to me is that we practice great medicine in the context of great science– that we really take the best possible care of our patients," Dr. Tawbi emphasized.

Dr. Tawbi has assiduously investigated five areas: epigenetic mechanisms of therapy resistance; melanoma brain metastases; DNA repair mechanisms; phase 1 drug development, and sarcoma. He has led and participated in a variety of clinical trials, based on promising laboratory-based research, whose purpose is to evaluate the effectiveness of different therapies in treating patients with melanoma, particularly hard-to-treat melanoma brain metastases. He is the principal investigator of a number of national clinical trials that he is bringing to MD Anderson.

Although it's still early days on his career timeline, Dr. Tawbi already has won impressive awards honoring him not only as a "health care hero," but also for excellence in mentoring, education, and innovative cancer research. Based on his record and his focus on delivering the best possible care to his patients here, he appears to be well on his way to many more.

Dr. Tawbi bringing key clinical trials to MD Anderson

Melanoma Medical Oncology Associate Professor Hussein Tawbi, M.D., Ph.D., the department's newest clinical faculty member, is the principal investigator of several national clinical trials that he will be bringing to MD Anderson.

First, Dr. Tawbi is leading a multi-center clinical trial evaluating the safety and efficacy in patients with melanoma metastatic to the brain who are treated with nivolumab, a programmed death-1 (PD-1) checkpoint inhibitor, combined with ipilimumab, a monoclonal antibody that activates the immune system by targeting the protein receptor CTLA-4.

On Sept. 30, 2015, the U.S. Food and Drug Administration (FDA) approved this combination treatment for patients with BRAFV600 wild-type, unresectable (inoperable) or metastatic melanoma. Dr. Tawbi's trial, called CheckMate 204, will be helpful in determining the effectiveness of this newly approved combination therapy in melanoma that has spread to the brain.

Second, Dr. Tawbi is leading a trial called coBRIM-B to evaluate the effectiveness of the combination of cobimetinib (Cotellic), a MEK enzyme inhibitor, with the BRAF inhibitor vemurafenib in patients with BRAF-mutated melanoma and active brain metastases. On Nov. 10, 2015, the FDA approved this combination to treat advanced melanoma that has metastasized or cannot be removed by surgery, and has a BRAF V600E or V600K gene mutation.

Third, Dr. Tawbi is leading an NCI-CTEP (National Cancer Institute Cancer Therapy Evaluation Program) Organ Dysfunction Working Group early phase study of the PARP inhibitor veliparib in patients who have solid tumors that are metastatic or cannot be removed by surgery, as well as varying degrees of hepatic or renal dysfunction.

The purpose of this phase I trial is to study the side effects and the best dose of veliparib when given with paclitaxel and carboplatin in treating patients with solid tumors that are metastatic or cannot be removed by surgery, and with liver or kidney dysfunction, as described on the National Institutes of Health clinical trials website. Veliparib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth, while paclitaxel and carboplatin are drugs used in chemotherapy that work in different ways to stop the growth of tumor cells either by killing the cells or stopping them from dividing, the description states. Giving veliparib together with paclitaxel and carboplatin may kill more tumor cells, according to the description.

Dr. Patel leads new adjuvant therapy trial

Dr. Sapna P. Patel

MD Anderson Melanoma Medical Oncology Assistant Professor **Sapna P. Patel, M.D.**, presented information on a new national clinical trial of adjuvant therapy at the department's Grand Rounds meeting Nov. 23, 2015.

Dr. Patel and Dr. Kenneth Grossmann, of Huntsman Cancer Institute in Utah, are the Southwest Oncology Group (SWOG) Study Coordinators for a National Clinical Trials Network cooperative group trial entitled "A Phase III Randomized Trial Comparing High Dose Interferon to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." The trial was designed to compare the use of pembrolizumab to high-dose interferon in melanoma patients at high risk of recurrence after surgery.

The primary goals of the study are to determine whether overall survival and relapse-free survival are improved with pembrolizumab, a monoclonal antibody against programmed cell death-1 protein (PD-1), compared to high-dose interferon in resected melanoma. Both pembrolizumab and high-dose interferon are forms of immune therapy that increase immune surveillance and eradication of residual melanoma in the body, Dr. Patel explained. Dr. Patel leads another important endpoint of the study, the quality of life determination in patients on each arm of the study.

On Sept. 4, 2014, the FDA granted accelerated approval to Keytruda (pembrolizumab) for the treatment of patients with unresectable or metastatic melanoma in the second-line setting. On Dec. 18, 2015, Keytruda maker Merck announced the FDA had approved an expanded indication for the drug to include the first-line treatment of patients with unresectable or metastatic melanoma, based on the results of the phase III trial KEYNOTE-006.

Until last year, two forms of interferon – high-dose interferon alfa-2b, the control arm in Dr. Patel's trial, and pegylated interferon alfa-2b -- were the only FDA-approved adjuvant treatment options for melanoma. On Oct. 29, 2015, the FDA expanded the approval of ipilimumab to include a new use at a higher dose as adjuvant therapy for patients with stage III melanoma, to reduce the risk that the melanoma will return after surgery. Ipilimumab (Yervoy), an immune checkpoint inhibitor, was originally approved in 2011 to treat late-stage melanoma that cannot be removed by surgery.

"Pembrolizumab is well tolerated in the Stage IV metastatic setting, and we have experience in several thousand melanoma patients to date," Dr. Patel commented. "Algorithms for managing toxicities are well established, and we anticipate safe and tolerable use of this drug in the adjuvant setting. It is reasonable and with sound optimism that we believe a study comparing pembrolizumab to standard FDA-approved therapy is a reasonable next step, and will further improve the outcomes of our patients with high-risk melanoma."

Therapies beyond checkpoint inhibition

By Adi Diab, M.D., Assistant Professor, Melanoma Medical Oncology

Dr. Adi Diab

Checkpoint inhibitor (CPI) therapy that augments T-cell function using monoclonal antibodies against CTLA-4 and PD-1 has transformed the treatment of metastatic melanoma. However, while the recent FDA approval of the two anti-PD-1 therapies, nivolumab and pembrolizumab, was exciting, we know that more than 50% of treatment-naïve patients do not respond to these therapies. Additionally, recent evidence suggests that systemic CPI combinations with concurrent, systemic ipilimumab and nivolumab result in higher response rates (>50%), progression-free survival and overall survival compared to ipilimumab alone in this disease.

Unfortunately, this improved clinical benefit comes at the cost of much higher toxicity (~60% grade 3/4 immune-related adverse events), which significantly limits tolerability. Thus, there remains a significant unmet need for novel CPI therapies with improved response rates and safety profiles, both in treatment-naïve patients and in those who have failed CTLA-4 and/or PD-1 inhibition.

Cancer progression is due to immune escape, which occurs when cancer cells are not recognized by the immune system (immune ignorance.) We believe that overcoming this immune ignorance is a major barrier for CPI therapy success. Administering intratumoral injections of immune agonists is one strategy that can augment the innate immune system, increase tumor recognition, and generate an immune response that can be further potentiated with CPI therapy against CTLA-4 or PD-1.

We recently opened an innovative clinical trial in this area: **Protocol 2015-0530**, "A Phase I/II Study to Assess the Safety and Efficacy of Intratumoral IMO-2125 in Combination with Ipilimumab in Patients with Metastatic Melanoma," and we have another in the wings: **Protocol 2015-0199**, "Phase I/II Dose Escalation and Cohort Expansion of Safety and Tolerability Study of Intratumoral rAd.CD40L (ISF35) in Combination with Systemic Pembrolizumab in Patients with Refractory Metastatic Melanoma."

In Protocol 2015-0530, we use an intratumorally injected toll-like receptor 9 (TLR9) agonist, IMO-2125, in combination with systemic CTLA-4 inhibition in patients with stage III or stage IV melanoma who have failed previous checkpoint inhibition. Toll-like receptor agonists, and in particular TLR9, are important in the immune response, as they activate plasmacytoid dendritic cells and facilitate generation of antigen-specific antibodies, cytotoxic T cells and memory T cells, all of which lead to heightened T cell-mediated tumor destruction.

The design of Protocol 2015-0199 is similar to that of Protocol 2015-0530, but instead, we use an intratumorally injected CD40 ligand, ISF35, in combination with pembrolizumab in patients with refractory, metastatic melanoma. There is a growing body of evidence supporting the crucial role of CD40 activation for full maturation and activation of dendritic cells that can promote antigen/tumor-specific T-cell responses and generate a potent antitumor response. Both highlighted trials are designed to overcome resistance to primary checkpoint inhibition by improving tumor recognition using the novel strategy of in situ vaccination, thereby improving response rates with limited extra toxicity.

In addition, while CPI therapy has been the major focus of immune activation in immunotherapy, we also know that direct stimulation using cytokines can drive immune-mediated cancer cures. In particular, aldesleukin (IL-2) directly stimulates the immune system by increasing the number of T cells, and has shown clinical benefit in metastatic melanoma and renal cell carcinoma.

In our recently opened clinical trial, **Protocol 2015-0573**, "A Phase I/2, Open-label, Multicenter Dose Escalation and Dose Expansion of NKTR-214 in Subjects with Locally Advanced or Metastatic Solid Tumor Malignancies", we use NKTR-214, which is an engineered IL-2 polymer conjugate that activates the beta and gamma but not the alpha subunits of the IL-2 receptor. Unlike aldesleukin, NKTR-214 is hypothesized to increase the number of effector T cells while minimizing expansion of regulatory T cells (as regulatory T cells are upregulated with aldesleukin.) This will result in a significant increase in the T effector/T regulatory cell ratio, which has been shown to be a relevant biomarker of response. Lastly, NKTR-214 was designed to have less toxicity than aldesleukin, and is administered in the outpatient setting.

-With thanks to Dr. Marc Uemura for his contributions to this story.

AIM Walk scores rousing success

Thanks to all those whose support made possible the tremendous success of the 8th annual AIM for the CURE Melanoma Walk and Fun Run held at MD Anderson Cancer Center on Sept. 26, 2015, which raised $115,000 to benefit MD Anderson melanoma research initiatives.

AIM cofounder Jean Schlipmann and Melanoma Medical Oncology Deputy Chair **Michael A. Davies, M.D., Ph.D.,** were among speakers. About 1,400 people participated in the 5-K, which featured ABC-TV "Good Morning America" co-host Robin Roberts as emcee.

A total of 125 people received free skin cancer screenings administered by MD Anderson Melanoma & Skin Center physicians who volunteered their time, including **Dr. Jeffrey Lee, Dr. Merrick Ross** and **Dr. Jeffrey Gershenwald,** all of Surgical Oncology, and **Dr. Adrienne Choksi** and **Dr. Ana Ciurea** of Dermatology, supported by myriad nurses and physician assistants.

Always a popular family affair, the entertaining event offered a variety of food vendors; skin cancer education information; live music; the puppets from MD Anderson's "Too Cool to Smoke" show and "Ray and the Sunbeatables" from the Sun Safety Program for Children, presented in thousands of schools as part of the CATCH (Coordinated Approach to Child Health) Program and MD Anderson's Melanoma Moon Shot program.

Clinical Trials in Melanoma Medical Oncology

For more information on these trials, call the toll-free AskMDAnderson number, 1-877-632-6789. The print version of this list was up to date as of our Jan. 4, 2016 copy deadline. To see all the MD Anderson Melanoma Department clinical trials that are current at any given time, please visit the MD Anderson Melanoma Clinical Trials website page at http://bit.ly/1bBxR4l

Neoadjuvant

Neoadjuvant and Adjuvant Dabrafenib and Trametinib Compared to Upfront Surgery in Patients with Clinical Stage III or Oligometastatic Stage IV Melanoma (Combi-Neo) (2014-0409) NCT02231775)

Principal Investigator: Jennifer Wargo, M.D.

Co-Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to compare receiving the combination of dabrafenib and trametinib before surgery to having surgery alone in patients with melanoma. The safety of the study drug combination will also be studied.

Adjuvant

Phase I/II Trial of a Long Peptide Vaccine (LPV7) Plus TLR Agonists for Resected Stage IIB-IV Melanoma (2014-0012) (NCT02126579)

Principal Investigator: Sapna P. Patel, M.D.

The goal of this clinical research study is to learn about the safety of giving LPV7, polyICLC, resiquimod, and montanide ISA-51 to patients with melanoma. Researchers also want to learn if the study drugs cause any changes in the immune system.

A Phase III Randomized Trial Comparing High Dose Interferon to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma (S1404) (NCT02506153)

Principal Investigator: Sapna P. Patel, M.D.

This randomized Phase III trial studies how well high-dose recombinant interferon alfa-2B works compared with pembrolizumab in treating patients with stage III-IV melanoma that has been removed by surgery but is likely to come back or spread. High-dose recombinant interferon alfa-2B may help shrink or slow the growth of melanoma. Monoclonal antibodies, such as pembrolizumab, may block tumor growth in different ways by targeting certain cells. It is not yet known whether high-dose recombinant interferon alfa-2B is more effective than pembrolizumab in treating patients with melanoma.

Chemotherapy-Naive Patients (no previous chemotherapy)

Phase II Study of Abraxane Plus Ipilimumab in Patients with Metastatic Melanoma (2011-1157) (NCT01827111)

Principal Investigator: Adi Diab, M.D.

The goal of this clinical research study is to learn if the combination of ipilimumab and ABI-007 (abraxane) can help to control metastatic melanoma. The safety of this drug combination will also be studied. Ipilimumab is designed to increase the immune system's ability to fight cancer. ABI-007 is designed to stop cancer cells from making new DNA (the genetic material of cells.) This may stop the cancer cells from dividing into new cells.

A Phase Ib, Open-label Study of the Safety and Pharmacology of MPDL3280A Administered in Combination with Vemurafenib in Patients with Previously Untreated BRAFV600-Mutation Positive Metastatic Melanoma (2012-0588) (NCT01656642)

Principal Investigator: Patrick Hwu, M.D.

The goal of this clinical research study is to find the highest tolerable dose of MPDL3280A that can be given in combination with vemurafenib (Zelboraf) to patients with locally advanced or metastatic melanoma that has a BRAF mutation. The safety of the drug combination will also be studied. MPDL3280A is designed to help the immune system recognize the tumors and may help stop their growth. Vemurafenib is designed to block the BRAF gene mutation. This mutation causes cancer cells to grow and multiply. By blocking this mutation, the drug may kill the cancer cells with the mutation and/or stop the tumor from growing.

Patients with Previous Chemotherapy

A Phase I/II Study to Assess the Safety and Efficacy of Intratumoral IMO-2125 in Combination with Ipilimumab in Patients with Metastatic Melanoma (2015-0530) (NCT02644967)

Principal Investigator: Adi Diab, M.D.

The purpose of this clinical research study is to find the highest tolerated dose of the study drug IMO-2125 that can be given in combination with ipilimumab to patients with metastatic melanoma. Researchers also want to learn if the study drug combination can help to control the disease. The safety of the drug combination will also be studied.

A Phase 1/2, Open-Label, Multicenter, Dose Escalation and Dose Expansion Study of NKTR-214 in Subjects with Locally Advanced or Metastatic Solid Tumor Malignancies (2015-0573)

Principal Investigator: Adi Diab, M.D.

The goal of this clinical research study is to find the highest tolerable dose of the study drug NKTR-214 that can be given to patients with advanced or recurrent solid tumors. Researchers also want to learn if NKTR-214 can help to control the disease. This is the first study using NKTR-214 in humans.

Phase I/II Study of Dabrafenib, Trametinib, and Navitoclax in BRAF Mutant Melanoma and Other Solid Tumors (2014-0020) (NCT01989585)

Principal Investigator: Michael A. Davies, M.D., Ph.D.

The purpose of the second part of this study (Phase II) is to compare the good and bad effects of navitoclax in combination with dabrafenib and trametinib to using the usual approach of dabrafenib and trametinib in patients with BRAF-mutant melanoma. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach.

A Phase I, Open-Label, Dose Escalation Study of PF-04518600 in Patients with Locally Advanced or Metastatic Hepatocellular Carcinoma (HCC), Melanoma, Clear Cell Renal Cell Carcinoma (RCC) or Squamous Cell Head and Neck Cancer (SCCHN) (2014-0996) (NCT02315066)

Principal Investigator: Adi Diab, M.D.

The goal of this clinical research study is to find the highest tolerable dose of the study drug PF-04518600 that can be given to patients with advanced cancer. Researchers also want to learn more about the effects of the study drug. The safety of the drug will also be studied.

A Phase II Open-Label, Two-Arm Study of the MEK Inhibitor, Trametinib, to Investigate the Safety and Anti-Cancer Activity in Subjects with Melanoma with BRAF non-V600 Mutations (2014-0766) (NCT02296112)

Principal Investigator: Michael Davies, M.D., Ph.D.

Some types of melanoma have a kind of BRAF mutation called a BRAF V600 mutation. A drug called trametinib is FDA-approved and commercially available to treat these types of melanoma. The goal of this clinical research study is to learn if trametinib can help to control melanoma with a BRAF mutation that is not a BRAF V600 mutation. The safety of this drug will also be studied.

Phase II Study of MK-3475 in Conjunction with Lymphodepletion, TIL, and High or Low Dose IL-2 in Patients with Metastatic Melanoma (2014-0922) (NCT02500576)

Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to learn if pembrolizumab, an infusion of T-cells, chemotherapy (cyclophosphamide and fludarabine), and either high- or low-dose interleukin-2 (IL-2) can help to control metastatic melanoma. The safety of this drug combination will also be studied. T-cells are white blood cells in your body that are important to the immune system. The T-cells used in this study will be collected and grown in a separate study (MD Anderson Protocol 2004-0069.)

An Open-Label, Multicentre, Corollary Study of Pre-Operative Therapy with Dabrafenib and the Combination of Dabrafenib with Trametinib in Subjects with BRAF Mutation-Positive Metastatic Melanoma to the Brain (2012-0208) (NCT01978236)

Principal Investigator: Michael Davies, M.D., Ph.D.

The goal of this clinical research study is to learn how much of the study drugs dabrafenib and trametinib get into the brain tumor, any tumor(s) outside the brain, and the blood stream. This will be tested in patients who have melanoma that has spread to the brain. Researchers also want to learn if and how long dabrafenib and trametinib may be able to help control the disease. Lab research will be done that may benefit future patients.

An Open-Label, Multicenter, Dose-Escalation, Phase 1b/2 Study of the Safety, Efficacy, Pharmacodynamics, and Pharmacokinetics of RTA 408 in Combination with Ipilimumab in the Treatment of Patients with Unresectable or Metastatic Melanoma (2014-0613) (NCT02259231)

Principal Investigator: Sapna Patel, M.D.

The goal of Part 1 of this clinical research study is to find the highest tolerated dose of RTA 408 that can be given with ipilimumab to patients with unresectable or metastatic melanoma. The safety of this drug combination will also be studied. The goal of Part 2 of this study is to learn if giving RTA 408 with ipilimumab can help to control unresectable or metastatic melanoma.

Lymphodepletion Plus Adoptive Cell Transfer with TGF-beta Resistant (DNRII) and NGFR Transduced T-Cells Followed by High-Dose Interleukin-2 in Patients with Metastatic Melanoma (2012-0758) (NCT01955460)

Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to find the highest tolerable dose of T-cells injected with the genes TGFb-DNR and NGFR that can be given in combination with chemotherapy (cyclophosphamide and fludarabine) and aldesleukin to patients with metastatic melanoma.This study involves gene therapy. T-cells are types of white blood cells that help your body fight infections. They may recognize and kill melanoma cells. Researchers want to grow your T-cells in a laboratory, inject them with TGFb-DNR and NGFR genes which may help them recognize tumor cells, and then give them back to you by vein. This may help to control melanoma. Cyclophosphamide is designed to block cancer cells from dividing, which may slow or stop their growth and spread throughout the body. This may cause the cancer cells to die. Fludarabine is designed to interfere with the DNA (genetic material) of cancer cells, which may cause the cancer cells to die. Aldesleukin is designed to block the activity of cells that may decrease the immune system's ability to fight cancer.

A Phase I/II Study of Lymphodepletion Plus Adoptive Cell Transfer with T-Cells Transduced with CXCR2 and NGFR Followed by High-Dose Interleukin-2 in Patients with Metastatic Melanoma (2009-0471) (NCT01740557)

Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to learn the side effects of T-cells injected with CXCR2 and NGFR when given in combination with chemotherapy (cyclophosphamide and fludarabine) and aldesleukin to patients with metastatic melanoma in an attempt to allow them to better localize the tumor. The safety of this combination will also be studied.

BRF117277: A Phase II, Open-Label, Multicentre Study of Dabrafenib plus Trametinib in Subjects with BRAF Mutation-Positive Melanoma that Has Metastasized to the Brain (2013-1020) (NCT02039947)

Principal Investigator: Michael Davies, M.D., Ph.D.

The goal of this clinical research study is to learn if the combination of dabrafenib and trametinib can help to control BRAF V600 positive melanoma that has spread to the brain. The safety of the study drugs will also be studied.

T-Cells +/- Dendritic Cells (2004-0069) Phase II (NCT00338377)

Principal Investigator: Patrick Hwu, M.D.

In this study, T-cells capable of recognizing and killing melanoma will be isolated from tumor biopsies and expanded in the laboratory. The T-cells will then be reinfused into the patients with or without dendritic cells, which are immune cells capable of potently activating T-cells. This study is for patients with a good performance status, with measurable metastatic melanoma, and a site that can easily be biopsied.

Activation of pDCs at tumor and vaccine sites with TLR agonist (2008-0416) Phase II (NCT00960752)

Principal Investigators: Patrick Hwu, M.D. and Richard Royal, M.D.

In this study, we are combining vaccines with a novel agent called resiquimod that can further stimulate the immune system. For patients with metastatic melanoma with measurable disease, Stage IIIC (in transit lesions) or Stage IV (M1A). Patients must be HLA-A201 and DP4 positive to participate and have at least 4 biopsiable lesions. No previous exposure to gp100 or MAGE-3 peptide.

A Phase Ib/II, Multicenter, Open Label, Study of LEE011 in Combination with MEK162 in Adult Patients with NRAS Mutant Melanoma (2013-0185) (NCT01781572)

Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to find the highest tolerable dose of LEE011 that can be given with MEK162.

A Phase I Study to Evaluate the Safety, Tolerability and Pharmacokinetics of MED14736 in Subjects with Advanced Solid Tumors (2012-0513) (2013-0814) (NCT01693562)

Principal Investigator: Wen-Jen Hwu, M.D., Ph.D.

The goal of this clinical research study is to learn about the safety of MED14736 when given to patients with advanced solid tumors.

Induction of antitumor response in melanoma patients using the antimicrobial peptide LL37 (2013-0422) (NCT02225366)

Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to find the appropriate dose of LL37 that can be given to patients with melanoma. Researchers also want to learn if LL37 can stimulate the immune system to help control the disease.

Phase II Study of Cellular Adoptive Immunotherapy Using Autologous CD8+ Antigen-Specific T Cells and Anti-CTLA4 for Patients with Metastatic Melanoma (2012-1055) (NCT02027935)

Principal Investigator: Cassian Yee, M.D.

The goal of this clinical research study is to learn about the safety of giving CD8+ T cells with ipilimumab, cyclophosphamide, and IL-2 (aldesleukin). Researchers also want to learn if this combination can help to control metastatic melanoma.

A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety and Tolerability of Urelumab Administered in Combination with Nivolumab in Advanced/Metastatic Solid Tumors and B Cell Non-Hodgkins Lymphoma (2014-0651) (NCT02253992)

Principal Investigator: Erminia Massarelli, M.D., Ph.D.

Co-Principal Investigator: Adi Diab, M.D.

The goal of Part 1 of this study is to find the highest tolerable dose of urelumab and nivolumab when given in combination to patients with advanced solid tumors or B-cell NHL. The goal of Part 2 is to learn if the dose found in Part 1 can help to control melanoma, NSCLC, SCCHN, and/or DLBCL. The safety of this drug combination will be studied in both parts of the study. The goal of this part of the study (called "Continuation of Therapy") is to continue to study the effects of the study drug after the disease has appeared to get worse.

Patients with Uveal Melanoma

A Phase 2 Study of CDX-011 (Glembatumumab Vedotin) for Metastatic Uveal Melanoma (NCI9855) (NCT02363283)

Principal Investigator: Sapna P. Patel, M.D.

The primary objective of this study is to characterize the clinical anti-tumor activity of CDX-011 (glembatumumab vedotin) as a single agent in the treatment of patients with metastatic uveal melanoma. Secondary objectives include a description of the clinical safety and benefit of CDX-011 and pharmacodynamics changes in glycoprotein NMB (GPNMB) expression. Exploratory objectives include characterization of the anti-tumor immunophenotype of patients receiving treatment. Post hoc, correlation of rash with clinical benefit, or lack of rash with lack of benefit, will also be explored.

Phase II Study of Nivolumab in Combination with Ipilimumab for Uveal Melanoma (2011-0919) (NCT01585194)

Principal Investigator: Sapna P. Patel, M.D.

The goal of this clinical research study is to learn if ipilimumab and nivolumab can help to control uveal melanoma. Ipilimumab is designed to increase the immune system's ability to fight cancer. Nivolumab is an antibody (a protein that attacks foreign cells) that is designed to allow the body's immune system to work against tumor cells.

A Randomized Two-Arm Phase II Study of Trametinib Alone and in Combination with GSK2141795 in Patients with Advanced Uveal Melanoma (2013-0893) (NCT01979523)

Principal Investigator: Sapna P. Patel, M.D.

The purpose of this study is to find out if treatment with trametinib alone or trametinib combined with GSK2141795 can stop your melanoma from growing. Trametinib is a pill that blocks a protein called MEK. Most uveal melanomas grow because of MEK overactivity. This overactivity occurs because a protein called Gnaq or Gna11 is abnormal in the majority of uveal melanomas. Blocking MEK may shut down this pathway and stop your cancer from growing. GSK2141795 is a pill that blocks a protein called AKT. AKT overactivity is also important for uveal melanoma to grow. Blocking both MEK and AKT together may be better than blocking MEK alone.

Special accolades for Melanoma Deputy Chair

Melanoma Medical Oncology Deputy Chair and Associate Professor **Michael A. Davies, M.D., Ph.D.**, was greeted with good news at year-end with respect to two major honors.

First, Dr. Davies was notified that he will be recommended by the Council of the American Society for Clinical Investigation (ASCI) for election to membership in the prestigious organization. He will officially be inducted into the society at its annual meeting in Chicago on April 15, 2016.

Established in 1908, ASCI is one of the oldest and most respected medical honor societies in the United States; its mission is "to support the scientific efforts, educational needs and clinical aspirations of physician-scientists to improve human health." The group comprises more than 3,000 active physician-scientists from all medical specialties elected to the Society for their outstanding records of scholarly achievement in biomedical research. Many of its senior members are widely recognized leaders in academic medicine. Because members must be 50 years of age or younger at the time of their election, membership reflects accomplishments by its members relatively early in their careers. ASCI publishes the Journal of Clinical Investigation and JCI Insight.

Drs. Hwu and McQuade flank Dr. Davies ***(Photo: Barry Smith)***

Second, Dr. Davies learned he was the recipient of the Division of Cancer Medicine's Gerald P. Bodey Award for Excellence in Education at the Division's annual faculty awards ceremony Dec. 15, 2015. The education award is presented each year to a Division faculty member who is judged by a review panel to have produced outstanding accomplishments in educational activities such as training/mentoring of clinical or postdoctoral fellows and residents, demonstrating excellence as a PI or co-PI on a training grant, and serving as chair or program committee member for a major continuing education program.

Dr. Davies was nominated by Cancer Medicine Division Head and Melanoma Department Chair **Patrick Hwu, M.D.**, whose letter described the key role Dr. Davies has played in the success of the Division's Hematology and Medical Oncology fellowship program since he began serving on its executive committee in 2012, particularly as the program's director of research activities. Dr. Hwu noted that Dr. Davies had initiated the T32 Research Training in Academic Medical Oncology Series. He also cited Dr. Davies' work as co-PI (with **Dr. Richard Champlin**) of the DOCM's T32 Training Program Grant in 2014, when he helped lead the successful submission of the program's NIH/NCI grant renewal application, resulting in a score correlating with an "exceptional" NIH merit rating.

Dr. Davies was further lauded as an outstanding educator and mentor in a letter penned by two of his mentees, Medical Oncology fellow **Jennifer McQuade, M.D.**, and Department of Leukemia Assistant Professor **Christopher Benton, M.D.**

Melanoma Philanthropic Funding

Special appreciation is extended to the following donors, who were reported by MD Anderson's Development Office as among those recently contributing $1,000 or more.

AIM at Melanoma Foundation
Mr. and Mrs. Anthony Altmann
Anonymous
Mr. John Barry
Mr. and Mrs. Brent R. Behrman
Mr. and Mrs. G. Alex Bernhardt, Sr.
Bernhardt Design
James L. and Doris Black
Mr. and Mrs. Kirt E. Black
Mr. and Mrs. Jay B. Boudreaux
Mr. and Mrs. Alexander M. Brauer
Mr. and Mrs. David Brink
Mr. and Mrs. William A. Burke
Mrs. Susan E. Burns
Mr. Charles Carducci
Dr. and Mrs. John S. Cargile
Mr. Brian D. Childress
Mr. Albert C. Cornish, Jr.
Couvillion Group, LLC
Mr. and Mrs. Christopher J. Crosby, Sr.
Mrs. Rachel Cruz-Auwarter and Mr. Todd Auwarter
Cypress Bayou Casino & Hotel
Mr. Earl N. Daniels
Mr. Daniel G. Darling
Mr. Theodore J. Dengler
Mr. and Mrs. Richard E. Dietrichson, Jr.
Don's Specialty Meats II, Inc.
ENT of Georgia, LLC
Ms. Christine M. Falgout
Jo Lynn and Gregg Falgout
Ms. Kimberly A. Falgout
Mr. Sam Fellows
Mr. Allen Ferguson
Mr. and Mrs. Jerry D. Fields
Mr. Johnnie M. Foco
Ms. Nikki A. Fowler
Mr. and Mrs. Doug Gilbert-Smith
Mr. and Mrs. Michael Gunter
Mr. and Mrs. Fernando M. Hernandez
Mr. and Mrs. Alan Hicks
Mr. and Mrs. James G. Humphrey
Island Operating Company, Inc.
Ms. Leslie Jackson
The John G. and Marie Stella Kenedy Memorial Foundation
KeyBank National Association
Mr. Jeremy Klapprodt
Mr. Josh Klapprodt
Dr. Janet Elisabeth Leigh
Linear Controls, Inc.
Longhorn, Inc.
Mr. and Mrs. Cecil J. Looke
Mrs. Seymour Luckoff
Malibu Floors
Mr. and Mrs. George Michulka
Mr. and Mrs. Danny Mills
Mr. and Mrs. David A. Mitteis
Modestus Bauer Foundation
Mr. and Mrs. David S. Morse
Ms. Flolyn Naegelin
Mr. William J. Navarre
Mr. Lance Nelson
Mr. and Mrs. Timothy J. Norris
Dr. Judith A. Peterson and Dr. Donald N. Peterson
Mr. William D. Pool
Ms. Anne Roberts
Mr. Ron Runnels
Scott Volunteer Fire Department, Inc.
Mr. Jeff Shannon
Simmons & Company International
Dr. Jerald L. Sklar
Surety Management, Inc.
Swingle, Collins & Associates
Louis Tiseo
Mr. and Mrs. Joseph C. Walter III
Walter Oil & Gas Corporation
Mr. Russell E. Wehrman
Mr. and Mrs. Patrick L. Whatley
Mr. and Mrs. Bryan Wick

MD Anderson melanoma research in the spotlight

MD Anderson melanoma research findings were prominently featured at national and international conferences during the last half of 2015.

Dr. Jeffrey E. Lee

On Sept. 18, 2015, MD Anderson Surgical Oncology Chair **Jeffrey E. Lee, M.D.**, presented "Inherited Susceptibility to Melanoma" at the Second Annual Summit on Practical and Emerging Trends in Melanoma in Pasadena, CA.

At the European Cancer Conference 2015, Sept. 25-29 in Vienna, Melanoma Medical Oncology Assistant Professor **Isabella Glitza, M.D., Ph.D.**, presented the poster "Long-term efficacy of intrathecal interleukin-2 (IT IL2) in metastatic melanoma (MM) in patients (pts) with leptomeningeal disease (LMD.)" Melanoma Medical Oncology Deputy Chair and Associate Professor **Michael A. Davies, M.D., Ph.D.**, was senior author on the abstract.

Dr. Isabella Glitza

Melanoma Medical Oncology Associate Professor **Willem Overwijk, Ph.D.**, and Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**, played key roles in SITC 2015, the Society for Immunotherapy of Cancer (SITC) 30th Annual Meeting and Associated Programs, Nov. 4-8, 2015 in National Harbor, MD. On Nov. 5, Dr. Overwijk opened the Primer on Tumor Immunology and Cancer Immunotherapy, which he co-organized, with a welcome followed by his presentation, "Introduction to Innate Immunity." Dr. Wargo was one of the organizers of the SITC 30th Anniversary Annual Meeting, which opened the next day. She co-chaired the session "Mechanisms and Responses to Immune Therapies," in which she presented "Understanding Responses to Therapy: the Tissue is the Issue" on Nov. 7.

Dr. Willem Overwijk

Also on Nov. 7, Melanoma Research Instructor **Manisha Singh, Ph.D.**, accepted a Young Investigator Travel Award, which "highlights promising young investigators who submitted high-scoring abstracts to the SITC Annual Meeting, based on the quality of their research and potential to advance the field." She presented a poster based on the abstract she lead-authored, entitled "Induction of potent systemic anti-melanoma immunity through intratumoral CD40 activation and checkpoint blockade"; Dr. Overwijk was senior author.

MD Anderson was well represented at the Society for Melanoma Research (SMR) 2015 International Congress, Nov. 18-21 in San Francisco. Melanoma Medical Oncology Assistant Professor **Chandrani Chattopadhyay, Ph.D.**, presented the poster "Targeting IGF-1R pathway in uveal melanoma: single and combination therapy." Surgical Oncology Assistant Professor **Zachary Cooper, Ph.D.**, presented the poster "Patterns of immune infiltrate differ at progression on targeted therapy versus immune checkpoint blockade for melanoma."

MD Anderson Cancer Medicine Division fellow **Jennifer L. McQuade, M.D.**, presented the poster "Mechanisms of resistance and predictors of response in a phase II trial of dabrafenib and trametinib in metastatic melanoma following progression on BRAF inhibitor monotherapy," coauthored by Dr. Davies.

Katherine G. Roth, M.D., a University of Southern California internal medicine resident, presented the poster "Mutation and clinical analysis of a large cohort of acral and mucosal melanoma"; senior author was Melanoma Medical Oncology Assistant Professor **Scott E. Woodman, M.D., Ph.D.** A 2015 SMR travel award recipient, Dr. Roth was a rotating research medical student in the Melanoma Department and a fourth-year medical student at The University of Texas Medical School at Houston when she conducted the research under Dr. Woodman's mentorship.

Former MD Anderson Melanoma fellow **Dae Won Kim, M.D.**, now at H. Lee Moffitt Cancer Center and Research Institute, presented the poster "Phase II trial of nab-paclitaxel (ABI) plus ipilimumab (ipi) in patients (pts) with metastatic melanoma (MM)"; Melanoma Assistant Professor **Adi Diab, M.D.**, was senior author.

On Nov. 20, Dr. Davies presented "The Role of the P13K-AKT Pathway in Melanoma Brain Metastasis" during the session "Mechanisms and Treatment of Brain Metastasis." MD Anderson Behavioral Science Instructor **Mary Tripp, Ph.D.**, presented "Innovative Behavioral Intervention Approaches to Reduce Ultraviolet Radiation (UVR) Exposure in Children and Adolescents" during the session "Melanoma Risk and Prevention."

At the 20th Annual Scientific Meeting of the Society for Neuro-Oncology Nov. 19-22 in San Antonio, Dr. Glitza presented "Therapeutic Outcomes of Intrathecal Interleukin-2 in Metastatic Melanoma Patients with Leptomeningeal Disease (LMD)," in the "Brain Metastases: Rapid Reports" session Nov. 20.

At the international Melanoma Bridge meeting Dec. 1-4 in Naples, Italy, Dr. Wargo gave the oral presentation, "Understanding Immune and Molecular Determinants of Response to Melanoma Therapy," and Dr. Davies gave the oral presentation, "Immunologic and Metabolic Consequences of PI3K/AKT/mTOR Activation in Melanoma."

Dr. Davies was the Co-Organizer and Co-Chair of the 1st Melanoma Brain Metastasis Summit, held Dec. 6-7, 2015, in Philadelphia. Sponsored by the Melanoma Research Foundation, the meeting included leading clinical and laboratory investigators from multiple academic centers across the nation, and focused on optimizing and accelerating research and treatments for melanoma brain metastases. Speakers from MD Anderson included Dr. Davies, Dr. Glitza, and **Dr. Hussein Tawbi** from the Department of Melanoma Medical Oncology, and **Dr. John DeGroot**, Interim Chair of the Department of Neuro-Oncology.

Gifts fuel MD Anderson melanoma mission: How to help

MD Anderson's Melanoma Medical Oncology and Research team is dedicated to helping our patients get the best treatment possible. Gifts from individuals provide a significant portion of the funding needed to get new laboratory and clinical research off the ground. To donate by mail to our melanoma research efforts, please send a check made out to "MD Anderson Cancer Center" specifying "Melanoma Vaccines" in the memo line to: Dr. Patrick Hwu, Chair, Melanoma Medical Oncology Department, MD Anderson Cancer Center, 1515 Holcombe Blvd., unit 430, Houston TX 77030.

The University of Texas
MD Anderson Cancer Center
Melanoma HORIZONS

EDITOR
Leslie Loddeke, B.J.
Publications Coordinator,
Melanoma Medical Oncology

EDITORIAL ADVISER
Michael A. Davies, M.D., Ph.D.
Deputy Chair and Associate Professor,
Melanoma Medical Oncology

DESIGN
Limb Design, Houston, TX

Email: Melanoma@mdanderson.org

The University of Texas
MD Anderson Cancer Center
Department of Melanoma
Medical Oncology
1515 Holcombe Blvd., unit 430
Houston, TX 77030

ADDRESS SERVICE REQUESTED

Non-Profit Org.
U.S. Postage
PAID
Houston, TX
Permit No. 7052

Award funds work to find improved treatments

Melanoma Medical Oncology Deputy Chair and Associate Professor **Michael Davies, M.D., Ph.D.**, received a $900,000 Individual Investigator Award on Nov. 19, 2015, from the Cancer Prevention and Research Institute of Texas (CPRIT), providing $900,000 to support his research to identify new, more effective treatments for patients with advanced melanoma.

The proposal, entitled "Exploiting Molecular and Metabolic Dependencies to Optimize Personalized Therapeutic Approaches for Melanomas," focuses on defining the significance and therapeutic potential of oxidative phosphorylation. **Vashisht Yennu Nanda, Ph.D.**, Assistant Professor in Melanoma, played a key role in developing this area of research and is a key collaborator on the grant.

Their research will test a novel treatment strategy for melanoma patients that overcomes two crucial challenges to improving outcomes in patients with advanced melanoma.

First, as noted in the proposal's lay summary, nearly 50% of melanomas have an activating mutation in the BRAF gene that activates the MAPK pathway and causes melanoma growth and metastasis. New targeted therapies that inhibit the mutated form of BRAF and/or the MAPK pathway have been shown to achieve significant tumor shrinkage in over half of metastatic melanoma patients with a BRAF mutation, leading to the U.S. Food and Drug Administration approval of three such agents for these patients since 2011. While these treatments are beneficial, many patients fail to respond, and almost all responding patients develop resistance in a short period of time. To date, no treatments have been effective at overcoming resistance in patients after it occurs. Second, there is also a critical need to develop effective targeted therapy strategies for patients who do not have a BRAF mutation. Thus, their research proposal is focused on the critical need to identify new treatments that can prevent or overcome resistance to targeted therapies in patients with BRAF mutations, and to identify effective strategies for patients with a normal BRAF gene.

Dr. Davies and his team found that 30-50% of melanomas that are resistant to targeted therapy have abnormal cellular metabolism, with high levels of energy production due to increased oxidative phosphorylation (OxPhos). They identified two novel treatments that inhibit OxPhos in cancer cells. Preliminary data show that these treatments overcome MAPK inhibitor resistance specifically in melanomas with high OxPhos, regardless of their BRAF status.

The proposal calls for the Davies team to further investigate the molecular events that drive the OxPhos metabolic phenotype, and optimize the new treatment strategies to accelerate the development of personalized clinical trials for patients with advanced melanoma.

"Our studies have the potential to rapidly translate into new treatments for patients with melanoma, and to improve our understanding of the significance of metabolism in cancer," Dr. Davies summed up.

To Schedule an Appointment

Call 713-563-9716 or 1-877-MDA-6789

Self Referral Form

https://www2.mdanderson.org/sapp/contact/selfreferral/index.cfm

Physician Referral Form

https://my.mdanderson.org/

If you are a patient or physician and wish to **track appointments, view reports, and send secure messaging** please register for on-line access at: https://my.mdanderson.org/

Please "Follow Us" on Facebook and Twitter

http://www.facebook.com/MDAMelanomaMedicalOncology

http://www.twitter.com/MDAMelanomaOnc