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Melanoma HORIZONS

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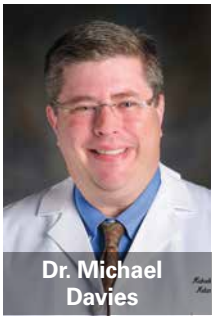
Breakthroughs in brain metastases

Even before the world's biggest cancer conference opened, two MD Anderson Melanoma Medical Oncology clinical investigators' research breakthroughs in melanoma brain metastases were hailed as among the most significant melanoma study findings presented at the 2017 Annual Meeting of the American Society of Clinical Oncology, June 2-6 in Chicago.

Two abstracts submitted by Melanoma Medical Oncology Deputy Chair **Michael Davies, M.D., Ph.D.**, and Associate Professor **Hussein Tawbi, M.D., Ph.D.**, were cited among five "Top Melanoma Studies to Be Presented at ASCO" in a May 26 Medscape commentary by Dr. Jeffrey Weber, deputy director of Perlmutter Cancer Center at New York University-Langone Medical Center. In addition, Dr. Tawbi's abstract was selected by an ASCO expert panel as one in four in the Melanoma/Skin Cancers category to be showcased in the Best of ASCO Program.


Dr. Michael Davies

The oncologists' abstracts described groundbreaking study results using different combination therapies which both evoked high response rates in melanoma patients with brain metastases. Dr. Davies' and Dr. Tawbi's combination regimen of two targeted therapies and two immunotherapies, respectively, significantly shrank metastatic tumors in at least 50% of patients in separate multi-center clinical trials which they designed and led. The two abstracts were among a total of nine chosen for oral presentation in the Melanoma/Skin Cancers Oral Abstract Session June 4.


Dr. Hussein Tawbi

"These encouraging results highlight the possibility of new treatment options and new hope for our patients with metastases to the brain, which are a leading cause of death from the disease," said Dr. Tawbi. Clinical trial protocols often exclude these patients or require them to have radiation treatment for their brain tumors before they can take experimental drugs.

"A key is to accelerate systemic treatments for these patients. These trials show you can have responses in the brain with systemic treatments without radiation first," Dr. Tawbi explained, noting that about 70% of patients with metastatic melanoma eventually develop brain metastases.

"In addition to showing that these combinations are safe and effective, these results demonstrate the overall feasibility of conducting clinical trials for melanoma patients with brain metastases. This result by itself will ultimately make more treatments available to these patients, and thereby address a critical unmet clinical need," said Dr. Davies.

Dr. Tawbi reported initial efficacy outcomes from the CheckMate 204 study, in which all patients were treated with a combination of ipilimumab and nivolumab. The brain tumors of 54% of the patients (41 of 75) significantly shrank; in 16 patients, all tumors disappeared completely. At 9 months' follow-up, only 1 of the 41 responders had developed disease progression.

And despite the potential risk of immune response-related inflammation, "we saw no increase in adverse neurological events in the combination trial," said Dr. Tawbi, "just the same range of toxicities that we find in patients without brain metastases."

Dr. Davies reported his COMBI-MB clinical trial results, which were published concurrently in Lancet Oncology in an article that was later highlighted in Cancer Discovery Research Watch. The trial enrolled metastatic melanoma patients with a BRAF V600 mutation, which is found in about half of melanoma patients. Patients received dabrafenib, targeting the BRAF 600 mutation, and trametinib, which binds to and inhibits MEK1 and 2. The trial included four groups of patients who varied in BRAF mutation types, prior treatment for brain metastases, and whether symptoms from the metastases were controlled.

The largest group had a BRAF V600E mutation, no prior treatment for their brain tumors, and symptoms caused by the brain metastases were under control. The brain tumors in 58% (44 of 76) of that group significantly shrank, and four had a complete response. Similar results were observed in the other groups. While the response rate approached those previously observed in patients without brain metastases, the duration of brain tumor control was shorter: an average of 6-7 months versus about 1 year in prior trials of patients without brain metastases, and in contrast to the results with ipilimumab and nivolumab.

"Treatment with dabrafenib and trametinib had impressive initial activity in the patients. The important question is, how do we make the responses last longer," Dr. Davies said. Combining the agents with other treatments, or using higher doses of each, could be potential approaches, he said.

Besides Medscape, their studies were covered by publications including The ASCO Post, The ASCO Daily News, MedicalXpress, Targeted Oncology, Cancer Therapy Advisor, The Pharmaceutical Journal, Cancer Research UK, and Neuroscience News.

'The prognosis is good': an apt forecast

Of the miles of media coverage of the American Society of Cancer Oncology (ASCO) 2017 Annual Meeting, The Economist's 6-word headline on ASCO opening day said it most succinctly:

"**The prognosis is good: cancer research**" ran under a large overhead shot of ASCO attendees packed into multiple poster board aisles June 2.

"Today one of the world's largest meetings on cancer treatment will draw more than 30,000 experts to Chicago," stated the brief "Espresso" article, describing it as a focal point of progress. Although cancer has "a rightful reputation as a terrible foe," it noted, "new medicines have started to make inroads," with more specific, targeted treatments joined by "promising" immuno-oncology and rapid development of earlier diagnosis.

MD Anderson melanoma investigators' strong representation at the meeting supported that optimistic forecast. Melanoma research-focused abstracts authored by Melanoma Medical Oncology Deputy Chair **Michael Davies, M.D., Ph.D.,** co-leader of MD Anderson's Melanoma Moon Shot; Melanoma Medical Oncology Associate Professor **Hussein Tawbi, M.D., Ph.D.**; and Surgical Oncology Associate Professor and Melanoma Moon Shot co-leader **Jennifer Wargo, M.D.**, were chosen for prestigious oral presentations, the first two of which are described on page 1.

Dr. Jennifer Wargo

Dr. Wargo's team found that the blend of bacteria in the digestive tract of metastatic melanoma patients is associated with disease progression or delay in patients treated with immunotherapy, as reported June 5 in Science Daily. Their analysis of fecal samples from about 100 patients treated with anti-PD-1 inhibitors indicated that greater diversity of bacteria in the gut microbiome is associated with a higher response rate to treatment as well as longer progression-free survival. They also found that an abundance of certain bacteria is associated with the same two outcome measures.

Dr. Wargo's team is developing the first immunotherapy-microbiome clinical trial in collaboration with the Parker Institute for Cancer Immunotherapy. The team is also conducting microbiome mouse model research, including a Stand Up to Cancer-funded study in which fecal samples from therapy-responsive patients and from non-responders are transplanted into germ-free mice.

Dr. Wargo's presentation was covered by The ASCO Post, GenomeWeb, and the American Journal of Managed Care, and hailed by the Society for Immunotherapy of Cancer as one of the "ASCO 2017 Annual Meeting Highlights."

Dr. Rodabe Amaria

Targeted Oncology interviewed Dr. Wargo and Melanoma Medical Oncology Assistant Professor **Rodabe Amaria, M.D.**, about their poster, "Relapse-free survival and target identification to enhance response with neoadjuvant and adjuvant dabrafenib + trametinib (D+T) treatment compared to standard-of-care (SOC) surgery in patients (pts) with high-risk resectable BRAF-mutant metastatic melanoma."

The story's headline spelled out the impressive bottom line of a study using this combination treatment and approach compared to standard of care surgery for these patients: "ORR raised to 85% with neoadjuvant, adjuvant dabrafenib/trametinib combo," showing not only an overall response rate of 85% but a pathologic complete response rate of 58%. The investigators are continuing to lead this promising "Combi-Neo" melanoma clinical trial at MD Anderson.

Dr. Amaria was chosen to co-chair the Melanoma/Skin Cancers Poster Discussion Session. Many MD Anderson melanoma investigators were first or senior authors of abstracts selected for poster presentation.

Dr. Wargo was senior author on an abstract submitted by first author Surgical Oncology fellow **Alexandre Reuben, M.D.**, and selected as a poster: "Multidimensional spatial characterization of the tumor microenvironment (TME) in synchronous melanoma metastases (SMM) to yield insights into mixed responses to therapy in metastatic melanoma (MM) patients (pts.)" She also was senior author on a poster of an abstract submitted by first author Pathology fellow **Wei-Shen Chen, M.D.,** "Molecular and immune predictors of response and toxicity to combined CTLA-4 and PD-1 blockade in metastatic melanoma (MM) patients (pts.)"

Dr. Amaria was senior author on an abstract submitted by first author Martin Schuler, M.D., of University Hospital Essen, "Phase 1b/2 trial of ribociclib+binimetinib in metastatic NRAS-mutant melanoma: safety, efficacy and recommended phase 2 dose (RP2D)," presented as a poster. On another poster, Dr. Amaria was senior author on an abstract submitted by Cancer Medicine Division Hematology-Oncology fellow **Meredith Ann McKean, M.D.,** "Prognostic factors for overall survival (OS) in metastatic melanoma (MM) patients (pts) treated with immune checkpoint inhibitors: A single institution study of 696 pts."

Surgical Oncology fellow **Emily Keung, M.D.**, was first author, while Dr. Tawbi was senior author on the poster, "A phase II study of oral azacitidine (CC-486) in combination with pembrolizumab (PEMBRO) in patients with metastatic melanoma (MM)." Additionally, Dr. Tawbi was senior and presenting author of a sarcoma abstract stemming from his work at a previous institution, which was selected for oral presentation. Melissa Burgess, M.D., of the University of Pittsburgh Cancer Institute, was first author of "Multicenter phase II study of pembrolizumab (P) in advanced soft tissue (STS) and bone sarcomas (BS): Final results of SARCO28 and biomarker analysis."

Division of Cancer Medicine Hematology/Oncology fellow **Gustavo Schvartsman, M.D.**, was first author of the abstract in the poster "Incidence, patterns of progression and outcomes of melanoma brain metastasis (MBM) during programmed-death 1 inhibitor (PD1i) therapy" (senior author Melanoma Medical Oncology Assistant Professor **Isabella Glitza Oliva, M.D., Ph.D.**)

Melanoma Medical Oncology Assistant Professor **Sapna Patel, M.D.**, presented the poster, "The safety and early efficacy of high-dose ipilimumab (IPI) and the combination nivolumab plus ipilimumab (NIVO + IPI) in patients (pts) with uveal melanoma (UM)."

During the meeting, Oncology Tube recorded a video of Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.**, in which he provided an overview of two abstracts involving promising results from use of cytokine NKTR-214 for treatment of patients with renal cell carcinoma and melanoma.

In the first abstract, Dr. Diab was senior author, while Melanoma Medical Oncology Assistant Professor **Chantale Bernatchez, Ph.D.**, was first author of a poster, "Effect of a novel IL-2 cytokine immune agonist (NKTR-214) on proliferating CD8+ cells and PD-1 expression on immune cells in the tumor microenvironment in patients with prior checkpoint therapy." Dr. Diab also was lead author of the abstract, "A phase 1/2 study of a novel IL-2 cytokine, NKTR-214, and nivolumab in patients with select locally advanced or metastatic solid tumors," published online in conjunction with the meeting.

Dr. Diab was senior author on two more posters at the meeting. In the first, Anthony B. El-Khoueiry, M.D., of the University of Southern California Norris Comprehensive Cancer Center, was first author of "The relationship of pharmacodynamics (PD) and pharmacokinetics (PK) to clinical outcomes in a phase 1 study of OX40 agonistic monoclonal antibody (mAb) PF-04518600 (PF-8600.)" In the second, **Aung Naing, M.D.**, Associate Professor, Investigational Cancer Therapeutics, was first author of "PEGylated human IL-10 (AM0010) in combination with pembrolizumab in anti-PD1 and CTLA4 refractory melanoma."

Ryan Sullivan, M.D., of Massachusetts General Hospital Cancer Center, presented the poster, "Atezolizumab (A) + cobimetinib (C) + vemurafenib (V) in BRAF V600-mutant metastatic melanoma (mel): Updated safety and clinical activity" (Cancer Medicine Division Head and Melanoma Medical Oncology Chair **Patrick Hwu, M.D.,** senior author.)

Melanoma Medical Oncology Professor **Cassian Yee, M.D.**, presented "Antigen Selection in T-Cell Therapy" in an education session and "Antigen Targeting of T Cell Therapies" in the Developmental Therapeutics Poster Discussion session.

Dr. Jeffrey Weber, deputy director of Perlmutter Cancer Center at New York University-Langone Medical Center, gave an oral presentation based on the abstract "Five-year overall survival (OS) update from a phase II, open-label trial of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600-mutant unresectable or metastatic melanoma (MM)" (MD Anderson coauthor **Sapna Patel, M.D.**) This study, like those of Dr. Tawbi and Dr. Davies in the same session, was hailed as one of the five "Top Melanoma Studies to be Presented at ASCO."

Exceptional show at this year's ASCO

By Jennifer McQuade, M.D., Instructor, Melanoma Medical Oncology

Dr. Jennifer McQuade

MD Anderson Melanoma Medical Oncology had an exceptionally strong showing at this year's American Society of Clinical Oncology meeting. Department Deputy Chair and Associate Professor **Michael Davies, M.D., Ph.D.**, and Associate Professor **Hussein Tawbi, M.D., Ph.D.**, presented two of the most highly anticipated melanoma studies of the meeting to a packed auditorium Sunday morning, June 4.

Although outcomes of patients with metastatic melanoma have improved dramatically with U.S. Food and Drug Administration approval of multiple targeted and immune therapies in the last 6 years, the large clinical trials of these drugs have excluded patients with brain metastases.

Brain metastases remain a major cause of morbidity and mortality in melanoma, and treatments for brain metastases remain an unmet need. Drs. Davies and Tawbi, therefore, designed and led trials specifically focused on testing targeted and immune therapies in melanoma patients with brain metastases.

Dr. Davies presented a study of the targeted therapy combination dabrafenib and trametinib, which showed that 58% of the patients in the largest group experienced significant shrinkage of their brain tumors, with similar results in the other three groups studied. His study findings were published concurrently in the prestigious journal Lancet Oncology.

Dr. Tawbi presented the findings of a study of the immune therapy combination, ipilimumab and nivolumab, which shrank melanoma brain metastases in over half of patients, and further showed that the responses in these patients were very long-lasting.

These two studies were hailed as practice-changing because they show that in melanoma patients with asymptomatic brain metastases, systemic treatments that are active against metastases outside the brain can also target brain metastases. Moreover, they are safe to use in these patients.

MD Anderson Associate Professor of Surgical Oncology **Jennifer Wargo, M.D.**, presented her fascinating work on the role of the microbiome in response to immunotherapy. She analyzed fecal (i.e., poop) samples from about 100 melanoma patients treated with anti-PD-1 immunotherapy and found that the microbiome (i.e., the bacteria in the feces) differed between those patients who had tumor shrinkage and those who didn't.

When she then transferred the feces from the patients with tumor response to mice with melanoma tumors, they had a better response to immunotherapy than the mice that had a fecal transplant from patients who were non-responders (yes, for real, poop transplants). What determines the microbiome of the responders vs. the non-responders and how we now translate this new factor into improved outcomes with anti-PD-1 and other treatments, are exciting questions that remain to be answered (e.g., poop pills, probiotics, fecal transplant, dietary changes, etc.)

Besides these presentations, MD Anderson melanoma researchers authored an additional 15 oral or poster presentations for an all-around spectacular showing. Our faculty were also well represented among the awards given this year by the Conquer Cancer Foundation of the American Society of Clinical Oncology. MD Anderson Assistant Professor **Adi Diab, M.D.**, and I both received Career Development Awards, and MD Anderson Cancer Medicine oncology fellow **Meredith McKean, M.D.**, received a Young Investigator Award for her melanoma research. These grants are key to funding the next generation of melanoma researchers, and we are so grateful to the generous donors who make them possible.

Clinical Trials in Melanoma Medical Oncology

For more information on these trials, call the toll-free Ask MD Anderson number, 1-877-632-6789. The print version of this list was up to date as of our July 3, 2017 copy deadline. To see all the MD Anderson Melanoma Medical Oncology clinical trials that are current at any given time, visit the MD Anderson Melanoma Medical Oncology Department website and click on the **Clinical Trials** *link.*

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.

Neoadjuvant and Adjuvant Checkpoint Blockade in Patients with Clinical Stage III or Oligometastatic Stage IV Melanoma (2015-0041) (NCT02519322)

Principal Investigator: Rodabe Amaria, M.D.

The goal of this clinical research study is to learn if giving nivolumab alone or in combination with ipilimumab before and after surgery can help to control metastatic melanoma. The safety of these drugs will also be studied.

Adjuvant

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)

A Phase Ib, Open-label Study of the Safety and Pharmacology of Atezolizumab (Anti-PD-L1 Antibody) Administered in Combination with Vemurafenib or Vemurafenib Plus Cobimetinib in Patients with BRAF (V600) Mutation-Positive Metastatic Melanoma (2012-0588) (NCT01656642)

Principal Investigator: Patrick Hwu, M.D.

The goal of this pre-screening test is to learn if you may be eligible to take part in the main study. The goal of the main clinical research study is to find the highest tolerable dose of MPDL3280A (Atezolizumab) that can be given in combination with vemurafenib (Zelboraf) or vemurafenib plus cobimetinib (GDC-0973) to patients with locally advanced or metastatic BRAF mutant melanoma. The safety of the drug combination will also be studied.

Patients with Previous Chemotherapy

A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects with Melanoma Metastatic to the Brain Treated with Nivolumab in Combination with Ipilimumab Followed by Nivolumab Monotherapy (2015-0696) (NCT02320058)

Principal Investigator: Hussein Tawbi, M.D., Ph.D.

The goal of this clinical research study is to learn about how treatment with the combination of Opdivo (nivolumab) and Yervoy (ipilimumab) may affect the disease that has spread to the brain. Researchers will also test if the drugs can control the disease outside the brain and the safety of the drugs.

Phase II Study of BEvacizumab in Combination with ATezolizumab in Patients with Untreated Melanoma Brain Metastases (BEAT-MBM) (2016-0866) (NCT03175432)

Principal Investigator: Hussein Tawbi, M.D., Ph.D.

The goal of this clinical research study is to learn if atezolizumab and bevacizumab can help to control the disease in patients with cancer that has spread to the brain.

Phase I/II Dose Escalation and Cohort Expansion of Safety and Tolerability Study of Intratumoral CD40 Agonistic Monoclonal Antibody APX005M in Combination with Systemic Pembrolizumab in Patients with Metastatic Melanoma (2015-0654) (NCT02706353)

Principal Investigator: Adi Diab, M.D.

You are being asked to take part in this study because you have metastatic (cancer that has spread) melanoma. The goal of Part 1 of this clinical research study is to find the highest tolerable dose of APX005M that can be given with pembrolizumab that can be given to patients with metastatic melanoma. The goal of Part 2 of this study is to learn if the combination can help to control metastatic melanoma. The safety of this drug combination will also be studied.

A Phase II Study of the Anti-PD-1 Antibody Nivolumab in Combination with Dabrafenib and/or Trametinib in Patients with BRAF or NRAS-mutated Metastatic Melanoma (2015-0605) (NCT02910700)

Principal Investigator: Hussein Tawbi, M.D., Ph.D.

The goal of this clinical research study is to learn if nivolumab and trametinib (either alone or in combination with dabrafenib) can help to control metastatic melanoma in patients who have a BRAF or NRAS mutation.

Phase II Study of Oral Azacitidine (CC-486) in Combination with Pembrolizumab (MK-3475) in Patients with Metastatic Melanoma (2016-0069) (NCT02816021)

Principal Investigator: Hussein Tawbi, M.D., Ph.D.

The goal of this clinical research is to learn if oral azacitidine (CC-486) and pembrolizumab (MK-3475) can help to control melanoma. The safety of this drug combination will also be studied.

A Phase 1/2, Open-Label, Multicenter, Dose Escalation and Dose Expansion Study of NKTR-214 and Anti-PD-L1 (Atezolizumab) or Anti-PD-1 (Nivolumab, Pembrolizumab) in Patients with Select Locally Advanced or Metastatic Solid Tumor Malignancies (2016-0753) (NCT02983045)

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 in combination with standard drugs to patients who have melanoma, non-small cell lung cancer (NSCLC), renal cancer, or bladder cancer that is metastatic (has spread) or has returned. Researchers also want to learn more about the safety and effects of the study drug combinations. There are 2 parts to this study: Part 1 (dose escalation) and Part 2 (dose expansion). The standard drugs being used in this study are Tecentriq (atezolizumab), Opdivo (nivolumab), and Keytruda (pembrolizumab).

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, 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.

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.

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: Vali Papadimitrakopoulou, M.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

Multi-Center Phase Ib Study of Intermittent Dosing of the MEK Inhibitor, Selumetinib, in Patients with Advanced Uveal Melanoma Not Previously Treated with a MEK Inhibitor (2016-0569) (NCT02768766)

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

The goal of this clinical research study is to find the highest tolerable dose of selumetinib when given on an intermittent dosing schedule that can be given to patients with uveal melanoma. Intermittent dosing means that the study drug will be given on a "3 days on, 4 days off" schedule.

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.

Grants, awards recognize enterprising research

Grants and merit awards often prove elusive in the increasingly competitive field of cancer research, but our productive MD Anderson melanoma investigators have been honored with a plethora.

The Fund for Innovation in Cancer Informatics has awarded a research grant to **Scott E. Woodman, M.D., Ph.D.**, Assistant Professor, Melanoma Medical Oncology, MD Anderson Cancer Center; **Anil Korkut, Ph.D.**, Assistant Professor, Bioinformatics and Computational Biology at MD Anderson; and **Chris Sander, Ph.D.**, Professor, Cell Biology, Harvard Medical School and Director, cBio Center at Dana-Farber Cancer Institute. The two-year grant, starting with $111,695 for first-year project costs, supports their project, "Genomics-Guided Discovery of Effective Combination Therapies in Cancer."

Dr. Scott Woodman

"This project will use computational biological approaches to identify key co-occurring genomic alterations in diverse cancer types, with a focus on melanoma, to accelerate the discovery and experimental testing of potentially effective combination therapies," Dr. Woodman explained.

Melanoma Research Alliance (MRA) Young Investigator Awards will fund innovative melanoma research projects proposed by **Lawrence Kwong, Ph.D.**, assistant professor of Translational Molecular Pathology (mentored by Melanoma Medical Oncology Deputy Chair **Michael Davies, M.D., Ph.D.**), and by Assistant Professor **Kunal Rai, Ph.D.**, assistant professor of Genomic Medicine (mentored by Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**) The awards were announced in April.

Dr. Lawrence Kwong

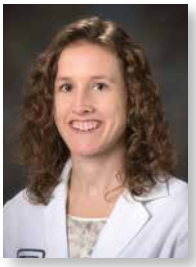
The University of Texas MD Anderson Cancer Center-MRA Young Investigator Award, 2017-2020, will provide $225,000 to fund Dr. Kwong's 3-year project, "PKC-alpha as a node to overcome intrinsic MEK inhibitor resistance in melanoma." The Tara Miller Melanoma Foundation-MRA Young Investigator Award, 2017-2020, will provide $225,000 to fund Dr. Rai's 3-year project, "Epigenetic effectors of responses to immune checkpoint blockade agents."

Stand Up to Cancer awarded a three-year, $750,000 Innovative Research Grant to Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**, to fund her groundbreaking microbiome research, aimed at understanding how the bacteria in the digestive tracts of melanoma patients affects their response to a common immunotherapy drug. The award was announced in April at the 2017 American Association for Cancer Research Annual Meeting.

Dr. Wargo, who co-leads the Melanoma Moon Shot, received further funding for her work delineating the role of the gut microbiome in modulating responses to cancer immunotherapy in May, when she was one of eight investigators named by MD Anderson to the second annual class of Andrew Sabin Family Fellows. The Andrew Sabin Family Fellowship Program provides $100,000 in funding over two years through a $30 million endowed gift to encourage research creativity, independent thinking and high-impact cancer research.

In a June 4 ceremony at the 2017 ASCO Annual Meeting, Melanoma Medical Oncology Instructor **Jennifer Leigh McQuade, M.D.**, received a three-year 2017 Conquer Cancer Foundation (CCF)/Genentech BioOncology Career Development Award totaling $200,000 to fund her project on the "Clinical, molecular and immunological significance of obesity in melanoma." Dr. McQuade was mentored by Melanoma Medical Oncology Deputy Chair **Michael Davies, M.D., Ph.D.** Dr. McQuade and Dr. Davies are each now recipients of both CCF Young Investigator Awards and Career Development Awards.

Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.**, received a three-year 2017 Conquer Cancer Foundation of ASCO–Melanoma Research Alliance Career Development Award for $200,000 to fund his research proposal, a "Phase I/II study of intratumoral CD40 agonistic monoclonal antibody APX005M in combination with systemic pembrolizumab in patients with metastatic melanoma." Dr. Diab was mentored by Cancer Medicine Head and Melanoma Medical Oncology Chair **Patrick Hwu, M.D.**



Dr. Meredith McKean

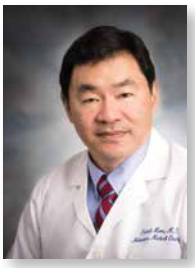
Cancer Medicine Hematology/Medical Oncology fellow **Meredith McKean, M.D.**, mentored by Systems Biology Chair **Gordon Mills, M.D.**, received a 1-year, $50,000 Conquer Cancer Foundation of ASCO Young Investigator Award for her research proposal, "Investigation of in situ predictors of response to immune therapy in metastatic melanoma."

MD Anderson Surgical Oncology fellow **Alexandre Reuben, Ph.D.**, was distinguished with a 2017 Conquer Cancer Foundation of ASCO Annual Meeting Merit Award as first author of abstracts he submitted for presentation at the ASCO Annual Meeting. Dr. Reuben was selected to present both an oral presentation based on his lung cancer work, as well as a poster based on his melanoma research, "Multidimensional spatial characterization of the tumor microenvironment (TME) in synchronous melanoma metastases (SMM) to yield insights into mixed responses to therapy in metastatic melanoma (MEL) patients (pts)," with senior author Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**

Surgical Oncology Graduate Research Assistant **Vancheswaran Gopalakrishnan, M.P.H.**, was honored with a Conquer Cancer Foundation Merit Award at the 2017 ASCO-SITC Clinical Immuno-Oncology Symposium in Orlando for his abstract, "Association of diversity and composition of the gut microbiome with differential responses to PD-1 based therapy in patients with metastatic melanoma."

MD Anderson melanoma research prominent at AACR 2017

MD Anderson melanoma leadership and research findings were prominent at the 2017 American Association for Cancer Research Annual Meeting (AACR), April 1-5 in Washington, D.C., where a record number of nearly 22,000 scientists, clinicians, advocates and others gathered to discover and discuss advances in the field.



Dr. Patrick Hwu

Cancer Medicine Division Head and Melanoma Medical Oncology Chair **Patrick Hwu, M.D.**, co-chaired the immunology minisymposium, "Novel Insights into Mechanisms of Response to Immunotherapy." Dr. Hwu, the outgoing chair of the Cancer Immunology Working Group (CIMM), also co-chaired a CIMM Town Meeting cosponsored by CIMM and the Society for Immunotherapy of Cancer (SITC), focused on SITC initiatives and immunotherapy. Additionally, Dr. Hwu co-chaired the joint CIMM/Tumor Microenvironment Working Group scientific session, "Microenvironmental Regulation of Immunotherapy Efficacy in Cancer."

The AACR Scholar-in-Training Award in Memory of William Maness was presented to **Vancheswaran Gopalakrishnan,** a Surgical Oncology graduate research assistant and doctoral student nearing his Ph.D. The honor was based on the quality of his award application and abstract, "Response to anti-PD-1 based therapy in metastatic melanoma patients is associated with the diversity and composition of the gut microbiome" (Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**, senior author), which he presented in the "Inflammation and Cancer" session.

Vancheswaran Gopalakrishnan

He also presented "Impact of diversity and composition of the gut microbiome on responses to cancer therapy" in the "Methods to Investigate the Microbiota" session. Dr. Wargo presented "Understanding response and resistance to cancer therapy: Lessons learned from melanoma" in the educational session "Deciphering Biomarkers and Mechanisms of Stromal-mediated Drug Responses and Resistance."

Melanoma Medical Oncology Professor **Wen-Jen Hwu, M.D., Ph.D.**, mentored a roundtable discussion on careers in academia during the Women in Cancer Research Career Mentoring Session.

Melanoma Medical Oncology Assistant Professor **Scott E. Woodman, M.D., Ph.D.,** gave an oral presentation, "Novel neoadjuvant targeted therapy trial yields insight into molecular mechanisms of response" (**Jennifer Wargo, M.D.**, abstract senior author) in the session "Novel Agent and Intervention Clinical Trials."

Dr. Sun-Hee Kim

Melanoma Medical Oncology Instructor **Sun-Hee Kim, Ph.D.**, presented "High microsomal PGE2 synthase-1 levels associate with low CD8 T cells and poorer melanoma survival" (senior author Melanoma Medical Oncology Professor **Elizabeth Grimm, Ph.D.**) as a poster in the Tumor Microenvironment session.

Melanoma Medical Oncology Instructor **Cara Haymaker, Ph.D.**, presented "Translational evidence of reactivated innate and adaptive immunity with intratumoral IMO-2125 in combination with systemic checkpoint inhibitors from a Phase I/II study in patients with anti-PD-1 refractory metastatic melanoma," in the poster session "Innate Immunity to Generate Adaptive Immunity." Her research pertained to an MD Anderson clinical trial led by abstract senior author and Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.**

Dr. Cara Haymaker

A poster entitled "Regulation of immune (TCGA) analysis-potential implications for improving immunotherapy" was presented by Melanoma Medical Oncology Professor **Elizabeth Grimm, Ph.D.,** on behalf of lead author Raya Leibowitz-Amit, M.D., Ph.D., of Sheba Medical Center in the session "Immune Checkpoints and Immunosurveillance." Dr. Leibowitz-Amit was a collaborator on a Sister Institution Network Fund grant awarded to Dr. Grimm as principal investigator.

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Conference offers wide-angle view of 'New Melanoma Landscape'

Health-care professionals who manage melanoma patients are invited to attend "The Art and Science of Managing the New Melanoma Landscape: A Case-Based Multidisciplinary Approach," an MD Anderson continuing medical education event slated for Sept. 22-23, 2017 at Houston Marriott Medical Center. Surgical Oncology Professor **Merrick Ross, M.D.**; Melanoma Medical Oncology Deputy Chair **Michael Davies, M.D., Ph.D.**; and Cancer Medicine Division Head and Melanoma Medical Oncology Chair **Patrick Hwu, M.D.**, are the co-chairs of the planning committee.

MD Anderson speakers and panelists will represent the Departments of Surgical Oncology (**Merrick Ross, M.D.**; **Jeffrey E. Lee, M.D.**; **Jeffrey Gershenwald, M.D.**; **Jennifer Wargo, M.D.**); Melanoma Medical Oncology (**Hussein Tawbi, M.D. Ph.D.**; **Rodabe Amaria, M.D.**; **Michael Wong, M.D., Ph.D.**; **Adi Diab, M.D.**; **Isabella Glitza Oliva, M.D., Ph.D.**); Pathology (**Alexander Lazar, M.D., Ph.D.**; **Michael Tetzlaff, M.D., Ph.D.**); Radiation Oncology (**Ashleigh Guadagnolo, M.D.**); and Dermatology (**Ana Ciurea, M.D.**; **Kelly Nelson, M.D.**) **Robert Andtbacka, M.D.**, of the Huntsman Cancer Institute, and **Ryan Sullivan, M.D.**, of Massachusetts General Hospital, will be guest speakers.

This conference is designed to meet the continuing medical education needs of medical oncologists, dermatologists, surgical oncologists, dermatopathologists and other health-care providers managing patients with melanoma. To obtain more information and register, visit the MD Anderson Conferences website page and scroll down to the conference title.

Melanoma Walk and Fun Run slated for Sept. 23 in Houston

The forecast: fair skies and a fine time for everyone at our 2017 AIM for the CURE Melanoma Walk and Fun Run, slated for Saturday evening, Sept. 23, at MD Anderson Cancer Center in Houston.

We think we've got the edge on good weather that night because popular meteorologist Casey Curry, of the ABC13 Houston Eyewitness weather team, has volunteered to serve as Walk emcee this year. Another high note for our 10th anniversary event: a performance by The CheckPoints, the Society for Immunotherapy of Cancer's rock band of oncologist musicians, featuring Cancer Medicine Division Head and Melanoma Medical Oncology Chair **Patrick Hwu, M.D.**, on keyboard.

Each year, AIM at Melanoma Foundation partners with MD Anderson for this event, which raises funds for research aimed at improving melanoma treatment, while also raising public awareness of the risks from exposure to ultraviolet radiation from the sun and sunbeds. Highlighted by free skin cancer screening exams, tasty food and entertainment, our event attracted 1,500 participants last year.

Registration starts at 6 p.m.; opening ceremony at 7:15 p.m.; and the walk/run kicks off at 8 p.m. Find out more and register in advance on the AIM at Melanoma website: **https://www.aimatmelanoma.org**

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