

# Melanoma HORIZONS

ISSUE 24

FEBRUARY 2018

## Microbiome research among ‘most groundbreaking’

By Elizabeth M. Burton, M.B.A., Scientific Project Director, Melanoma Moon Shot Program

Over the past several years, there has been growing evidence that the bacteria in our bodies play a significant role in cancer development and response to treatment. The gut microbiome, in particular, has been shown to shape responses to immunotherapy in laboratory models. However, it had not been studied well in patients until very recently.

We vividly remember when **Jennifer Wargo, M.D.**, Associate



Dr. Jennifer Wargo

Professor of Surgical Oncology and Genomic Medicine and co-leader of MD Anderson Cancer Center's Melanoma Moon Shot Program, returned from a conference a couple of years ago after seeing the preclinical data presented at the Annual Meeting of the Society of Surgical Oncology. Based on the data presented, Dr. Wargo was highly enthusiastic about the prospect of collecting microbiome samples from melanoma patients prior to

the initiation of anti-PD-1 immunotherapy.

Within two years, Dr. Wargo and colleagues had collected oral and gut microbiome samples from over 200 patients with metastatic melanoma. They found distinct differences in the composition and diversity of the gut microbiome at baseline between patients who responded to the immunotherapy and those who did not.

The team also analyzed tumors from a subset of the patients from whom they obtained microbiome samples. They found that patients who had a more favorable microbiome also had more favorable immune infiltrate within their tumors, which helps explain why the patients responded better to immunotherapy.



Dr. Vancheswaran Gopalakrishnan

Surgical Oncology Postdoctoral Fellow **Vancheswaran (Deepak) Gopalakrishnan, Ph.D.**, and Dr. Wargo presented their findings at the ASCO-SITC Clinical Immuno-Oncology Symposium and at the American Society of Clinical Oncology (ASCO) Annual Meeting in June 2017. In November 2017, their groundbreaking results were published and highlighted in the prestigious journal *Science*.

Although this data is very exciting, how the gut microbiome impacts the immune system and response to therapy is still not completely understood. To help gain insight into this, the lab performed studies in germ-free mice (mice without an existing microbiome) and transplanted them with fecal samples

from patients who either responded well or failed to respond to anti-PD-1 therapy. They then implanted melanoma tumors in the mice and treated them with anti-PD-1-based therapy.

In these studies, they found that the mice that received a fecal transplant from responding patients had significantly delayed tumor outgrowth and strong responses to immune checkpoint blockade, whereas mice that received a fecal transplant from nonresponding patients had rapid tumor outgrowth and poor responses to immune checkpoint blockade.

What does all of this mean, and where do we go from here?

Dr. Wargo and her team hypothesize that high diversity and increased abundance of beneficial bacteria in the gut microbiome will enhance the anti-tumor immune response in patients. Notably, multiple factors are known to impact the gut microbiome, including lifestyle, diet, antibiotic use, geographic location, genetics and physical activity.

Thus, a key question is whether or not we can manipulate the microbiome of melanoma patients to induce a more favorable response. Dr. Wargo feels the answer to this question is a resounding “yes,” although we need to work together as a team to understand how to best do this.

Microbiome modulation is an approach that has already been used successfully in other diseases, such as *Clostridium difficile* (C. diff) infections and ulcerative colitis. Melanoma Medical Oncology Assistant Professor **Isabella Glitza Oliva, M.D., Ph.D.**, and Melanoma Medical Oncology Associate Professor **Hussein Tawbi, M.D., Ph.D.**, together with the Parker Institute for Cancer Immunotherapy and Seres Therapeutics, are developing a clinical trial to evaluate the safety and feasibility of strategies, including fecal microbiome transplant, to manipulate the microbiome of patients with metastatic melanoma prior to treatment with anti-PD-1 immunotherapy. This clinical trial is planned to open in 2018.



Dr. Isabella Glitza Oliva



Dr. Hussein Tawbi

We will continue to build on Dr. Wargo's exciting research findings on “the gut's role in cancer” – cited on a short list identifying “The Most Groundbreaking Cancer Research of 2017” in a Reader's

Digest story – to find better ways to treat cancer, and perhaps even to reduce therapy-associated toxicity.

# MD Anderson melanoma research shines at annual meetings

MD Anderson melanoma research was prominently represented at major international and national scientific conferences and in the media during the last half of 2017.

**ESMO 2017:** At the European Society for Medical Oncology (ESMO) 2017 Congress, Sept. 8-12 in Madrid, Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.**, presented a poster, "A Phase 1/2 trial of intratumoral IMO-2125 (IMO) in combination with checkpoint inhibitors (CPI) in PD-(L)1-refractory melanoma," based on results from the dose-selection phase of the trial he is leading at MD Anderson.

Dr. Diab also presented the poster, "PIVOT-02: A phase 1/2, open-label, multicenter, dose escalation and dose expansion study of NKTR-214 and nivolumab in patients with select, locally advanced or metastatic solid tumor malignancies."

Melanoma Medical Oncology Assistant Professor **Isabella Glitza Oliva, M.D., Ph.D.**, presented the poster, "Characteristics of metastatic melanoma (MM) patients with leptomeningeal disease (LMD) and survival of > 1 year."

**WCM/SMR 2017:** At the joint meeting of the 2017 World Congress of Melanoma/International Congress of the Society for Melanoma Research, Oct. 18-21 in Brisbane, Australia, both oral and poster presentations by MD Anderson melanoma investigators were plentiful.

Melanoma Medical Oncology Assistant Professor **Rodabe Amaria, M.D.**, was selected to make two oral presentations. Dr. Amaria presented "TGF-beta dominant negative receptor (TGF-DNR) and NGFR-transduced tumor infiltrating lymphocytes (TIL) and high dose interleukin-2 (IL-2) in patients (pts) with metastatic melanoma (MM)." Her presentation was covered by OncLive in an Oct. 20 story headlined "Early Study Shows Promise for Genetically Modified TILs in Advanced Melanoma."

Dr. Amaria also gave the oral presentation "Neoadjuvant approaches in advanced regional and oligo metastatic melanoma: experience to date," as well as a case presentation during a panel discussion co-moderated by MD Anderson Surgical Oncology Professor **Jeffrey Gershenwald, M.D.**

MD Anderson Assistant Professor **Isabella Glitza Oliva, M.D., Ph.D.**, gave the oral presentation "Managing leptomeningeal metastases in the era of BRAF/MEK inhibitors and immune checkpoint inhibitors."

MD Anderson Assistant Professor **Sapna Patel, M.D.**, gave the oral presentation "A phase II study of glembatumumab vedotin for metastatic uveal melanoma," which was covered by OncLive in an Oct. 30 story headlined "Glembatumumab Vedotin Induces 61% DCR in Uveal Melanoma." Dr. Patel also presented the poster, "Origin of vascular progenitors driving melanoma angiogenesis in vivo."

Melanoma Medical Oncology Assistant Professor **Vashisht Yennu Nanda, Ph.D.**, presented the poster, "Inhibition of mitochondrial oxidative phosphorylation overcomes de novo and acquired resistance to MAPK pathway inhibitors."

Melanoma Medical Oncology Instructor **Jennifer McQuade, M.D.**, presented two posters: "Clinical and molecular associations of body mass index (BMI) in regional melanoma metastases," and "Clinical and biologic associations of body mass

index (BMI) with survival in patients (pts) with BRAFV600-mutated metastatic melanoma (MM) treated with dacarbazine (DTIC), vemurafenib (V), or cobimetinib + vemurafenib (C+V)." Dr. McQuade's outstanding work was recognized with an SMR Travel Award.

**SITC 2017:** Eight abstracts involving MD Anderson melanoma research were selected for oral presentations among a total of 35 chosen for this distinction at the 32<sup>nd</sup> Annual Meeting of the Society for Immunotherapy of Cancer (SITC) and Pre-Conference Programs, Nov. 8-12, 2017, in National Harbor, MD.

Multiple MD Anderson melanoma research presentations were highlighted by media coverage including the online publications OncLive and Targeted Oncology, and many received SITC awards.

Breast Medical Oncology Instructor **Sangeetha Reddy, M.D.**, and Immunology Graduate Research Assistant **Ashvin Jaiswal, Ph.D.**, were two of the four researchers chosen to receive a prestigious 2017 SITC Presidential Travel Award. This award is presented to individuals whose abstracts were the top scoring among those submitted for the Annual Meeting by young investigators based on quality of research and the potential of their work to advance the field.

Dr. Reddy presented "Neoadjuvant nivolumab versus combination ipilimumab and nivolumab followed by adjuvant nivolumab in patients with resectable stage III and oligometastatic stage IV melanoma: preliminary findings." Dr. Reddy's oral presentation reported early findings of an MD Anderson melanoma clinical trial led by Melanoma Medical Oncology Assistant Professor **Rodabe Amaria, M.D.**, and Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**, senior author.

Dr. Reddy's presentation was covered in a Nov. 12 OncLive story entitled "Neoadjuvant Nivolumab/Ipilimumab Combo Effective but Toxic for Melanoma." A Nov. 12 Targeted Oncology story, "Nivolumab/Ipilimumab Combo May Hold Potential in Neoadjuvant Melanoma," quoted Dr. Reddy as summing up: "Treatment with combination ipilimumab/nivolumab is associated with higher response rates in the neoadjuvant setting, but also with significant toxicity, suggesting we need to optimize this regimen further in this setting."

Dr. Jaiswal presented "Metabolic adaptations establish immunotherapy resistance in melanoma" based on the abstract he submitted, on which he was first author. Immunology Assistant Professor **Michael Curran, Ph.D.**, was senior author of the abstract; coauthors included Melanoma Medical Oncology Deputy Chair **Michael Davies, M.D., Ph.D.**, and Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**

Melanoma Medical Oncology Instructor **Cara Haymaker, Ph.D.**, and Melanoma Medical Oncology Assistant Professor **Weiyei Peng, M.D., Ph.D.**, both won SITC Abstract Travel Awards for promising young investigators who submitted high-scoring abstracts to the SITC Annual Meeting with the potential to advance cancer immunotherapy.

Dr. Haymaker was first author and presenter of "TLR9 agonist harnesses innate immunity to drive tumor-infiltrating T cell

expansion in distant lesions in a phase 1/2 study of intratumoral IMO-2125+ipilimumab in anti-PD1 refractory melanoma patients" in the Combination Therapy session. Dr. Haymaker presented exciting new information about the immune results of this regimen, which is being evaluated in a clinical trial led by senior author Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.**

Dr. Peng presented "Functional correlation of increased tumor intrinsic glycolytic activity with resistance to adoptive T cell therapy" in the Mechanisms of Acquired Resistance to Immunotherapy session. Her work has identified cancer cell metabolism as a potential new player and target in immunotherapy resistance.

In the Combination Therapy category, Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.**, presented "Pivot-02: Preliminary safety, efficacy and biomarker results from the Phase 1/2 study of CD-122-biased agonist NKTR-214 plus nivolumab in patients with locally advanced/metastatic solid tumors," which was covered by OncLive in a story headlined "NKTR-214/Nivolumab Combination Shows Promise in Early Study." OncLive reported that the combination of the CD122-biased cytokine NKTR-214 and the PD-1 inhibitor nivolumab demonstrated target lesion reductions of 71% for patients with advanced cancers, based on Dr. Diab's presentation of his clinical trial findings.

Surgical Oncology Postdoctoral Fellow **Vancheswaran Gopalakrishnan, Ph.D.**, was first author of "Diversity and composition of the gut microbiome influence responses to anti-PD1 therapy through beneficial changes in innate and adaptive immunity," and gave the oral presentation in the session "Behind the Therapy: Mechanisms of Efficacy and Toxicity." Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**, was senior author of the abstract.

Investigational Cancer Therapeutics Chair **Funda Meric-Bernstam, M.D.**, was lead author of "A phase 1/2 study of CB-839, a first-in-class glutaminase inhibitor, combined with nivolumab in patients with advanced melanoma (MEL), renal cell carcinoma (RCC), or non-small cell lung cancer (NSCLC)," an oral presentation in the Clinical Trials: Novel Combinations session. Melanoma Medical Oncology Associate Professor **Hussein Tawbi, M.D., Ph.D.**, was a coauthor.

MD Anderson poster presentations also proliferated. **Jonathan L. Curry, M.D.**, Associate Professor, Department of Pathology, presented the poster, "Gene expression profiling of dermatologic toxicities from immune checkpoint therapy" in the Oncogenetics and Immunogenomics category. Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.**, was senior author, while Melanoma Medical Oncology Deputy Chair **Michael Davies, M.D., Ph.D.**, was a coauthor.

Division of Cancer Medicine Fellow **Daniel Hartman Johnson, M.D.**, was first author of the poster, "Phase I/II dose escalation and expansion cohort safety and efficacy study of intratumoral CD40 agonistic monoclonal antibody APX005M in combination with systemic pembrolizumab in treatment-naïve metastatic melanoma patients" in the Trials in Progress category. Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.**, was senior author.

Dr. Johnson was also first author on the poster, "TNF-alpha blockade associated with sooner symptom resolution than corticosteroids alone for management of immune mediated enterocolitis," with senior author Dr. Diab.

**Noha Abdel-Wahab, M.D., Ph.D.**, Instructor, Department of General Internal Medicine, presented the poster, "Inflammatory arthritis induced by the use of checkpoint inhibitors for immunotherapy of cancer," on which Dr. Diab was a coauthor.

Melanoma Medical Oncology Senior Research Scientist **Marie Andree Forget, Ph.D.**, presented the poster, "Utilizing T-cell activation signals 1, 2 and 3 for tumor-infiltrating lymphocytes (TIL) expansion: the advantage over the sole use of interleukin-2 in cutaneous and uveal melanoma," a late-breaking abstract in the Cellular Therapy Approaches category. Senior author was Melanoma Medical Oncology Instructor **Cara Haymaker, Ph.D.**

Melanoma Medical Oncology Postdoctoral Fellow **Meenu Sharma, Ph.D.**, presented the poster, "NKTR-214 enhances anti-tumor T cell immune responses induced by checkpoint blockade or vaccination." MD Anderson Melanoma Medical Oncology Professor **Willem Overwijk, Ph.D.**, was senior author.

In the Pre-Conference Programs, as part of the Primer on Tumor Immunology and Cancer Immunotherapy, Melanoma Medical Oncology Professor **Cassian Yee, M.D.**, presented "Adoptive T-cell therapy," which was covered by OncLive in a Nov. 9 story entitled "Combinations Required to Further Advance Adoptive T-Cell Therapy." Also in the Primer, Immunology Assistant Professor **Michael Curran, Ph.D.**, presented "Targeting regulatory molecules in cancer therapy: new insights and opportunities."

Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**, presented "Influence of gut microbiome upon PD1/I-O responses" in the Predictor Response and Liquid Biopsy session of the CME Workshop on Single Cell Techniques in Immunology and Cancer Immunotherapy Nov. 9. An interview with Dr. Wargo, who described the role of the gut microbiome in patients' responses to treatment with immune checkpoint inhibitors, was published by Targeted Oncology in a Nov. 10 story entitled "Gut Microbiome Can Influence Response to PD-1 Blockade in Melanoma."

Melanoma Medical Oncology Professor **Michael K. Wong, M.D., Ph.D.**, presented "Basic Principles of Tumor Immunotherapy" in the Tumor Immunology 101 session.

**MELANOMA BRIDGE 2017:** Melanoma Medical Oncology Deputy Chair **Michael Davies, M.D., Ph.D.**, presented "BIG News: The Obesity Paradox of Melanoma" in the Systems Biology session at Melanoma Bridge 2017, an international conference which took place from Nov. 30-Dec. 2, 2017, in Naples, Italy.

Additionally, Surgical Oncology Professors **Jeffrey Gersh-enwald, M.D.**, and **Merrick Ross, M.D.**, discussed "Lymphadenectomy: Pros and Cons" in the Great Debate session of the conference.

**ESMO Immuno17:** Melanoma Medical Oncology Assistant Professor **Sapna Patel, M.D.**, presented "A Phase 1b/2 study of omaveloxalone in combination with checkpoint inhibitors in patients with unresectable or metastatic melanoma" in the Proffered Paper session at the ESMO Immuno Oncology Congress 2017, which took place Dec. 7-10, 2017, in Geneva.

At the same conference, Surgical Oncology Professor **Merrick Ross, M.D.**, presented "Oncolytic immunotherapies: the future of adjuvant therapy?" in the Biological Therapy: Infectious Agents at the Service of Immunotherapy session.



# Clinical Trials in Melanoma Medical Oncology

For more information on these trials, call the toll-free AskMDAnderson number, 1-877-632-6789. The print version of this list was up to date as of our Jan. 2, 2018, 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](#) list.

## 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 3, Randomized Study of Adjuvant Immunotherapy with Nivolumab Combined with Ipilimumab Versus Nivolumab Monotherapy after Complete Resection of Stage IIb/c/d or Stage IV Melanoma (2017-0185) (NCT03068455)**

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

The goal of this clinical research study is to compare how well 2 different drugs may be able to control melanoma when given separately or in combination with each other after the tumors have been surgically removed. The two study drugs are Opdivo (nivolumab) and Yervoy (ipilimumab). The safety of these drugs will also be studied.

## Chemotherapy-Naïve Patients (no previous chemotherapy)

**A Randomized, Double-Blind, Placebo-Controlled, Phase III Study Comparing the Combination of PDR001, Dabrafenib and Trametinib Versus Placebo, Dabrafenib and Trametinib in Previously Untreated Patients with Unresectable or Metastatic BRAF V600 Mutant Melanoma (2017-0134) (NCT0296-7692)**

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

There are 3 parts to this study. The goal of Part I of this clinical research study (called "Safety Run-In") is to find the recommended dosing schedule of PDR001 when given with Taffinlar (dabrafenib) and Mekinist (trametinib) in patients with melanoma. The goal of Part 2 of this study (called "Biomarker Study") is to understand the effects of the combination of PDR001, dabrafenib, and trametinib. Researchers also want to study the biomarkers in patients receiving the study drugs. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drugs. The goal of Part 3 of this study (called "Randomized") is to learn if the recommended dosing schedule of PDR001 found in Part 1 can help control melanoma when given in combination with dabrafenib and trametinib. In Part 3 of the study, PDR001 will be compared to a placebo. A placebo is not a drug. It looks like the study drug but is not designed to treat any disease or illness. It is designed to be compared with a study drug to learn if the study drug has any real effect.

## Patients with Previous Chemotherapy

**Phase I/II Study of the Selective PI3K-beta inhibitor GSK2636771 in Combination with Pembrolizumab in Patients with Metastatic Melanoma and PTEN Loss (2016-0774) (NCT03131908)**

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

The goal of this clinical research study is to learn if GSK2636771 given in combination with pembrolizumab can help to control the disease in patients with refractory (has not responded to treatment) metastatic melanoma. The safety of this drug combination will also be studied.

**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.

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.

**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 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 fight infections. They may recognize and kill melanoma cells. Researchers grow 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 the patient 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 potentially 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.

## 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 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.

**Phase Ib Study of Cellular Adoptive Immunotherapy Using Autologous CD8+ Antigen-Specific T Cells and Anti-CTLA4 for Patients with Metastatic Uveal Melanoma (2016-0414) (NCT03068624)**

**Principal Investigator:** Sapna Patel, 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) to patients with uveal melanoma that is metastatic (has spread.) Researchers also want to learn if this combination can help to control the disease.

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

**Principal Investigator:** Sapna 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.

## Special recognition: 'Top Performers' honored

Accolades continue to pour in to honor our MD Anderson melanoma team members for turning in top performances in clinical, research and administrative settings.



Dr. Isabella Glitza Oliva

**Isabella Glitza Oliva, M.D., Ph.D.**, Assistant Professor, Melanoma Medical Oncology; **Wen-Jen Hwu, M.D., Ph.D.**, Professor, Melanoma Medical Oncology; and **Patrick Hwu, M.D.**, Melanoma Medical Oncology Chair and Cancer Medicine Division Head, were among MD Anderson faculty who were honored as "2017 Top Performers" at the 2017 Physicians Referral Service (PRS) Annual Business Meeting.

The three Melanoma Medical Oncology Department clinical faculty were distinguished for scoring in the top 1 percentile nationally on patient care experience-related scores on the Consumer Assessment of Healthcare Providers and Systems survey. In the survey, patients are asked to report on their experiences with a range of health care services at multiple levels of the delivery system.

Among the evaluation criteria, three categories key to the medical practice were used in the analysis: accessibility, communication, and quality experience. Each honoree was recognized as a "2017 Top Performer" with a special certificate.

**Chantale Bernatchez, Ph.D.**, Assistant Professor, Melanoma Medical Oncology-Research, was Co-Principal Investigator with Translational Molecular Pathology Chair **Ignacio Wistuba, M.D.**, on an \$11 million, 5-year NIH grant awarded for a new MD Anderson Cancer Immune Monitoring and Analysis Center (CIMAC), one of four centers that will be part of a Partnership for Accelerating Cancer Therapies (PACT) announced in October 2017.



Dr. Michael Davies

Melanoma Medical Oncology Deputy Chair **Michael Davies, M.D., Ph.D.**, is co-principal investigator on a new U54 grant awarded by the National Cancer Institute, "Rational Approaches to Melanoma Therapy." The grant was awarded to Dr. Davies and **Meenhard Herlyn, D.V.M.**, Director of The Wistar Institute Melanoma Research Center in Philadelphia, to utilize a large collection of melanoma patient-derived xenograft (PDX)

tumors to identify more effective, personalized therapeutic approaches for patients with melanoma.

The PDX model system represents a significant advance over the use of traditional cell line-based xenograft models because PDXs are directly derived from human tumors and can better maintain their original architecture and heterogeneity.

Results of therapeutic studies in PDXs more closely resemble actual effects in human tumors, thereby greatly improving the odds of translating findings from these models to new treatments for patients. Melanoma Medical Oncology Assistant Professor **Vashisht Yennu Nanda, Ph.D.**, will co-lead studies conducted at MD Anderson. The grant will provide up to \$7 million over 5 years to support this new effort.

MD Anderson Melanoma Medical Oncology Research Instructor **Manisha Singh, Ph.D.**, was granted a 2-year award totaling \$545,486 from the U.S. Department of Defense Office of Congressionally Directed Medical Research Programs in support of her research proposal, entitled "B-Cell Mediated Anti-melanoma Immunity."

Dr. Singh, who won a Peer Reviewed Cancer Research Program Idea Award with Special Focus, noted in her application that melanoma is one of the most frequently diagnosed cancers among Veterans Affairs cancer patients and military service members, who are often exposed to sunlight. Current immunotherapies, which kill cancer cells through activated immune cells called CD8+T cells, have shown effectiveness against melanoma, but more than half of patients do not respond to this class of drugs. A key objective of her study will be to identify the mechanism by which immunotherapy-induced B cells help CD8+ T cells suppress melanoma growth, paving the way to the discovery of new therapeutic interventions offering better treatment options for patients.

MD Anderson Melanoma Medical Oncology Research Instructor **Cara Haymaker, Ph.D.**, was among 29 young



Dr. Cara Haymaker

investigators chosen from institutions across the country to participate in the inaugural Society for Immunotherapy of Cancer (SITC) Sparkathon 2018 Cohort. Entitled "Sparkathon-Emerging Leaders, Igniting Innovation," the SITC program is an opportunity for young scientists seeking to advance their career and the cancer immunotherapy field.

The high quality of the abstracts of several Melanoma Medical Oncology faculty members was recognized with travel awards to attend major research organizations' annual meetings (see related story.) Melanoma Medical Oncology Instructor **Jennifer McQuade, M.D.**, received a travel award from the Society for Melanoma Research, while Instructor **Cara Haymaker, Ph.D.**, and Assistant Professor **Weiye Peng, M.D., Ph.D.**, won SITC abstract travel awards.

Further, Breast Medical Oncology Instructor **Sangeetha Reddy, M.D.**, won a SITC 2017 Presidential Travel Award for her melanoma research-based abstract, coauthored by Melanoma Medical Oncology Assistant Professor **Rodabe Amaria, M.D.**, and Surgical Oncology Associate Professor **Jennifer Wargo, M.D.**

**Mayra A. Whittington, B.S.**, Laboratory Coordinator, Melanoma Medical Oncology-Research, was awarded the MD Anderson Division of Cancer Medicine's 2017 Citation for Excellence in Clinical Laboratory Practice. Melanoma Medical Oncology Senior Research Nurse **Lauren Simpson, R.N.**, received the 2017 MD Anderson Clinical Research Nurse Committee Excellence Award.



## Melanoma specialists make headlines for timely response post-Harvey

MD Anderson Melanoma Medical Oncology Department members made national headlines in multiple media for the extraordinary measures they took to provide timely medical assistance after Hurricane Harvey.



Dr. Adi Diab

Melanoma Medical Oncology Assistant Professor **Adi Diab, M.D.**, was extensively lauded for his valor in meeting a patient's needs after the catastrophic storm struck southeast Texas on Friday, Aug. 25, 2017, and proceeded to flood much of Houston, including streets in the Texas Medical Center.

Dr. Diab trekked three miles the following Monday through foot-deep water to provide timely treatment to a stage 4 melanoma patient at MD Anderson, as described in *The Wall Street Journal*, STAT News, NBC News, The Today Show and National Public Radio.

"We always promise our patients one thing: They'll never walk alone," Dr. Diab was quoted in the STAT News story.

Several of the stories focusing on Dr. Diab made note of others who helped to ensure that the patient received his scheduled treatment on an adoptive T-cell therapy clinical trial. They included Melanoma Medical Oncology Professor **Michael Wong, M.D., Ph.D.**; Advanced Practice Registered Nurse **Natalie Jackson**; and TIL team members including Clinical Cell Therapy Specialist **Rene Tavera**, Cell Therapy Lab Supervisor **Orential J. Fulbright**, and Senior Research Scientist **Marie Andree Forget, Ph.D.**

Dr. Forget told STAT that her journey to the hospital had been less perilous than Dr. Diab's, "but she'd left behind a water

stain in her ceiling that had grown about 2 feet wide" and didn't know if she'd return to a flooded apartment.

But being there early was important, because, as STAT reported, "she had to test 14.5 billion T cells harvested from the patient to make sure it was safe to proceed with the infusion." Ultimately, all went according to plan; the patient received his infusion successfully and on time.



Dr. Jennifer McQuade

National Public Radio (NPR) highlighted the rapid response of Melanoma Medical Oncology Instructor **Jennifer McQuade, M.D.**, describing how she used social media to promptly round up other physician-mother volunteers and medical supplies to help evacuees in Melissa Block's Sept. 8 story, "You Have to Help: Gulf Coast Neighbors Fly, Cook and Drive for Harvey Evacuees." The story ran both on air and on the NPR website.

Dr. McQuade's personal Hurricane Harvey response and exceptional networking skills also were described at length in the feature article, "Emergency Medicine," in the Winter 2017 issue of *Virginia Magazine*, published by the University of Virginia, Dr. McQuade's undergraduate alma mater.

The introduction to the story noted that when Dr. McQuade volunteered to help at a Houston Harvey shelter, she had no idea of the lives she would change – including her own.

"I've met this amazing group of people, some in person, this whole network, from other physicians to volunteer pilots. This is my story, but there are so many others," Dr. McQuade modestly summed up her experience at the end of the article. "I'm just so grateful to be connected to so many people."

## Melanoma Philanthropic Funding

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

Mr. Charles Adams  
AIM at Melanoma Foundation  
Mr. and Mrs. Greg Ardoin  
Mr. Michael Autin  
Mr. and Mrs. Howard M. Berk  
Mr. and Mrs. G. Alex Bernhardt, Sr.  
Bernhardt Design  
Mr. and Mrs. James L. Black  
BP Consulting, Inc.  
Mr. and Mrs. Alexander M. Brauer  
Brav Ventures, L.P.  
Broussard & Kay, L.L.C.  
Mr. and Mrs. William A. Burke  
Mr. Charles Carducci  
The Andy Caress Melanoma Foundation  
Ms. Alicia G. Carner  
Mr. and Mrs. Don Carpenter

Mr. Jack T. Clift  
Mr. and Mrs. Chris Crosby  
Mr. and Mrs. Christopher J. Crosby, Sr.  
Mr. Mark Cruse  
Mr. Earl N. Daniels  
Mr. Jim Davie  
Mr. Don Deluzio  
Mr. and Mrs. Richard E. Dietrichson, Jr.  
Mr. Brian D. Doricko  
Mr. and Mrs. Gregg H. Falgout  
Ms. Kimberly A. Falgout  
Ms. Christine M. Falgout and  
Mr. William T. Gutknecht III  
Mr. Sam Fellows  
Mr. Eric Fontenot  
Mr. and Mrs. Miguel A. Hernandez  
Mr. and Mrs. Alan Hicks

Mr. and Mrs. Richard O. Hunton  
The Hunton Group  
Island Operating Company, Inc.  
Mr. Jared Johnson  
Mr. Wayne Joseph  
KeyBank National Association  
Mr. Josh Klapprodt  
Mr. Jeremy Klapprodt  
Mrs. Kathleen R. Leach  
Mr. and Mrs. Ross G. Lyle  
Malibu Floors  
Mr. David Mitteis  
Modestus Brauer Foundation  
Noble Tile Supply, Inc.  
Mr. and Mrs. Timothy J. Norris  
Mr. and Mrs. Alan E. O'Martin  
Mr. and Mrs. Jeff M. Peterson

Mr. Wick Phillips  
Piper Jaffray & Co.  
Redbird Capital Partners LLC  
Mr. Jeff Shannon  
Dr. Jerald L. Sklar  
Mr. Louis J. Tiseo  
TRUIST Matching  
U.S. Concrete, Inc.  
USI Southwest  
Mr. Wade Walters  
Mr. Russell E. Wehrman  
Mr. and Mrs. Patrick L. Whatley  
Ms. Heather Wilhelm  
Mr. Ray P. Williams  
Mr. and Mrs. Kirk Zambetti

**Gifts fuel MD Anderson melanoma mission:** To donate by mail to our melanoma research efforts, please send a check made out to "MD Anderson Cancer Center" specifying "Melanoma Vaccines" in the memo line to **Dr. Patrick Hwu**, Chair, Melanoma Medical Oncology Department, 1515 Holcombe Blvd., unit 430, Houston, TX 77030. Thank you!

# The University of Texas MD Anderson Cancer Center Melanoma HORIZONS

## EXECUTIVE EDITOR

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

## EDITOR

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

## DESIGN

Limb Design, Houston, TX

Email: [Melanoma@mdanderson.org](mailto:Melanoma@mdanderson.org)

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

ADDRESS SERVICE REQUESTED

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

## FDA approves nivolumab for adjuvant treatment of melanoma

On Dec. 20, 2017, the Food and Drug Administration (FDA) approved the anti-PD1 monoclonal antibody, nivolumab (Opdivo), for the adjuvant treatment of melanoma patients with involvement of lymph nodes or in patients with metastatic disease who have undergone complete resection. Nivolumab was previously approved for treatment of patients with unresectable or metastatic melanoma.

The Melanoma Research Alliance (MRA) hailed this new approval in a statement: "This new indication for nivolumab offers patients a new, improved option to reduce the risk of melanoma returning with fewer side effects than currently available treatments."

The MRA noted that an estimated 9% of new cases of melanoma have spread to lymph nodes or nearby sites around the tumor, with correspondingly high risk of disease recurrence and death in these patients. "Reducing the risk that melanoma returns after surgery represents a major opportunity to

eliminate melanoma suffering and death," stated the Alliance, the leading nonprofit funder of research into the treatment and cure of melanoma.

The FDA approval is based on results from the CheckMate 238 trial, in which nivolumab significantly improved recurrence-free survival at 18 months (66%) versus standard ipilimumab (Yervoy, 53%) in patients with resected Stage III or Stage IV melanoma. Nivolumab also had fewer serious treatment-related toxicities (Grade 3 or 4) (25% vs 55%, respectively) and fewer adverse events leading to treatment discontinuation (9% vs 42%, respectively), the MRA noted.

"This is a clear win for patients," said MRA Chief Science Officer Louise M. Perkins, Ph.D. "Not only does nivolumab work better than existing treatments to reduce the risk of melanoma recurrence, it is also easier to tolerate, which means that more people will be able to take the drug."

## Save the date: next Melanoma Walk set for September

Once again in 2017, AIM at Melanoma and MD Anderson Cancer Center partnered together to plan the Houston AIM for the CURE Melanoma Walk and Fun Run, our joint annual 5K event aimed at raising awareness and support for MD Anderson melanoma research. Unfortunately, Hurricane Harvey struck Houston in late August and the event, which had been

scheduled for the following month, had to be canceled. Funds that had already been raised, totaling \$21,000, were donated to MD Anderson in support of melanoma research.

The next Melanoma Walk at MD Anderson has been scheduled for Saturday, Sept. 29, 2018. Please check the AIM at Melanoma website for event registration and details.

## To Schedule an Appointment

Phone: 1-877-632-6789

MD Anderson website (<https://www.mdanderson.org>): Click "Request an Appointment"

Please "Follow Us" on Facebook



<https://www.facebook.com/MDAMelanomaMedicalOncology>