THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER

Melanoma HORIZONS

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
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Dr. Grimm receives Research Faculty Mentor Award

Dr. Patrick Hwu and Dr. Elizabeth Grimm

MD Anderson Melanoma Medical Oncology Professor **Elizabeth A. Grimm, Ph.D.**, was honored with the Provost's Distinguished Research Faculty Mentor Award at the 2014 Provost's Distinguished Faculty Mentoring Awards Ceremony.

Mentorship is of key importance to MD Anderson Cancer Center as a whole, and to our Melanoma Program in particular. It is noteworthy that Melanoma Medical Oncology Chair **Patrick Hwu, M.D.**, won the 2013 Distinguished Clinical Faculty Mentor Award, which took place during the same month the year before.

Dr. Grimm was one of three MD Anderson faculty members who were honored at the Oct. 14, 2014 ceremony for their commitment to education and training of the next generation of leaders in their roles as mentors to other MD Anderson faculty members.

Faculty from throughout the institution submitted nominations for a total of 32 faculty mentors.

In addition to her position in the Melanoma Department, Dr. Grimm also serves as Waun Ki Hong Distinguished Chair in Translational Oncology and Deputy Head for Research Affairs, Division of Cancer Medicine.

Melanoma Associate Professor **Suhendan Ekmekcioglu, Ph.D.**, and Breast Medical Oncology Assistant Professor **Chandra Bartholomeusz, M.D., Ph.D.**, were among the many who wrote letters nominating Dr. Grimm for the award, enthusiastically described their appreciation for Dr. Grimm's generous mentoring in a video at the ceremony.

The other two 2014 award winners were Systems Biology Chair **Gordon Mills, M.D., Ph.D.**, also a Distinguished Research Faculty Mentor winner, and Leukemia Professor **Michael Keating, M.D.**, Distinguished Clinical Faculty Mentor.

"Mentoring is recognized as a vital part of academia, and is recognized as one of our top priorities to keep faculty on track and satisfied with their careers," said MD Anderson Provost and Executive Vice President **Ethan Dmitrovsky, M.D.**, who presided over the ceremony.

Of Dr. Grimm, Dr. Dmitrovsky commented: *"Her mentees were particularly moved by her 'integrity, dignity and elegant professionalism' and 'exceptional inclusive skill on diversity' which 'reaches high levels of global intelligence,"* which were quotes extracted from Dr. Ekmekcioglu's nominating letter.

"Dr. Grimm is an amazing role model for women faculty like me," was another mentee quote, excerpted from the letter penned by Dr. Bartholomeusz. *"I now strive every day to be a supportive mentor to my postdoctoral fellows and classified staff just as I have learned from her."*

Dr. Grimm voiced her appreciation to Dr. Dmitrovsky, to Melanoma Chair Patrick Hwu, M.D., and myriad others in her faculty "family," noting: *"Our mission is simply too broad for anyone alone to conquer. And by giving and growing this family, ensuring our future through mentoring, we will continue to make real progress and continue the legacy of success."*

Dr. Ekmekcioglu, Dr. Grimm and Dr. Bartholomeusz (l-r)

Dr. Grimm credited her own mentors, including her department chair, Dr. Patrick Hwu, and **Waun Ki Hong, M.D.**, professor and former division head of Cancer Medicine, for inspiring her.

When Dr. Hwu won his mentoring award the year before, he astutely observed: *"If you mentor someone, that person will go on and influence 50 other people. It's a lifelong contribution."*

Dr. Dmitrovsky closed the ceremony by observing: *"All of us in this room are blessed. We wake up every day and have purposeful, meaningful work."* He went on to underscore the importance of serving as a mentor, to give the next generation *"the gift of having a purposeful, meaningful life."*

Melanoma chair elected to key AACR post

MD Anderson Melanoma Medical Oncology Chair **Patrick Hwu, M.D.**, has been elected to the prestigious post of chairperson-elect 2015-16 of the Cancer Immunology Working Group (CIMM) of the American Association of Cancer Researchers.

Dr. Hwu will assume the office at the AACR Annual Meeting 2015, April 18-22, 2015, in Philadelphia. In making the announcement, the AACR website recounted Dr. Hwu's multiple positions of responsibility at MD Anderson, including chair of both the Melanoma and Sarcoma Medical Oncology Departments, co-director of the Center for Cancer Immunology Research, and co-director of the immunotherapy platform, which supports MD Anderson's Moon Shots Program.

"As a tumor immunologist, my work has focused on developing novel vaccine and adoptive T-cell therapies," Dr. Hwu stated in describing his research interests on the site. *"My laboratory and clinical work have led to insights and advances in the understanding of the interactions between tumors and the immune system, and the development of cellular immunotherapies including some of the initial T-cell gene therapy studies using CARs and chemokine receptor genes. A major focus of my current research is applying the principles learned from melanoma immunotherapy to other common cancers and to understand immune resistance at the molecular level. This includes the important area of combining targeted and immune therapies."*

"We are at an unprecedented, exciting time in the field of tumor immunology due to the durable long-term responses seen in some cancer patients following immune therapy," Dr. Hwu observed in his statement of proposed goals. *"Despite global interest in tumor immunology, currently there are not enough laboratory and clinical investigators in the field to enable maximum progress in both academia and industry. Therefore, the mission of the AACR regarding tumor immunology is more important now than ever before.*

"Having been in the field for more than 20 years with a strong track record in leadership and mentorship, I will focus efforts on helping the AACR fill the void to train and educate the next generation of tumor immunologists. In addition, in my opinion, there is too much separation between tumor biology and tumor immunology, but in fact these areas are highly interrelated. My own research now focuses on understanding the molecular pathways in tumors and how they influence the immune microenvironment.

"One of my goals as a leader within the AACR will be to bring strong scientists together in the areas of tumor biology and tumor immunology in order to understand resistance to therapies and to make maximum impact through the rational combination of targeted and immune therapies."

The AACR is self-described as the world's oldest and largest scientific organization focused on all aspects of high-quality, innovative research, with the mission of preventing and curing cancer through research, education, communication and collaboration.

Innovative clinical trials highlight melanoma research coups

MD Anderson scored myriad melanoma research achievements during fiscal year 2014, when innovative clinical trials, novel therapies and creative combination treatments offered patients the prospect of longer lives and new hope for the future.

At the MD Anderson Moon Shots Program update Oct. 30, 2014, MD Anderson President **Ronald DePinho, M.D.**, cited a broad array of accomplishments during year 2 of the overall program, launched in fall 2012 to accelerate the conversion of scientific discoveries into clinical advances and significantly reduce cancer deaths.

Developing personalized treatment approaches through all stages of the disease was described as a central project of the Melanoma Moon Shot, based on improved prognostic and predictive models combining clinical, pathological, molecular and immunological factors. A series of clinical trials is under way based on this work.

Notably, Melanoma Moon Shot investigators have launched the first clinical trial to compare presurgical treatment with a targeted therapy combination to surgery alone for stage III melanoma. In this innovative trial, the investigators are combining dabrafenib and trametinib, now approved for metastatic melanoma patients with BRAF mutations, as presurgical treatment aimed at preventing recurrence after surgery for stage III disease.

Dr. Jennifer Wargo

Dr. Rodabe Amaria

The trial, entitled "Neoadjuvant and Adjuvant Dabrafenib and Trametinib Compared to Upfront Surgery in Patients with Clinical Stage III or Oligometastatic Stage IV Melanoma (Combi-Neo)," is listed as MD Anderson Clinical Trial No. 2014-0409 (NCT02231775.) The trial's principal investigator (PI) is **Jennifer Wargo, M.D.**, assistant professor of Surgical Oncology, while the co-PI is **Rodabe Amaria, M.D.**, assistant professor of Melanoma Medical Oncology. In November 2014, Dr. Wargo was honored at the Society for Melanoma Research Congress in Zurich with the Young Investigator Award, which is presented annually to an independent researcher in the junior stage of his/her career *"who has made contributions in the area of melanoma research that significantly exceed the average for this career stage,"* according to the SMR.

Additional melanoma clinical trials are pairing targeted therapy with immune checkpoint blockade drugs that unleash an immune system attack on tumors. For further information, see the MD Anderson Melanoma Clinical Trials list, which is frequently updated to show our extensive and growing array of the latest and most promising treatments available.

FDA OKs new immunotherapy drugs for advanced melanoma

A landmark event in the history of cancer therapy occurred Sept. 4, 2014, when the U.S. Food and Drug Administration granted accelerated approval to Merck's Keytruda (pembrolizumab), which became the second immunotherapy drug that the agency had approved for the treatment of advanced melanoma.

Dr. James P. Allison

In a Houston Chronicle interview, MD Anderson Immunology Chair **James P. Allison, Ph.D.**, executive director of the MD Anderson Moon Shots Program's immunotherapy platform, said the move showed the FDA's understanding that "this class of drugs works and that they want to accelerate patients' access to them." He said it was a good day for melanoma patients "and potentially, for lots of other future cancer patients too."

Dr. Allison has been widely hailed as validating the immunotherapy approach to cancer treatment. He identified an immune checkpoint molecule called CTLA-4 on T-cells that turns them off before they can attack tumors, and developed an antibody that blocks the CLTA-4 immune checkpoint, unleashing a T-cell attack. In 2011, the antibody ipilimumab was approved by the FDA for treatment of metastatic melanoma after many years of clinical trials.

Keytruda, which targets the programmed cell death-1 (PD-1) receptor, was given accelerated approval for the treatment of patients with advanced or unresectable melanoma who are no longer responding to other drugs. It is intended for use after treatment with ipilimumab, or after treatment with ipilimumab and a BRAF inhibitor in patients with BRAF V600-mutated melanoma.

The Chronicle quoted Melanoma Medical Oncology Chair **Patrick Hwu, M.D.**, co-director of the immunotherapy platform, as saying "pretty much every advanced melanoma patient" should have one of the anti-PD-1 drugs at some point in their treatment because of their efficacy. The immunotherapy platform provides MD Anderson investigators with support for immunotherapies in the treatment of a wide variety of tumor types, and helps link immunologic data with the genomic and proteomic platforms.

In late December 2014, the FDA granted accelerated approval to another anti-PD-1 drug, nivolumab (Opdivo, Bristol-Myers Squibb), for the same melanoma patient subset and intended use.

Pembrolizumab, previously known as MK-3475, was a major focus at the American Society of Clinical Oncology (ASCO) Annual Meeting in 2014. An ASCO press briefing June 2 highlighted findings presented by lead author Dr. Antoni Ribas from a phase I study of the drug in 411 advanced melanoma patients. The 1-year survival rate was 69% across all patient subgroups, and responses were ongoing in nearly 90% of patients after a median follow-up of 12 months.

"Our dedicated Melanoma clinical research team contributed maximally to the FDA approval of MK-3475, now known as Keytruda, which has had an extraordinarily positive impact on a very large number of advanced melanoma patients, and continues to benefit patients all over the world today," MD Anderson Melanoma Medical Oncology Professor **Wen-Jen Hwu, M.D., Ph.D.**, noted in a department report. Melanoma Research Nurse Manager **Anna Vardeleon, R.N., M.B.A.**, oversees the team's daily operations.

"First, we had the highest patient enrollment –36 of the trial's total of 411 patients – among the 15 international sites involved in the pivotal Phase 1 trial of the revolutionary anti-PD-1 therapeutic agent," Dr. Hwu noted. *"Second, we recorded an extraordinary number of long-term responders: 16 of the 30 evaluable patients, or 55%. Third, more than half of our responders achieved a complete response, with minimal toxicity. Fourth, our site was the first to be audited by the Food and Drug Administration, resulting in accelerated approval. Fifth, our site enrolled the largest number of patients –68– on the international Expanded Access Program while waiting for FDA approval of the drug from May 2014 to September 2014."*

The broader potential is the impact that this agent is expected to have on patients with other types of cancer, including lung and renal cell cancer, in two clinical trials that she now leads at MD Anderson (see "MK-3475" on our Clinical Trials page.)

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 Patrick Hwu, M.D., Chair, Melanoma Medical Oncology Department, MD Anderson Cancer Center, 1515 Holcombe Blvd., unit 430, Houston TX 77030.

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Current Clinical Trials in Melanoma Medical Oncology

This list shows all open and approved Melanoma Medical Oncology clinical trials as of January 22, 2015.
For more information on these trials, call the toll-free AskMDAnderson number, 1-877-632-6789. **Click to access Melanoma Clinical Trials page**.

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.

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 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. This is the first study of LPV7 in humans.

Chemotherapy-Naive Patients (no previous chemotherapy)

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: Patrick Hwu, 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.

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.

Open-Label, Randomized, Multi-Center Study Comparing the Sequence of High-Dose Aldesleukin (Interleukin-2) and Ipilimumab (Yervoy®) in Patients with Metastatic Melanoma (2013-0147) (NCT01856023)

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

The goal of this clinical research study is to compare if and how long 2 different study treatment plans with aldesleukin (also known as interleukin-2 or IL-2) and ipilimumab may be able to help control metastatic melanoma. The safety of these treatment plans will also be studied.

IPI-Biochemotherapy for Chemonaive Patients with Metastatic Melanoma (2011-0073) (NCT01409174)

Principal Investigator: Rodabe Amaria, M.D.

The goal of the Phase I part of this clinical research study is to find the highest tolerable dose of the drug Yervoy (ipilimumab) that can be given with the drugs Temodar (temozolomide), Intron-A (interferon alfa-2b), Proleukin (aldesleukin, IL-2), and Platinol (cisplatin) to patients with metastatic melanoma. The safety of this combination will also be studied in Phase I. The goal of Phase II is to learn if this combination can help to control metastatic melanoma. Ipilimumab, interferon alfa-2b, and aldesleukin are designed to block the activity of cells that decrease the immune system's ability to fight cancer. Temozolomide 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. Cisplatin is designed to poison the cancer cells, which may cause them to die.

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 Investigators: 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 Clinical Trial to Study the Safety and Tolerability of MK-3475 Plus Pegylated Interferon alfa-2b (PEG-IFN) and MK-3475 Plus Ipilimumab (IPI) in Subjects with Advanced Melanoma (MEL) and Renal Cell Carcinoma (RCC) (Keynote 029) (2014-0032) (NCT02089685)

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

The goal of this clinical research study is to find the highest tolerable dose of MK-3475 that can be given in combination with pegylated interferon alfa-2b (PEG-IFN). The safety of these drug combinations will also be studied.

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: Patrick Hwu, 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.

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.

Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinomas, Melanoma and Non-Small Cell Lung Carcinoma (2011-0757) (NCT01295827)

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

There are 5 parts to this clinical research study. MD Anderson will be taking part in Parts B, D and F. The goal of Part B is to further test the highest tolerable dose of MK-3475 that was found in Part A when given to patients with melanoma. The safety of this drug will also be studied. The goal of Part D is to study 2 dose levels of MK-3475 when given to patients with melanoma. The goal of Part F is to study 2 dose levels of MK-3475 when given to patients with lung cancer. MK-3475 is a drug that includes a protein naturally created by living cells. It is designed to help the body's natural defense system react against tumors by blocking proteins that cancer cells create to "turn off" the body's immune (defense) system. This is the first study using MK-3475 in humans.

An Open-Label Phase II Study of the Combination of GSK2118436 and GSK1120212 in Patients with Metastatic Melanoma which is Refractory or Resistant to BRAF Inhibitor (2011-0579) (NCT01619774)

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

The goal of this clinical research study is to learn if the combination of two drugs (GSK2118436 and GSK1120212) can help to control melanoma. The safety of this drug combination will also be studied. GSK2118436 is designed to block the mutated BRAF protein. This mutation is only found in moles of the skin and in melanoma cells. By blocking the protein, the drug may slow the growth of or kill cancer cells that have the protein. GSK1120212 is designed to block certain proteins that cause cancer cells to grow and multiply. This may cause the cancer cells to die.

Phase I/II Study of the Combination of Doxycycline with Temozolomide and Ipilimumab in Patients with Metastatic Melanoma (2011-1165) (NCT01590082)

Principal Investigator: Sapna Patel, M.D.

The goal of this clinical research study is to find the highest tolerable dose of doxycycline that can be combined with temozolomide and ipilimumab in patients with advanced melanoma. The safety and level of effectiveness of the study drug combination will also be studied.

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 (2012-0238) (NCT01543698)

Principal Investigator: Sapna Patel, M.D.

The goal of Phase IB of this clinical research study is to find the highest tolerable dose of the targeted therapy drugs called LGX818 and MEK162 that can be given to patients with advanced colorectal cancer or melanoma that has a mutation (genetic change) called BRAF. Only melanoma patients with the BRAF mutation will be enrolled at MD Anderson. The goal of Phase II of this clinical research study is to learn if the highest tolerable dose combination of LGX818 and MEK162 can help to control advanced colorectal cancer and/or melanoma with BRAF mutations. The safety of the study drug combination will also be studied. LGX818 is designed to block chemical reactions in cancer cells that are needed for tumor cells to grow, survive, and form the blood vessels needed for tumor growth. This may cause the cancer cells to die. MEK162 is designed to block certain proteins that cause cancer cells to grow and multiply. This may cause the cancer cells to die.

A Phase I/IB Study for the Evaluation of SAR260301, Administered Orally in Monotherapy in Patients with Advanced Solid Tumors or Lymphomas, and in Combination with Vemurafenib in Patients with Unresectable/Metastatic BRAF Mutated Melanoma (2012-0470) (NCT01673737)

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

The goal of this clinical research study is to learn the highest tolerable dose of the drug SAR260301 when it is given alone or in combination with vemurafenib. The safety of this drug will also be studied.

Systemic Therapy of Metastatic Melanoma with Multidrug Regimen Including Interferon, Interleukin-2 and BRAF Inhibitor (2011-0847) (NCT0160312)

Principal Investigator: Rodabe N. Amaria, M.D.

The goal of the Phase I part of this clinical research study is to find the highest tolerable dose of vemurafenib and aldesleukin (interleukin-2) that can be given in combination with interferon alfa-2b in patients with advanced or metastatic melanoma. The safety of this combination will also be studied. The goal of Phase II is to learn if this study drug combination can help to control advanced or metastatic melanoma.

Phase I Study of the BRAF Inhibitor Dabrafenib +/- MEK Inhibitor Trametinib in Combination with Ipilimumab for V600E/K Mutation Positive Metastatic or Unresectable Melanoma (2012-0976) (NCT01767454)

Principal Investigator: Sapna Patel, M.D.

The goal of this clinical research study is to find the highest tolerable dose of the combination of dabrafenib and ipilimumab that can be given with or without trametinib to patients with metastatic melanoma that is positive for the BRAF mutation. Mutations are abnormal changes in the DNA, the genetic material in the cells of the body. Dabrafenib is designed to block the mutated BRAF protein. By blocking the protein, the drug may slow the growth of or kill cancer cells that have the protein. Trametinib is designed to block certain proteins that cause cancer cells to grow and multiply. This may cause the cancer cells to die, especially in cells with BRAF mutation. Ipilimumab is designed to increase the immune system's ability to fight cancer. The drug blocks a molecule that is believed to shut down the part of the immune system that attacks cancer cells.

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.

A Dose-Escalation, Phase I/II, Open-Label, Three-Part Study of the MEK Inhibitor, Trametinib, Combined with the CDK4/6 Inhibitor, Palbociclib, to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Anti-Cancer Activity in Subjects with Solid Tumors (2013-0793) (NCT02065063)

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

The goal of Part I of this clinical research study is to find the highest tolerable dose of trametinib combined with palbociclib that can be given to patients with solid tumors. The goal of Part 2 is to learn if the combination of trametinib and palbociclib can help to control the disease. The safety of this drug combination will also be studied.

Patients with Metastatic Uveal Melanoma

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.

Uveal melanoma is a rare type of melanoma. It is very hard to treat once it has spread to other parts of the body. Dacarbazine, interleukin-2, vemurafenib, dabrafenib, trametinib and ipilimumab are the drugs approved to treat advanced melanoma by the Food and Drug Administration (FDA.) They sometimes work for skin melanoma,but have not been thoroughly tested in uveal melanoma. We are doing this study to try to find better treatments for your disease. 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 and GSK2141795 are experimental drugs since they are not FDA-approved for uveal melanoma. An experimental drug is a medication that is not approved by the FDA to treat a specific condition. 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.

Dr. Davies granted MRF Team Award

The Melanoma Research Foundation (MRF) granted $500,000 in funding over two years for a Team Award proposal by Melanoma Medical Oncology Associate Professor **Michael A. Davies, M.D., Ph.D.**, which started Oct. 1, 2014.

Dr. Michael Davies

Dr. Davies submitted an innovative proposal entitled "Identifying rational therapeutic approaches to 'wild type' melanoma" as team leader of the project, which was summarized in a story in the MRF Matters Fall 2014 online newsletter issue:

"About 30% of people with melanoma do not have one of the more common mutations, BRAF and NRAS. Members of this team are involved in clinical trials for this 'wild-type" population and will use this support to conduct extensive analysis on samples collected through these trials. The goal is to find indicators of who will respond to what treatment, and to identify potential new treatments for this group of melanoma patients."

Under the direction of Dr. Davies, the multi-institutional team includes **Alexander Lazar, M.D., Ph.D.**, of Pathology Administration and **Veerabhadran Baladandayuthapani, Ph.D.**, Biostatistics, both of MD Anderson; Jeffrey Sosman, M.D., of Vanderbilt-Ingram Cancer Center; Keith Flaherty, M.D., Massachusetts General Hospital Cancer Center; and Lynn Schuchter, M.D., University of Pennsylvania Abramson Cancer Center.

The team award proposal by Dr. Davies was one of three selected for funding in a new, specific topic proposal (STP) category providing up to $250,000 a year for two years to a team addressing one of six areas the MRF deemed "critical." The topic areas, comprising the most significant unmet medical needs and high-priority areas in melanoma research, were: prevention, to identify biomarkers of risk for development of melanoma; rare forms of melanoma; metastases; brain metastases; response to treatment; and resistance.

In his lay abstract, Dr. Davies observed that recently developed treatments for BRAFV600 and NRAS mutations are rapidly improving the survival of melanoma patients with those mutations, but "a critical unmet need" remains to develop effective treatments for those without either mutation.

The development of new strategies for the 30% of melanoma patients with wild-type melanoma has been slowed by a dearth of relevant models for researchers to use to test new therapies in the laboratory, Dr. Davies wrote.

"Based on these critical unmet needs, we have developed a team focused on improving research and clinical outcomes for patients with 'Wild-Type' melanoma," he noted. *"Together, we have developed two clinical trials specifically for these patients,"* and the grant will support the collection of tumor biopsies from enrollees in these trials for in-depth analyses by these investigators.

"We will use multiple laboratory techniques to study the tumor biopsies to identify molecular features that predict which patients will respond to the treatments and to understand the genes and pathways that cause resistance to them," Dr. Davies, a molecular biology expert, wrote in describing his plan. "We will also use the tumor biopsies to establish new laboratory models that can be used to test new treatment approaches.

"These studies will help us to maximize the benefit of these current clinical trials. Further, this research will provide information and tools vital to the future development of improved treatments for patients with "Wild-Type" melanoma."

Selected presentations

Our faculty reported the following presentations during the last half of 2014.

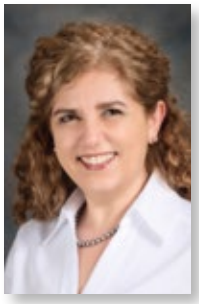
Melanoma Medical Oncology Instructor ***Chandrani Chattopadhyay, Ph.D.***, presented the poster, "Analyses of the level of liver borne growth factors, IGF-1 and HGF in metastatic and non-metastatic uveal melanoma patient serum: correlation with outcome," at the American Association of Cancer Research Special Conference on Advances in Melanoma: From Biology to Therapy on Sept. 21, 2014 in Philadelphia.

Melanoma Associate Professor **Willem Overwijk, Ph.D.**, served in two key roles related to the Society for Immunotherapy of Cancer Annual Meeting in National Harbor, MD. First, with **Padmanee Sharma, M.D., Ph.D.**, MD Anderson Professor of Genitourinary Oncology and scientific director of the immunotherapy platform, Dr. Overwijk co-organized the Primer on Tumor Immunology and Cancer Immunology, which took place Nov. 6, 2014. Second, Dr. Overwijk gave the oral presentation, "Cancer Vaccines," at the daylong event.

Melanoma Associate Professor **Michael A. Davies, M.D., Ph.D.**, gave an oral presentation entitled "The multi-faceted role of the PI3K-AKT pathway in melanoma" at the Melanoma Bridge 2014 meeting Dec. 3-6, 2014, in Naples, Italy. Additionally, Dr. Davies presented the poster, "Next generation sequencing of 201 cancer-related genes in melanoma," based on the abstract on which he was senior author, at the Society for Melanoma Research Eleventh International Congress meeting Nov. 13-16, 2014, in Zurich, Switzerland.

Dr. Vashisht Gopal Yennu Nanda

Further, Melanoma Assistant Professor **Vashisht Gopal Yennu Nanda, Ph.D.**, presented the poster, "mTOR kinase inhibition promotes nuclear exclusion of MITF and prevents oxidative phosphorylation-mediated resistance to MAPK pathway Inhibitors," at the Society for Melanoma Research Eleventh International Congress (also known as SMR 2014), a major gathering of researchers, clinicians and other health-care professionals from all over the world who met in the Kongresshaus Zurich.



Dr. Suhendan Ekmekcioglu

Also at the Society's international meeting in Zurich, Melanoma Associate Professor **Suhendan Ekmekcioglu, Ph.D.**, presented the poster, "Association of CD74 expression with clinical outcome in stage III melanoma."

The Society for Melanoma Research, comprised of scientific and medical investigators devoted to alleviating the suffering of people with melanoma, was founded to unify the field by increasing communication among researchers and building bridges of collaboration between basic, translational and clinical investigators.

Dr. Overwijk awarded CPRIT funding for vaccine project

Melanoma Medical Oncology Associate Professor **Willem Overwijk, Ph.D.**, has been tapped to receive nearly $1 million in funding over a 3-year period from the Cancer Prevention and Research Institute of Texas (CPRIT) in support of his proposal, "Reversing vaccination-induced impairment of anti-CTLA-4-based cancer therapy."

Dr. Overwijk was notified in August 2014 of CPRIT's approval of $899,991 to fund his project, which he expects to lead to the identification of vaccine strategies that will enhance the anti-tumor effect of ipilimumab, a cancer therapy categorized as an immune checkpoint inhibitor. In the process, he expects to identify novel molecular candidates for the development of new immunotherapies.

Ipilimumab is an anti-CTLA-4 monoclonal antibody that has shown efficacy in the treatment of advanced melanoma patients based on its design, geared toward strengthening the immune system's attack on cancer cells. The antibody helps in the activation of killer T-cells that travel to tumors and destroy them.

Experimental vaccines against melanoma, like the gp100 peptide vaccine, are designed to do the same thing. Therefore, it came as a surprise when combining anti-CTLA-4 with gp100 vaccine did not work better, and in fact fared slightly worse, than anti-CLTA-4 alone, Dr. Overwijk wrote in the lay summary of his proposal. When gp100/incomplete Freund's adjuvant (IFA) vaccination was added, the killer cells became trapped at the vaccine injection site, he noted.

In his proposal, Dr. Overwijk cited the groundbreaking study findings he and his colleagues reported in April 2013 in Nature Medicine pertaining to this conundrum. They found that vaccination with gp100 peptide in IFA, a mineral oil-based substance used in many vaccines to boost immune attack, facilitated a buildup of T-cells at the vaccination site, where most remained stuck. He and his team reported their development of a nonpersistent, saline adjuvant-based cancer vaccine formula that allowed T-cells to travel to and shrink tumors in a mouse model (Hailemichael Y et al, "Persistent antigen at vaccination sites induces tumor-specific CD8+ T cell sequestration, dysfunction and deletion.")

Dr. Overwijk raised three questions in his proposal. First, "Why do killer cells go to vaccination sites instead of tumor sites?" Second, "How can we best reverse this process by using new and different vaccines that redirect killer cells to the tumor?" Third, "Can we identify other inhibitory molecules, similar to CTLA-4, to target with new and even more powerful therapies for patients with cancer?"

Dr. Overwijk plans to conduct tests designed to answer each question. First, he will determine the mechanism of localization of the anti-CTLA-4 therapy-induced, tumor-specific T-cells. Second, he plans to reverse the vaccination-induced inhibition of anti-CTLA-4 therapy with a short-lived vaccine formulation. He also will study the mechanism of action, and combination with anti-CTLA-4, of a highly effective new peptide vaccine formula that he developed based on amino acid microcrystals. Finally, he plans to identify new mediators of T-cell inactivation at the tumor site by testing a series of molecules that he has identified which, like CTLA-4, may limit T-cell activity against tumors.

Dr. Prieto named Pathology chair

Victor G. Prieto, M.D., Ph.D., has been named chair of the MD Anderson Department of Pathology, effective Jan. 1, 2015. He had served as chair ad interim for the year prior to his selection for this prestigious appointment after an exhaustive search by a review committee. The globally acclaimed Dr. Prieto, who has served on the board of directors of both the American Society of Dermatopathology and International Society of Dermatology, is a longstanding leader in the field of dermatopathology.

Since 2000, the year after he joined MD Anderson, Dr. Prieto has served as co-director of the institution's Melanoma Tissue Bank. In 2001, Dr. Prieto created MD Anderson's Dermatopathology Fellowship Program and served as its director for 11 years. He has served as medical director of MD Anderson's Histology Laboratory for 6 years. In 2014, he began serving as program director of MD Anderson's Surgical Pathology fellowship.

Dr. Prieto's work in cutaneous lesions, particularly melanoma, has resulted in more than 300 original research articles in peer-reviewed publications. He is well known for his studies of primary and metastatic melanoma, including the analysis of prognostic factors in sentinel lymph node for melanoma, detection of prognostic markers in vivo, and discovery of potential targets for specialized therapies in melanoma.

Dr. Prieto participates in MD Anderson's Continuing Medical Education-accredited Melanoma Multidisciplinary Conference (MelCo), directed by Melanoma Medical Oncology Professor **Wen-Jen Hwu, M.D., Ph.D.** The weekly MelCo meetings are emblematic of our multidisciplinary approach to melanoma cases, as they provide a forum for vibrant consultative discussion of each case presented for review. Seasoned oncologists representing the Departments of Melanoma Medical Oncology, Diagnostic Radiology, Surgical Oncology, Radiation Oncology and Pathology meet in the Melanoma and Skin Cancer Clinic conference room, bringing their specialized training, experience and expertise to the table for the benefit of the melanoma patient.

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Donations help advance promising research in new SPORE projects

Melanoma postdoctoral fellows **Jodi McKenzie, Ph.D.**, and **Yurri Hashimoto, Ph.D.**, have been selected to receive SPORE Year 10 Career Development Awards, while Developmental Research Program Awards went to Melanoma Associate Professor **Greg Lizee, Ph.D.** and Melanoma Instructor **Sun-Hee Kim, Ph.D.**

Elizabeth Grimm, Ph.D., the overall principal investigator and director of the MD Anderson Melanoma SPORE, made the announcement. Dr. Grimm is deputy division head for research affairs in MD Anderson's Division of Cancer Medicine and professor-research in the Department of Melanoma Medical Oncology.

Award recipients were presented with $25,000 each for their designated melanoma research projects, supported by the MD Anderson SPORE in Melanoma Grant, the AIM at Melanoma Foundation, and the Miriam and Jim Mulva Melanoma Research Fund.

Because of MD Anderson's strength in moving innovative discoveries from the laboratory bench into doctors' hands, the National Cancer Institute has awarded the institution a number of Specialized Programs of Research Excellence (SPORE) awards addressing different types of cancer, including melanoma. SPORE projects aim at understanding the basic underpinnings of various cancers and to use this knowledge to target aspects of the disease to ultimately improve cancer prevention, detection, diagnosis and treatment.

Melanoma Walk scores another resounding success

Far from serving as a deterrent, the spate of rain that fell shortly beforehand proved a prelude to increased participation and support of the 7th Annual AIM for the CURE Melanoma Walk and Fun Run 5K Saturday evening, Sept. 20, 2014, at MD Anderson.

This major fundraising event attracted 1,400 participants, compared to 1,200 in 2013, and 200 volunteers versus 150 the year before.

The 2014 walk generated a total of $125,000 for MD Anderson melanoma research, including a $115,000 check formally presented by AIM officials in an October 2014 ceremony, plus an additional $10,000 representing a direct donation, said Melanoma Medical Oncology Special Events Coordinator Judy Sager.

The annual event, co-hosted by MD Anderson and the AIM at Melanoma Foundation, aims to generate melanoma research funds and raise awareness of the most dangerous form of skin cancer.

A total of 116 free skin-cancer screenings were performed by an all-volunteer MD Anderson clinical team headed by **Ana M. Ciurea, M.D.**, associate professor of Dermatology.

ABC-13 Houston news anchor **Melanie Lawson** graciously served as emcee of the event, which boasted an extended open-air food court featuring an array of hot and cold treats and a variety of entertainment.

MD Anderson Melanoma Assistant Professor **Rodabe Amaria, M.D.**, described recent melanoma therapy breakthroughs to the audience in a well-received presentation.

To Schedule an Appointment

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

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