



We Are

MELANOMA
RESEARCH

Features from the 2024 MRA Scientific Retreat

Melanoma
Research Alliance

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Letter from MRA's Chief Science Officer



Hosting the Melanoma Research Alliance (MRA) Annual Scientific Retreat — a premiere convening of key stakeholders in the melanoma community — is something we look forward to each year. The 2024 Scientific Retreat was held February 21st through the 23rd in Washington, D.C. and brought together over 300 participants from diverse backgrounds. Academic investigators, pharmaceutical and biotech representatives, government officials, partners and donors, and patient advocates all joined MRA to engage in scientific discourse, collaboration, and learning.

At the Retreat, participants shared the latest breakthroughs in melanoma prevention, diagnosis, and treatment — most updates stemming directly from the contributions of MRA-funded researchers. Moreover, the personal anecdotes and perspectives shared by the patient advocate community resonated deeply, reminding us of our shared mission to end suffering and death due to melanoma.

The spectrum of discussions and presentations at this year's Scientific Retreat was expansive, covering various relevant and emerging topics. From pioneering new cellular and immune therapies, to managing metastatic melanoma and in-transit disease, and investigating the tumor microenvironment — many facets of melanoma research were touched on over the course of the program.

Beyond the formal sessions, the Scientific Retreat featured programs aimed at supporting the next generation of scientific leaders — specifically a breakfast for MRA's Young Investigator Awardees featuring the topic “How to Work with Industry”. The event also included an interactive Poster Session, providing a platform for investigators to showcase their work. Diverse networking roundtables facilitated focused discussions on an array of topics, fostering interdisciplinary collaboration and knowledge exchange.

We continue to believe that the connections made, and insights gained at the MRA Scientific Retreat will resonate throughout future melanoma research discoveries. Together, we are accelerating progress in prevention, early diagnosis, and treatment to improve outcomes for this disease.

With gratitude for your commitment to our shared mission,

Joan Levy, PhD

Chief Science Officer, Melanoma Research Alliance

**“Research is the beacon
that illuminates our path
to better treatments,
increased understanding,
and, ultimately, cures.”**

LEAH ADAMS, PATIENT ADVOCATE




(L to R): Leah Adams, Kellie Cereceres — Melanoma Patient Advocates

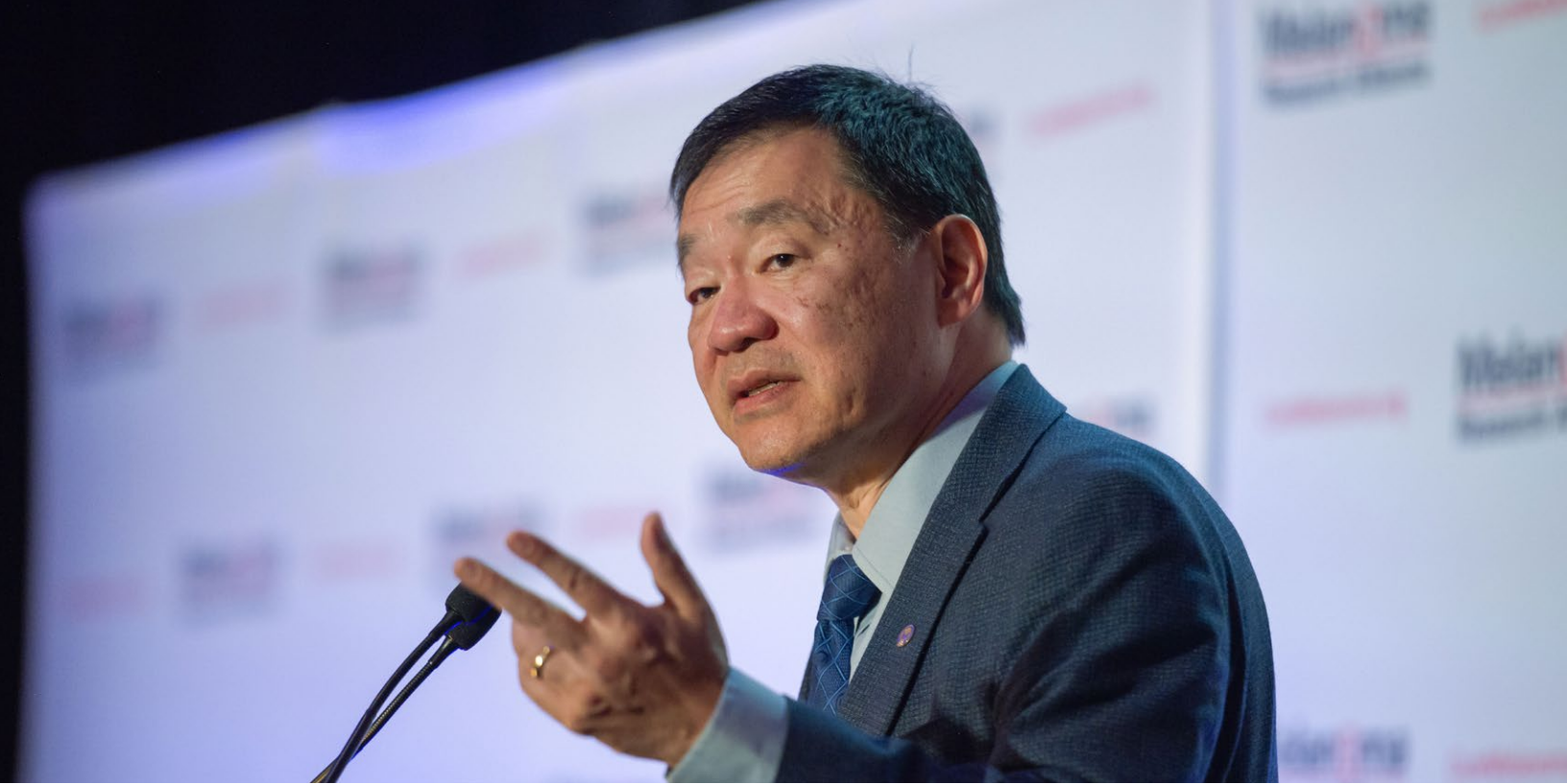
We Are Melanoma Research: MRA’s 2024 Scientific Retreat

Each year, the Melanoma Research Alliance brings together melanoma thought leaders from across the global research community to exchange ideas, share recent scientific successes and hurdles, forge new collaborations, and connect with the patient advocate community.

To start the Scientific Retreat, patient advocate Leah Adams shared her melanoma journey. Her early-stage melanoma diagnosis, surgery, and frequent follow-up dermatology visits have completely changed how she views the world around her. While learning to balance her new reality, Leah’s father was unexpectedly diagnosed with Stage IV melanoma just two years after her diagnosis. “My dad’s late-stage melanoma is now stable due to treatment advances made in the last decade. This progress gives hope to and improves the quality of life of patients — regardless of the stage of their melanoma,” she told attendees. Leah emphasized that without the scientific progress of the last ten years, her dad would not have survived long after his diagnosis. Emphasizing the importance of melanoma research, she shared, “Research is the beacon that illuminates our path to

better treatments, increased understanding, and, ultimately, cures.”

Melanoma patient advocate Kellie Cereceres took the stage next to share her difficult journey of receiving a Stage 4 melanoma diagnosis after months of extreme pain and visits to the doctor. She started targeted therapy to treat her advanced disease, but soon had trouble tolerating treatment. Through her own self-advocacy, Kellie was able to make a plan with her oncologist to receive the lowest possible treatment dose to mitigate further side effects. “I continued to be my own advocate as I researched everything that could keep me alive and healthy,” she said. Today, Kellie is No Evidence of Disease (NED), and she expressed gratitude for the research and advances in the field of melanoma. She remains hopeful and excited for future developments that will help improve the lives of all patients. She closed her remarks by sharing a poem she wrote about the cancer experience, “... tomorrow is another day, another chance to grab onto hope, another day to find joy ...” 



Patrick Hwu, MD — Moffitt Cancer Center

Harnessing the Power of Cell-Based Therapies

Dr. Patrick Hwu, Moffitt Cancer Center, gave a keynote address that discussed the progress and potential of T cells, a type of immune cell, for treating melanoma. He emphasized how T cells recognize and kill tumor cells, leading to long-lasting responses in some patients, saying “These T cells ... can live in the body for decades, giving patients what they’re really looking for — the ability to have long-term, durable responses.”

Dr. Hwu reviewed the history of T-cell therapy development. The process starts with surgery to isolate a patient’s own T cells from their tumor or lymph node, called tumor-infiltrating lymphocytes (TILs). Next, these TILs are isolated in the lab and multiplied into billions of copies, and then reinfused back into the patient. Dr. Hwu highlighted that transient responses were seen with T-cell therapy, but that the responses were improved upon by the addition of lymphodepletion, a process that temporarily reduces the number of lymphocytes (a type of white blood cell) in the body. Lymphodepletion reduces the number of blood cells in the body and makes room for the billions of copies of TILs to be reinfused into the patient and allows proliferation and long-term durable survival of the re-infused TILs.

Next, Dr. Hwu highlighted promising approaches like engineering T-cell receptors against specific tumor antigens and using gene editing to enhance T cells. Dr. Hwu

“T cells can live in the body for decades, giving patients what they’re really looking for — the ability to have long-term, durable responses.”

DR. PATRICK HWU

“We’ve seen robust peripheral expansion and persistence of the [engineered] CAR T cells.”

DR. ANUSHA KALBASI



Anusha Kalbasi, MD — Stanford University

stressed, however, that “we’re just scratching the surface” of how to optimize cell-based therapy approaches for melanoma and other solid tumors and he emphasized that more work is needed, stating “we still have to get better because that curve still drops,” referring to patient survival over time.

Researchers are focusing on three principal areas to try to improve how T cells work in the body. First, they want to find ways to help T cells move more easily to where they are needed inside of the tumor. Second, they are looking at how to give T cells better energy sources and processes to use that energy efficiently. Third, they are studying how to keep T cells in a longer-lasting state so they can continue renewing themselves and function effectively.

Dr. Hwu also described work to make T cells more resistant to the hostile environment inside tumors. One major challenge is a protein called TGF-beta that shuts down T cells and is found at elevated levels in many cancers. The T cells can be modified by adding genes that act like a “gas mask,” protecting them from TGF-beta’s harmful effects. This allows the engineered T cells to keep functioning and attacking the tumor despite the presence of TGF-beta. Early results show this approach can lead to long-term survival in some patients. The goal is to make the T cells “bulletproof.”

He also described knocking out the PDH gene, which forces T cells into a rapid growth state reminiscent of cancer cells themselves. He stated, “you can see the difference ... you get explosive proliferation when these knockout cells hit a tumor cell.” These knockout T cells also enhance antitumor activity. Dr. Hwu was optimistic about continuing progress, with the goal to keep improving T-cell therapies until they can provide long-term cures for many more patients.

Novel Chimeric Antigen Receptor (CAR) T-Cell Therapy Shows Promise Against Melanoma

Dr. Anusha Kalbasi, Stanford University, described a new treatment approach using engineered immune cells called CAR T cells, which are currently being tested in a clinical trial for patients with melanoma. The trial involves taking a patient’s own T cells and genetically engineering them to recognize a protein called IL-13R α 2, which is present on the surface of cancer cells in some patients with melanoma. The modified T cells can find and kill the melanoma cells that express this protein. IL-13R α 2 is not found on healthy cells, which makes it a promising target in terms of safety. So far, five patients with advanced melanoma have been treated with their own personalized CAR T cells. Dr. Kalbasi summarized, “We’ve seen robust peripheral expansion and persistence of the CAR T cells.” This means the engineered cells successfully grew and remained in the patients’ bodies.

There have been some encouraging signs that the treatment is working as intended, with evidence that “the CAR T cells are getting into the tumor and they’re recognizing the target.” In addition, one patient’s lung tumor appeared to resolve initially. However, another patient in the clinical trial experienced a severe side effect of cytokine release syndrome (CRS), which may have contributed to their death. CRS is a potentially life-threatening condition in which the immune system becomes overly activated and floods the body with inflammatory proteins called cytokines.

Moving forward, the researchers have adjusted the CAR T dosage and they continue to treat additional patients across multiple cancer centers. They also aim to expand the trial to include patients with other cancer types that also express the IL-13R α 2 protein, that may respond to this approach.



Navin Varadarajan, PhD — University of Houston



Cristina Puig-Saus, PhD — UCLA

T-Cell Heterogeneity Complicates Immunotherapy Response

Dr. Navin Varadarajan, University of Houston, discussed research into understanding why some patients with melanoma respond better than others to immunotherapy with engineered T cells. The US Food and Drug Administration recently granted accelerated approval to lifileucel, a tumor-derived immunotherapy that utilizes a patient’s own T cells – specifically a type known as tumor-infiltrating lymphocytes (TILs) – for the treatment of advanced melanoma. T cells that are infused into patients to fight melanoma are a heterogeneous mix with vastly different biological capabilities, which makes them difficult to study. Dr. Varadarajan’s lab has tried to understand the interaction between these T cells and a patient’s melanoma cells at a single-cell level using specialized tools. In patients who didn’t respond well to the treatment, the tumor cells were able to move away and detach from the T cells, preventing the T cells from latching onto and killing the tumor cells. The ability of the tumor cells to change shape and move around freely helped them get away from and avoid being killed by the T cells. The key difference between responders and non-responders was in how the T cells used fatty acids from the tumor environment under conditions of scarce nutrients. Dr. Varadarajan concluded that “it’s important for us to...quantify the interactions of T cells and tumor cells” to better understand responses to immunotherapy.

Novel CAR T-Cell Therapy Targets Melanoma

Dr. Cristina Puig-Saus, UCLA, presented another novel CAR T-cell therapy approach. One major challenge in developing a CAR T-cell therapy for solid tumors like melanoma is finding proteins that are present on the surface of cancer cells but not on healthy cells. The researchers designed a specific CAR T cell that can recognize a protein called TYRP1 on the surface of melanoma cells and kill them. Extensive testing in mouse models showed “the TYRP1 CAR T has low toxicity and potent antitumor activity.” TYRP1 is highly expressed in many melanoma tumors, especially acral, mucosal, and uveal melanomas, which often don’t respond well to current immunotherapies. She noted, “approximately 60% of patients with recurrent acral or mucosal melanoma have high expression of TYRP1. And almost all the patients with uveal melanoma have high expression.”

To develop this CAR T-cell therapy, some of a patient’s own immune cells are removed and genetically modified in a special lab to recognize and attack cancer cells. The modified cells are returned to the patient to treat their melanoma. Preparations are underway for a clinical trial to test the safety and efficacy of this TYRP1-targeted CAR T-cell therapy in patients with melanoma—particularly cutaneous, acral, mucosal, and uveal types—whose tumors highly express TYRP1. This new personalized cellular therapy shows great promise as a potential treatment for melanoma, especially rare sub-types and treatment resistant forms. 📍



“We want to find brain metastases before they cause symptoms so treatments have the best chance of working.”

DR. MICHAEL DAVIES

Michael Davies, MD, PhD — University of Texas, MD Anderson Cancer Center

Advancements in Metastatic Melanoma and In-Transit Disease

The treatment landscape for metastatic melanoma has seen remarkable progress in recent years, yet significant challenges remain. This session from the 2024 Melanoma Research Alliance Scientific Retreat described the latest research efforts aimed at improving understanding and management of metastatic disease.

Melanoma Central Nervous System Metastases—Progress, Challenges, and Opportunities

Metastatic melanoma remains an important topic for patients, explained Dr. Michael Davies, University of Texas, MD Anderson Cancer Center. “Predicting, preventing, and treating central nervous system (CNS) metastasis from melanoma remain critical research challenges,” he says. Historically, the median survival for melanoma patients with brain metastases was only around four months. However, considerable progress has occurred in recent years, with median survival now improved to around 15 months and long-term survival rates increasing from 5% to 30%. This progress is attributed to better radiation approaches and

improved systemic therapies, particularly immunotherapies like combination immunotherapy ipilimumab and nivolumab. In clinical trials, 50% to 60% of patients with asymptomatic brain metastases responded durably to this combination. Dr. Davies emphasized the importance of early detection, stating, “We want to find brain metastases before they cause symptoms so that treatments have the best chance of working.” There are also critical needs for additional research and trials for patients with symptomatic brain metastases.

Brain metastases have a unique biology, and they often use signaling pathways and metabolic dependencies that are different than those used by tumors growing at other metastatic sites. The metabolic pathway of oxidative phosphorylation (a metabolic pathway cells use to generate energy) was stimulated in brain metastases and the same pathway was activated when human melanoma cells were injected into the brains of mice compared with when they were injected under the skin in mice.



Georgia Beasley, MD — Duke University

The introduction of checkpoint therapy was associated with improved survival in patients with in-transit melanoma.

Inhibiting this pathway prevented brain metastasis development in animal models, without affecting primary tumor growth.

Dr. Davies also highlighted the significant challenges posed by leptomeningeal disease, a form of central nervous system metastasis for which minimal improvements in survival have been seen. A recent first-in-human clinical trial testing nivolumab given to patients with leptomeningeal disease in two ways — via the spinal fluid and the veins — showed that the dual route of administration was safe. Dr. Davies called for more clinical trials in this patient population. He also added that there are good animal models to screen for potential therapies to take to the clinic for patients with leptomeningeal disease.

Findings from the In-Transit Metastatic Melanoma Consortium

Dr. Georgia Beasley, Duke University, described a study aimed at understanding in-transit melanoma, which refers to the spread of melanoma cells from the primary tumor that have not yet reached the lymph nodes. The study had two aims: 1) review of data from patients with in-transit melanoma by collecting all relevant information (treatments, recurrences, and survival) to better understand in-transit melanoma and determine the treatments that worked best; and 2) analysis of tumor specimens from these patients to determine if molecular differences in the tumors could account for the different outcomes and help clarify whether certain therapies were better than others in some situations.

The study collected data from 1,944 patients with in-transit melanoma from two institutions, Duke University and Memorial Sloan Kettering Cancer Center, between 1991-2021. This is the largest known study conducted on in-transit melanoma. Dr. Beasley noted that 54% of patients eventually developed distant metastatic disease, which was associated with increased mortality. In addition, 43% of patients had additional in-transit recurrences after treatment of their first in-transit lesion. The introduction of checkpoint therapy, a type of immunotherapy, was associated with improved survival in patients with in-transit melanoma. Patients treated with checkpoint immunotherapy had improved overall survival compared with the patients who did not receive it.

The study analyzed tumor samples to identify gene expression patterns associated with disease progression and survival. The analysis revealed that patients with in-transit melanoma lesions enriched for immune pathways were less likely to develop nodal and distant metastases and more likely to have improved survival. On the other hand, patients whose tumors showed upregulation of cell cycle and epithelial-to-mesenchymal transition (EMT) pathways were more likely to develop distant metastases and had worse overall survival (EMT is a cellular process in which some cells change from one type to another, which typically happens during development and tissue repair).

The study also found differences in gene expression patterns between acral (those that involve skin on the palms, soles, and nail beds) and non-acral in-transit melanomas. The researchers



David Liu, MD, MPH, MS — Dana-Farber Cancer Institute, Harvard Medical School

found that acral lesions had higher levels of genes involved in sensing stimuli compared with lesions elsewhere on the body (non-acral lesions). They think this may be related to the specialized sensory functions of the hands and feet and could help explain why cancers in different body locations can have distinct genetic characteristics.

In summary, the Duke study highlights the heterogeneity of in-transit melanoma and the potential for using molecular signatures to predict disease progression and survival, guiding treatment decisions.

Tumor and Immune Evolution in In-Transit Melanoma

The next talk was on the evolution of unresectable in-transit melanoma, a form of melanoma that metastasizes between the primary tumor and the draining lymph node. Dr. David Liu, Dana-Farber Cancer Institute, Harvard Medical School, presented two contrasting cases and genomic analyses to understand the drivers behind distant metastasis progression in some patients and spontaneous remission in others. The first case involved a patient who developed widespread unresectable disease and died from metastasis. Through genomic analysis, seven distinct lineages (subgroups) were identified, with one lineage comprising all distant metastases, suggesting a specific genomic clone associated with metastatic spread. Another lineage comprised tumors that exhibited a phenotype of T-cell exclusion and growth along the outside of blood vessel walls (angiotropic growth). Overall, the tumor exhibited aggressive

features, low immune infiltration, and significant intra-tumoral heterogeneity (the coexistence of distinct tumor cell populations within a single tumor mass).

The second case involved a patient who experienced spontaneous remission after chemotherapy-induced high tumor mutational burden (TMB), a large number of genetic mutations present in the DNA of tumor cells. This patient's tumors showed an active antitumor immune response, increased T-cell receptor diversity, and long-term disease control without additional systemic therapy despite the development of progressive metastases. Histologically, different parts of the same progressive metastases showed both evidence of tumor growth and immune attack with tumor regression. Despite developing new clones and lineages from chemotherapy, each tumor was genetically homogeneous.

Further analysis on a cohort of progressors and non-progressors found that distant progressors had higher intra-tumoral genomic heterogeneity compared with non-progressors. The study highlights the importance of understanding tumor evolution and heterogeneity in melanoma progression and response to treatment. Different tumor cell lineages within the same patient exhibited distinct clinical behaviors and characteristics. In addition, chemotherapy-induced TMB is associated with increased immune response and T-cell receptor diversity, potentially contributing to spontaneous remission in some cases. This project is ongoing, Dr. Liu explained, and there is a need for further characterization. ☺



Yochai Wolf, PhD — Sheba Medical Center

Exploring New Avenues in the Tumor Microenvironment

This session from the 2024 MRA Scientific Retreat covered innovative research in melanoma focused on understanding and manipulating the tumor microenvironment to improve treatment effectiveness.

mRNA Based Reprogramming of Terminally Differentiated TILs

Dr. Yochai Wolf, Sheba Medical Center, provided background on the basic concept of tumor-infiltrating lymphocyte (TIL) therapy, noting “This approach is kind of straightforward, taking TILs from resected tumors, expanding them ... and then infusing them back to the patient.” Initially, TIL therapy showed high durable response rates. However, TIL therapy is only given to patients in the second-line treatment setting — and the success rate for TILs taking hold following infusion and attacking the tumors is much lower for these pre-treated patients, creating a need for improved cell-based products.

Dr. Wolf explained, “We understand that the T cells in the tumor really exist in multiple flavors, particular different T-cell states... the most important two states are the stem-like precursor effector state and the terminally exhausted state.” Dr. Wolf’s team’s strategy to improve TIL therapy was to focus on reprogramming exhausted T cells into more stem cell-like populations using mRNA engineering. T cells with stem-like properties promote tumor control.

mRNA was chosen for a few key reasons, one being that it is anticipated to be safer than gene editing approaches like CRISPR, with less risk of off-target effects or causing otherwise healthy cells to become malignant. Another reason is that mRNA is easy to deliver to cells using electroporation (the process of using an electric pulse to transfect cells with DNA), and expression is transient and temporary, avoiding permanent genetic changes. Lastly, mRNA is flexible, allowing the introduction of single genes or entire gene pathways, tailored expression to specific cell states, and optimized mRNA design. mRNA can be used to



Andrew White, PhD — Cornell University

“We were interested in trying to take a step back and understand how macrophages and tumor cells co-evolve through the course of BRAFi + MEKi targeted therapy.”

DR. ANDREW WHITE

reprogram exhausted T cells into more potent stem-like cells by screening libraries of genes and factors known to support a stem-like state.

Promising early results showed that the experimental approach was able to decrease the number of exhausted T cells and increase the number of stem-like T cells. Seeing this shift from an exhausted to a stem-like T-cell population was an encouraging sign that the researchers' method for reprogramming T cells using mRNA may be working, although more research is still needed to validate the functional effects.

Understanding the Role of Macrophages in Drug Resistance

Understanding drug resistance in melanoma is another key research area of interest to MRA and many investigators in the field. Dr. Andrew White, Cornell University, is working to understand this problem by focusing on the role of tumor-associated macrophages. Macrophages, which are often the largest immune cell component within tumors, are an important part of the tumor microenvironment.

In a mouse model, melanoma cells were transplanted into the mice, allowed to grow, and then the mice were treated with BRAF and MEK inhibitors. These drugs block specific proteins involved in cell signaling that promote uncontrolled cell growth. Treatment with these inhibitors induces tumor regression, which is nearly always followed by the development of drug resistance.

Dr. White explained, “We were interested in trying to take a step back and understand how macrophages and tumor cells co-evolve through the course of BRAFi + MEKi targeted therapy.” The researchers found that during the residual disease state, after tumor regression, there was a significant influx of tumor-associated macrophages. This suggests that the co-evolution of macrophages and tumor cells may play a crucial role in the development of drug resistance during residual disease.

To explore this further, the researchers used a mouse model lacking the *Ccr2+* gene, which is important for monocyte (a type of white blood cell) recruitment into tumors, thereby reducing tumor-infiltrating macrophages. They observed that depleting *Ccr2+* macrophages delayed the onset of resistance, although it did not eliminate it. However, their results showed that the tumor-associated macrophages were involved in the development of resistance. Next, cultured melanoma cells were evolved with or without *Ccr2+*-positive macrophages and then treated with BRAF and MEK inhibitors. The tumor cells that evolved with macrophages developed cell-intrinsic resistance, while those evolved without macrophages remained sensitive to the treatment. Furthermore, when these tumor cells were transplanted into mice and treated with BRAF and MEK inhibitors, the same pattern emerged – tumor cells that evolved with macrophages quickly became resistant, while those evolved without macrophages took longer to develop resistance.



Emily Bernstein, PhD — Icahn School of Medicine at Mount Sinai

Dr. Bernstein and her team found that the histone variant macroH2A acts as a suppressor of inflammatory gene expression in CAFs within the melanoma tumor microenvironment.

Changes in T cell populations were also seen, with a decrease in potentially exhausted T cells and an increase in activated T cells in the Ccr2+ knockout mouse model, suggesting that macrophages may modulate the adaptive T-cell immune response. The study highlights the co-evolutionary relationship between tumor cells and tumor-associated macrophages through tumor regression, residual disease, and the onset of drug resistance. Additional research is needed on the role of macrophages in melanoma progression and treatment response in resistance. Understanding and potentially predicting the trajectories of resistance could lead to the development of more effective strategies for addressing this significant challenge in melanoma treatment.

Histone Variant Regulation of the Melanoma Microenvironment

Dr. Emily Bernstein, Icahn School of Medicine at Mount Sinai, described her research on histone variants in the development of melanoma. Histone variants are specialized proteins that help package DNA into chromatin and regulate various genomic functions. Mutations or alterations in these histone variants can lead to diseases like melanoma. MacroH2A is a unique histone variant that is associated with heterochromatin formation and gene repression. Dr. Bernstein explained, “MacroH2A, which is a tumor suppressor in melanoma... is a very specialized histone variant, it’s quite unique.” To study the role of macroH2A in melanoma, a mouse model was created that was deficient in this

histone variant. Surprisingly, the loss of macroH2A accelerated tumor growth and was associated with increased inflammatory signals in the tumor microenvironment.

Single-cell RNA sequencing in the macroH2A-deficient tumors revealed increased infiltration of macrophages and cancer-associated fibroblasts (CAFs), along with decreased cytotoxic T cells. The CAFs were identified as a major source of inflammatory factors that contributed to the immunosuppressive environment. Mechanistically, macroH2A appeared to regulate chromatin looping and enhancer-promoter contacts at inflammatory gene loci in CAFs. The variability in macroH2A levels was also observed in human melanoma-derived CAFs, with lower levels correlating with higher secretion of inflammatory factors.

In summary, Dr. Bernstein and her team found that the histone variant macroH2A acts as a suppressor of inflammatory gene expression in CAFs within the melanoma tumor microenvironment. Its loss leads to chromatin remodeling, increased secretion of inflammatory factors, and an immunosuppressive environment that promotes tumor growth.

Decoding the Tumor Microenvironment: Tertiary Lymphoid Structures as Enhancers of Immunotherapy Effectiveness

Currently available immunotherapies have limited effectiveness, explained Victor Engelhard, University of Virginia. “One of the things that we may not have focused on adequately as a



Victor Engelhard, PhD — University of Virginia

Dr. Engelhard discussed the importance of tertiary lymphoid structures (TLS) within tumors and their role in enhancing immune response and the effectiveness of immunotherapies.

field is the role that the blood vessels in the tumor play in constraining the influx of any kind of immune cell that could mediate effective tumor control.” He discussed the importance of tertiary lymphoid structures (TLS) within tumors and their role in enhancing immune response and the effectiveness of immunotherapies like checkpoint inhibitors. The presence of TLS in patient tumor samples are often associated with enhanced patient survival. TLS are like lymph nodes and contain B cells, T cells, and other immune cells organized together. The presence of TLS is often associated with improved patient survival, leading to the idea that inducing or augmenting their formation could be a potential immunotherapy approach.

His laboratory has identified cancer associated fibroblasts (CAFs) that drive the formation of TLS. These CAFs produce a protein called CXCL13, which attracts B cells to come together and form clusters. Production of CXCL13 causes the B cells to accumulate and group together in those areas, which is how the lymphoid structures are formed.

In addition, the CXCL13-expressing CAFs also produce cell adhesion molecules that facilitate interactions with immune cells, further supporting the formation and maintenance of TLS. Interestingly, the presence of TLS and the CXCL13-expressing CAFs appears to be influenced by the tumor microenvironment. TLS also play a vital role in mediating the response to checkpoint immunotherapies like anti-PD-1 and anti-CTLA-4 monotherapies or combinations. Furthermore, the absence of TLS resulted in a

diminished tumor control effect of immunotherapy, underscoring the crucial role of TLS in their efficacy.

In summary, CAFs within tumors play a key role in orchestrating the formation of TLS. These structures are critical for enhancing immune cell infiltration and promoting the antitumor effects of checkpoint inhibitor immunotherapies, highlighting the potential of targeting or manipulation of TLS as a therapeutic strategy. 🕒





Yardena Samuels, PhD — The Weizmann Institute of Science

Supercharging T-Cell Responses Against Melanoma

Dr. Yardena Samuels, The Weizmann Institute of Science, delivered a keynote address at MRA's 2024 Scientific Retreat that discussed revisiting the neoantigen approach to immunotherapies. Neoantigens are unique peptides derived from mutations in cancer cells that can be recognized by the immune system as foreign. Dr. Samuels explained her work in identifying these neoantigens, particularly in cutaneous melanoma, with the goal of developing personalized immunotherapies. She highlighted the importance of neoantigens, stating, "We know that immune checkpoint inhibitors will not work unless these neoantigens are being presented [to immune cells]."

Collaborative efforts to establish a highly annotated cutaneous melanoma tumor bank have helped researchers to identify driver mutations and subsequently predict neoantigens. One approach used in her lab is computational analysis (bioinformatics) to predict specific neoantigens that might be present, based on the genetic mutations found through genomic sequencing of a patient's tumor, combined with information about the specific protein markers (human leukocyte antigens, or HLA types) that each patient's immune system is able to recognize.

"We know that immune checkpoint inhibitors will not work unless these neoantigens are being presented [to immune cells]."

DR. YARDENA SAMUELS



Linda Bradley, PhD — Sanford Burnham Prebys

Dr. Samuels also highlighted additional approaches to identify presented neoantigens using immunoproteomics, where major histocompatibility complex molecules from tumor cells are purified and the presented peptides were identified using mass spectrometry. It is crucial to identify neoantigens that: 1) can strongly activate the immune system against the tumor; 2) are caused by mutations that are fundamental drivers of that tumor; and 3) are present in all the tumor cells, not just some of them. Finding such high-quality, recurrent neoantigens across patients would allow development of more effective immunotherapies.

In addition to neoantigens, Dr. Samuels talked about the “dark matter” of peptides not yet identified or characterized. These unidentified peptides may come from non-standard ways that proteins are made (called non-canonical translation) or from other sources like bacteria. Dr. Samuels also discussed her team’s work in trying to make cancer cells display unique peptides that can be recognized by the immune system. She explained, “We wanted to see if we can induce the expression of aberrant peptides in a cancer-specific manner. That way, the cancer doesn’t tell us what to target, we tell the cancer what we want to target to make it more immunogenic.” To do this, they targeted part of the machinery that cells use to make proteins, specifically an enzyme called TYW2. Disrupting this enzyme caused errors in protein production by the tumor cells, leading the cells to produce unique abnormal peptides. The idea is that if tumor cells can be induced to display more of these peculiar peptides, it is easier for the immune system to recognize and attack them.

Overcoming Resistance to Checkpoint Blockade Therapies

Dr. Linda Bradley, Sanford Burnham Prebys, shared research her lab has been conducting on a protein called P-selectin glycoprotein 1 (PSGL-1) and its potential role in overcoming resistance to immunotherapies like checkpoint blockade. PSGL-1 is normally an adhesion receptor, but it can also act as an immune checkpoint inhibitor in tumors. “We found another novel and atypical and very compelling function as an immune checkpoint... one of the earliest checkpoint inhibitors working in the T cells in the tumor microenvironment.” Studies in mouse models of melanoma showed that knocking out PSGL-1 prevented T-cell exhaustion, promoted T-cell function, and enabled tumor control. This was associated with much greater T-cell infiltration into tumors and increased production of cytokines like interferon-gamma that are important for killing cancer cells.

In mouse models, blocking PSGL-1 with antibodies enhanced antitumor immunity, even in tumors resistant to anti-PD-1 therapy (checkpoint blockade). “We found that we also could see significant [tumor] control.” This correlated with increased T-cell infiltration into tumors. The researchers are now developing human anti-PSGL-1 antibodies with the goal of testing them in combination with existing immunotherapies like anti-PD-1 in patients with melanoma. Preliminary data suggest that these antibodies can reinvigorate exhausted human T cells. “We are now ready to study the impact of our antibodies [on patient T cells]. We are looking for the capacity




Vijay Kuchroo, PhD — Harvard University

[of the antibodies] to reactivate exhausted T cells.” PSGL-1 is a promising new immunotherapy target that could help overcome resistance to current checkpoint blockade drugs by preventing T-cell exhaustion in the tumor microenvironment.

Checkpoint Inhibitors and T-Cell Exhaustion

Dr. Vijay Kuchroo, Harvard University, discussed the role of checkpoint molecules in antitumor immunity. Checkpoint molecules are proteins on the surface of immune cells that act as “brakes” or “stop signs” to prevent the immune system from becoming too activated and attacking the body’s own healthy cells. Dr. Kuchroo’s research focuses on understanding how checkpoint molecules, such as PD-1, CTLA-4, and TIM-3, are expressed on tumor-infiltrating T cells, leading to their exhaustion and inability to fight against the tumor. He emphasized that these checkpoint molecules are co-expressed as a module, rather than individually, suggesting the need to block multiple checkpoints for effective antitumor immunity.

Although new immunotherapy drugs that block co-inhibitory receptors like CTLA-4 and PD-1 have revolutionized melanoma treatment, the number of patients who respond to these treatments is still low. Discovering novel co-inhibitory receptors and understanding the immune cells they impact could lead to more effective combination therapies that boost the body’s anticancer immune response. In this regard, another checkpoint molecule called TIGIT is expressed on T cells and is part of the module. TIGIT plays a crucial role in modulating immune responses in cancer, with TIGIT-expressing regulatory T cells potentially directing cancer progression through their interactions with cancer cells. 

Upcoming Melanoma Research Funding Opportunities

\$40 Million Available from the Congressionally Directed Medical Research Programs

Dr. Amie Bunker, Melanoma Research Program, Congressionally Directed Medical Research Programs, provided information about anticipated funding opportunities for fiscal year 2024 that will become available once the federal budget is approved. They anticipate offering five different award mechanisms in the 2024 Melanoma Research Program, including the **Idea Award** for new and exciting ideas. There is also the **Melanoma Academy Scholar Award** for early career investigators within 7 years of their first faculty appointment. A new **Survivorship and Patient Wellness Research Award** aims to support research to improve the quality of life for patients, survivors, and their families and caregivers by supporting research in areas like treatment side effects, lifestyle factors, and psychosocial issues. The **Team Science Award** funds two to three investigators looking to tackle multidisciplinary projects that require collaboration. Finally, the **Focus Program**

Award – Rare Melanomas supports funding specifically for research on rare melanoma subtypes with the goal of understanding and addressing challenges specific to these subtypes.

Dr. Bunker encouraged researchers to sign up to receive program-related news and notifications when the funding opportunities are released (ebrap.org/eBRAP/public/index.htm). More details can be found on the Melanoma Research Program website (cdmrp.health.mil/pubs/press/2024/24mrppreann). The various awards reflect the program’s vision “to prevent melanoma initiation and progression and reduce hardship of melanoma on the patients and survivors and their family members,” said Bunker.



(L to R): Suzanne Topalian, MD — Johns Hopkins Medicine, Joan Levy, PhD — Melanoma Research Alliance & Rodabe Amaria, MD — MD Anderson Cancer Center

Industry Roundtable: Neoadjuvant Studies as Drug Development Launchpads

The melanoma treatment landscape has been transformed by the advent of novel systemic therapies, such as BRAF/MEK inhibitors that target specific molecular pathways, as well as immunotherapies like immune checkpoint inhibitors. These drugs were first tested and approved for use in patients with unresectable, metastatic melanoma that were not candidates for surgery. They were next evaluated in patients with an earlier stage melanoma that could be surgically removed and delivered systemically after surgery to reduce the risk of recurrence (known as the adjuvant setting, or post-surgery setting) with recent approval of several of these drugs for adjuvant use.

Now, researchers are studying delivering drugs before surgery in patients whose melanoma can be removed (i.e., the neoadjuvant setting). The standard goal of any neoadjuvant treatment is to shrink a tumor to make surgery less invasive and more effective; however, in the case of immune-based therapies, a major aim is to mount a more effective systemic immune response against the tumor before it is removed. Furthermore, tumor samples obtained from patients before, during, and after neoadjuvant treatment (longitudinal sample collection) can be used to identify new targets for drug development as well as biomarkers to predict response and resistance to different therapies. To address the growing

“We’ve seen the field of neoadjuvant therapy explode to the point where we have had a lot of great success, but still have unanswered questions and work to do.”

DR. RODABE AMARIA

interest in the use of neoadjuvant treatment, the Melanoma Research Alliance (MRA) convened a roundtable discussion of approximately 35 representatives from industry, academia, and the US Food and Drug Administration (FDA) during the 2024 Scientific Retreat, which was co-chaired by Dr. Rodabe Amaria, The University of Texas MD Anderson Cancer Center, and Dr. Joan Levy, MRA.

Optimal Surgical Plan After Neoadjuvant Therapy

“We’ve definitely seen the field of neoadjuvant therapy for melanoma explode to the point where we have had a lot of great success but still have unanswered questions and work to do,” said Dr. Amaria. “We are not like breast cancer with large numbers of patients for neoadjuvant therapy; the patient population we are first exploring for neoadjuvant use in melanoma, clinical Stage 3 patients, is small.” Initial neoadjuvant trials showed that BRAF and MEK inhibitors can work in patients whose tumors have BRAF mutations, and those who achieve a pathologic complete response (defined as lack of any viable melanoma left in a biopsy after surgery) do best. However, with newer immunotherapy treatments, even patients with less than 50% viable tumor left (called a pathologic partial response) can have good long-term outcomes.

Based on the extent of pathological response, it is important to determine whether surgery is needed after neoadjuvant treatment. Dr. Charlotte Ariyan, Memorial Sloan Kettering Cancer Center, suggested that additional clinical trial data would be informative. Some patients with one involved lymph node that has completely responded to neoadjuvant therapy may not need surgery. However, if multiple nodes were initially involved, even if they all shrink, surgery may still be warranted because residual disease could remain.

Melanoma is unique in that neoadjuvant therapy is being administered in patients with stage 3 lymph node metastases — whereas in other cancers neoadjuvant therapy is used to treat the primary tumor. Thus, the decision of whether surgery is still needed after an excellent response to neoadjuvant systemic therapy cannot be compared to what is known for other cancer types and is still under investigation. Dr. Michael Lowe, Emory University, commented “I think the onus is on us as a surgical community to determine whether or not we collectively agree, and if we’re willing to put the effort into doing a randomized trial to answer the question when surgery is not needed.” Many

Melanoma is unique in that neoadjuvant therapy is being administered in patients with stage 3 lymph node metastases.

patients agree that they would like to have less surgery and being able to avoid additional surgery is appealing.

The other consideration about surgery is whether the melanoma field has selected the optimal time for surgery after the start of neoadjuvant therapy. Dr. Suzanne Topalian, Johns Hopkins University School of Medicine stated, “I think with surgical resection we are just looking at the specimen we remove as a snapshot in time. The timing of surgery has been anywhere from three to nine weeks after starting neoadjuvant therapy and we do not know if a pathologic partial response would have evolved into a pathologic complete response with longer neoadjuvant treatment”.

Considerations for Post-Surgical Adjuvant Treatment Plans

Panelists agreed that for pathologic non-responders of neoadjuvant treatment — patients whose tumors do not respond to the treatment with over 50% viable tumor found at time of surgery — there is a clear need for postoperative treatment.

(L to R): Priya Nagarajan, MD – MD Anderson Cancer Center, Michael Lowe, MD — Emory University



But for those with a partial response short of a major/complete response, the optimal post-surgical management is unclear. Going forward, larger trials with designs that randomize patients based on their degree of pathologic response may be needed to better define specific subgroups that need adjuvant therapy after neoadjuvant treatment and surgery. Adding complication is that if a patient has more than one site of melanoma, there may be differences between the sites of tumor with respect to pathologic response after neoadjuvant therapy, i.e. certain tumor sites may show a complete response while other sites show no response — indicating the presence of varying tumor “clones” of melanoma that are affected by neoadjuvant treatment differently. Dr. Priya Nagarajan from The University of Texas MD Anderson Cancer Center explained why it is important to study this effect. “The clone of viable tumors that did not respond may have the answers that we’re looking for. This clone needs to be genomically sequenced to find why it became resistant to the neoadjuvant treatment.” Dr. Amaria added, “You must report out all outcomes which will be highly helpful in judging response, and then perform translational research to understand and learn from these differences.”

Increasing Access to Data

Dr. Omid Hamid, The Angeles Clinic & Research Institute, A Cedars Sinai Affiliate, Los Angeles, noted that access to tissue samples and blood from large neoadjuvant clinical trials is often restricted or nonexistent. This prevents researchers from using already collected data from pivotal clinical trials to answer some of the unknown questions. A central repository could provide

(L to R): Giri Ramsingh, MD – Obsidian Therapeutics, Christian Blank, MD — Netherlands Cancer Institute, Marc Hurlbert, PhD – MRA



access to valuable pooled data and tissue, and requests for these resources can be used to answer very focused questions. Dr. Amaria added that it is very possible to have a centralized digital repository as all the pathology slides can be scanned and uploaded. As Dr. Levy noted, “This idea of a centralized pooled resource for the community is a place that foundations like the MRA can act as the neutral third party in coordinating the building of these resources.” Dr. Clemens Krepler, Merck, agreed and added that starting with a repository for scanned images makes a lot of sense and is where digital pathology and the application of artificial intelligence (AI) and machine learning can play a big role.

Alternative Endpoints

The importance of pathologic assessment of response and its standardization represents clear challenges to overcome. Dr. Christian Blank, Netherlands Cancer Institute, encouraged, “We should think about other assessments like the disappearance of circulating tumor DNA (ctDNA) in the blood as another type of measurement of response, that is independent of the personal view of a pathologist.” However, this assay is not yet sensitive and reliable enough to be used instead of assessment of response by a pathologist. Panelists agreed that the use of ctDNA should be achievable within a few years as the sensitivity of the test improves.

“From my experience in lung cancer treatment, assessing pathologic complete response can be challenging,” said Dr. Drew Pardoll, Johns Hopkins University. There are two key issues: 1) concern about missing small traces of remaining tumor when a patient is believed to have a complete pathologic response; and 2) the need for thorough evaluation of all tissue sections to determine if there is any viable tumor, which is extremely time-consuming and labor-intensive. To overcome these challenges, some groups are working on using AI to analyze pathology samples.

Industry perspectives acknowledged the challenges in designing trials and obtaining regulatory approval based on neoadjuvant studies. Dr. Krepler first mentioned that the strategy for neoadjuvant studies most often is a pure ‘signal finding’ study to evaluate new combination approaches in this setting with the quick endpoint of pathologic complete response. He reminded attendees that for large randomized registrational clinical trials (trials that determine whether a drug should be approved for standard use), the FDA uses other endpoints, such as Overall Survival and Event Free Survival, to evaluate the benefit of a



Asha Das, MD - U.S. Food & Drug Administration

treatment which would require enrollment of a lot of melanoma patients that are difficult to find for the neoadjuvant setting. Dr. Karl Lewis, Regeneron, added that another unknown part of the regulatory pathway for neoadjuvant studies is the selection of the appropriate standard treatment to use to compare the drug under investigation. Dr. Amaria emphasized that there is an appetite for industry to do neoadjuvant trials, but a critical need for future conversations with and guidance from the FDA to shed light on how neoadjuvant trials should be conducted for regulatory approval.

The Value of Analyzing Samples Collected from Neoadjuvant Studies

The importance of translational research and biomarker analysis was emphasized, with experts highlighting the need for funding and infrastructure to support these efforts. “Funding is critically needed to obtain tissue biopsies from melanoma patients, both before and during treatment”, stated Elizabeth Burton, The University of Texas MD Anderson Cancer Center. While stored tissue samples can provide some insights, the true power lies in analyzing how the tumor changes over time in response to different treatments. And funding is required not only to collect baseline and on-treatment biopsies, but also to analyze the samples and gain insights into treatment combinations and mechanisms of response.

Dr. Pardoll stated that recent neoadjuvant studies in lung and head and neck cancer have identified several promising new targets or drug combinations with existing agents that could be quickly tested. New genomic technologies like single-cell transcriptional profiling analysis have been revolutionary in this identification as more cells can be analyzed using this technology,



(L to R): Clemens Krepler, MD - Merck and Suzanne Topalian, MD — Johns Hopkins Medicine

resulting in more insights gained, especially for understudied immune cell types surrounding the tumor.

Dr. Genevieve Boland, Massachusetts General Hospital, added that analyzing tumor samples from neoadjuvant trials is incredibly valuable. These patients have not received prior treatments, so their tumor biology is relatively “clean” and has not been muddied by previous therapies. Neoadjuvant trials provide an opportunity to deeply study the underlying tumor characteristics and mechanisms before they become too convoluted by prior treatments. This knowledge can help prioritize or deprioritize certain therapeutic approaches and inform the development of next-generation therapies.

Dr. Levy added that the MRA is looking at ways to facilitate collaborations between academic investigators and industry partners to advance testing novel combinations in the neoadjuvant setting. The MRA has issued requests for proposals to perform biomarker analyses from neoadjuvant trials and co-funded grants with other foundations interested in doing similar work. Going forward, the MRA is considering issuing a request for proposals for a well-designed neoadjuvant study of novel drug combinations that includes using state of the art technologies for sample analysis. In addition, there is interest in establishing a centralized resource to make pathology slides, data, and tissue samples from neoadjuvant trials more widely available. While challenging to implement, having a centralized repository could be a valuable resource.

Overall, the discussion highlighted the potential of neoadjuvant therapy in melanoma but also underscored the need for further research, standardization, and collaboration between academia, industry, and regulatory bodies to overcome the challenges and fully realize its potential benefits. ☉



(L to R): Omid Hamid, MD — The Angeles Clinic & Research Institute, Rajan Kulkarni, MD, PhD — Oregon Health & Science University, Charlotte Ariyan, MD, PhD — Memorial Sloan Kettering Cancer Center, & Harriet Kluger, MD — Yale School of Medicine

Navigating Melanoma’s Continuum with Dermatology, Surgery, Oncology, and Survivorship Strategies

Melanoma management is extraordinarily complex, particularly with regard to the complexity of adjuvant/neoadjuvant decision making. Other concerns include the need for multidisciplinary collaboration, long-term toxicity data, and improved patient education and support, especially in community settings.

A panel of experts was convened during MRA’s 2024 Scientific Retreat to discuss some of these complexities. Dr. Omid Hamid, The Angeles Clinic & Research Institute, A Cedars Sinai Affiliate, Los Angeles moderated the panel, which included: Dr. Rajan Kulkarni, Oregon Health and Science University; Dr. Charlotte Ariyan, Memorial Sloan Kettering Cancer Center; Dr. Harriet Kluger, Yale School of Medicine; and Dr. Rachel Vogel, University of Minnesota.

The Changing Treatment Paradigm

The panelists discussed the complex decision-making process around adjuvant and neoadjuvant therapy for patients with melanoma. Dr. Kluger spends a significant amount of time discussing treatment options with patients eligible for adjuvant

Melanoma management is extraordinarily complex, especially with adjuvant/neoadjuvant decision making.



(L to R): Omid Hamid, MD — The Angeles Clinic & Research Institute, Rajan Kulkarni, MD, PhD — Oregon Health & Science University, Charlotte Ariyan, MD, PhD — Memorial Sloan Kettering Cancer Center, Harriet Kluger, MD — Yale School of Medicine, & Rachel Vogel, PhD — University of Minnesota

or neoadjuvant therapy, because the decision is complicated: “I actually spend more time nowadays on patients who are candidates for adjuvant therapy or neoadjuvant therapy than the patients that have metastatic disease. For a new diagnosis of metastatic disease, it’s pretty clear what we need to do, whereas the adjuvant or neoadjuvant remain quite a conundrum.” There is a lack of long-term survival data for patients treated in the adjuvant or neoadjuvant setting, and some may not need treatment as they are surgically cured, leading to unnecessary toxicities: “We still don’t have data on the long-term survival for patients. We are treating a lot of patients who may not need treatment beyond surgery, and we are inducing some long-term toxicities that some of these young folks are going to live with forever.” The discussion about treatment starts early, even during the initial consultation with a surgical oncologist, explained Dr. Ariyan.

The dermatologist can also play a role in initiating the treatment conversation and helping decide next steps, including ordering genomic tests, although their utility is still being further refined in clinical studies. While there is potential for these genomic tests to provide useful information, there are limited data about how to effectively utilize the results from testing. Some of the tests are based on only a few genes and their validity is still being established. As Dr. Kulkarni mentioned, “There is potential to utilize genomic profiling, but there’s also limited data in terms of what we can actually utilize that information for in clinical

decision making. Some of [the tests] are based upon only a few genes, for example, and ... they’re not well validated.”

Individualized Decision Making and Supportive Care

“Early-stage survivors still experience a lot of issues and concerns both physical and emotional,” said Dr. Vogel. The field of oncology still has work to do in understanding each individual patient’s needs and ensuring consistent messaging about their identity as a [melanoma] survivor from all providers involved in their care, including dermatologists, surgeons, medical oncologists, and primary care physicians.

Making treatment decisions around adjuvant and neoadjuvant therapy for melanoma is a very individualized process, given the complexity involved. Dr. Kluger stated, “I find that because it’s so complicated, the vast majority of patients will say, ‘Well, what would you do if I were your family member?’ and then we’re essentially giving our own opinion, and we’re making it quite personal.” Rather than strongly pushing one way, she aims to present an unbiased view: “So what I say to my patients is, I think in this case you could choose to go either way. These are the advantages. These are the disadvantages. At the end of the day, it’s your decision.”

When discussing supportive care, panelist discussed how major medical centers typically offer programs which brings together

an interdisciplinary team that can include doctors, nurses, social workers, psychologists, and other specialties. Such a holistic approach can be an important part of the overall treatment plan for a patient. When to provide detailed information to a patient about the various aspects of care for melanoma depends on the individual's readiness and needs, explained Dr. Vogel: "The appropriate time is going to depend on the person. So, some people, as soon as they hear the word cancer, have no idea what you said after that. And it takes another visit or two for that information to be heard. Other people are information seekers, and so they want that information all right away."

Addressing potential barriers like transportation and missed work is crucial to ensure patients can attend follow-up visits and receive support care: "Are we losing people during that process because of social barriers?" said Dr. Vogel. While supportive care colleagues at major centers understand the nuances, there are gaps in the community setting. Counseling should focus on aligning treatment with the patient's personal values. A patient's dermatologist can also play an ongoing role, especially for lower-risk individuals because they need to follow up with the same provider every 6 months.

The Future of Melanoma Treatment

This conversation revolved around the future of melanoma treatment, with a focus on early-stage disease, survivorship, and the challenges that come with new therapies. The panelists discussed the need for better prognostic markers, an understanding of the biological potential of early melanoma, and determination of when treatment is necessary. One of the key areas highlighted was the lack of understanding about the long-term effects of different drugs and combinations, including their impact on quality of life, fertility, and other aspects of survivorship. Dr. Vogel commented: "I think what's really important for our research moving forward is incorporating patients in all the steps of research, and that keeps us really grounded in the survivorship long-term phase. And the other piece that I've been really wanting to think through is, how do we break down those barriers to getting survivorship care? I think that it is really important in our understanding of the long-term effects of these different therapies and combinations." Panelists noted that there is a lack of large, pooled clinical trial data that can provide insight into how melanoma treatments not only impact the course of melanoma itself, but also the overall quality of life of patients over the long-term. There is also a personal toll on patients from having to come in for appointments and imaging very frequently in addition to the financial burden of

“Early-stage survivors still experience a lot of issues and concerns both physical and emotional.”

DR. RACHEL VOGEL

numerous visits and testing. While some patients appreciate the close monitoring and care, for others, this high frequency of appointments and testing is disruptive and intrusive in their daily lives.

The panelists also discussed the potential for over-treatment. Sometimes melanoma treatments are too aggressive and may cause severe side effects that can negatively impact a quality of life. Some therapies can result in lifelong toxicity or side effects for the patient. There is a need to look at patient imaging and blood tests together in a coordinated way to understand the long-term impacts of melanoma treatment. Developing a database and focusing research in this area could be an important way to move forward.

The panelists agreed that disseminating the latest knowledge and best practices for melanoma treatment outside of major academic medical centers is challenging. It is important to continue having conversations and sharing information about the best identified practices for managing melanoma patients, so that community doctors outside of major centers can stay up to date. The conversation touched on the need for better collaboration between different specialties, including medical oncology, surgical oncology, and dermatology. There was also a discussion about the role of survivorship clinics and the importance of long-term follow up, even for patients who have been disease-free for several years.

The potential role of social media and other platforms in educating patients and providing them with accurate information also was discussed. However, the panelists expressed concerns about the risks associated with physicians engaging on social media and the need for proper training and guidelines.

Throughout the conversation, there was a strong emphasis on the importance of involving patients in research, breaking down barriers to care, and improving communication and collaboration between different specialties to provide the best possible care for patients with melanoma. ○

The MRA Melanoma > Exchange Patient and Advocate Forum

MRA's **Melanoma Exchange Patient and Advocate Forum**, held in-person in Washington DC and virtually on February 21, 2024, brought together hundreds of melanoma patients, survivors, advocates, and their loved ones to provide lay-friendly, state-of-the-science education, promote collaboration and networking across the melanoma community.

The forum brought 650 people together for the in-person and simulcast program. Participants left with practical tips and strategies to get the most out of their care while navigating the challenges of melanoma diagnosis, treatment, and beyond.

Videos from the 2024 Melanoma Exchange Patient and Advocate Forum are available at CureMelanoma.org/Forum



Eugene Semenov, MD, MA — Massachusetts General Hospital

Melanoma Unraveled: Decoding Individual Risk, Amplifying Awareness, and Pursuing Precision

In recent years, the rate of new melanomas has risen worldwide, but research advancements and improved treatments have fortunately led to declining mortality. Understanding individual risk factors beyond the well-known risks of UV exposure is crucial for enhancing prevention and early detection efforts. This article explores the perspectives of leading experts on key melanoma risk factors, innovative public awareness campaigns, and the importance of accurate diagnosis and staging in increasing early detection and further reducing deaths due to melanoma.

Exploring Risk Factors

Dr. Yevgeniy (“Eugene”) Semenov, a dermatologist at Massachusetts General Hospital, stated that he and other dermatologists are invested in answering the question “how do we prevent melanoma from occurring in the first place?” During Dr. Semenov’s presentation at MRA’s 2024 **Melanoma > Exchange Patient Forum** he focused on risk factors for melanoma beyond exposure to UV rays, the latter being extensively covered and well-known to most patients.

Moles

First, Dr. Semenov talked about moles as a risk factor. He mentioned that atypical or dysplastic moles can increase your melanoma risk. “If an individual has 5 or more [atypical moles], it’s almost a tenfold higher risk by comparison to those who don’t have

Dr. Eugene Semenov’s presentation focused on risk factors beyond exposure to UV rays.

“There’s a 75% lifetime risk of melanoma among those who used tanning beds before age 35.”

DR. EUGENE SEMENOV

any atypical moles.” He showed examples of what atypical moles look like — irregular borders, variations in color, and larger-than-typical moles. In addition, the total number of moles an individual has also matters. Dr. Semenov shared that “patients with more than 100 moles had nearly a seven-fold increased risk of developing melanoma by comparison to patients who had 15 moles or fewer.”

Skin Phototype

One’s skin type and ability to tan, also known as phototype, is another major factor that influences their risk of developing melanoma. For example, a person with Type 1 phototype cannot tan without burning, while a person with Type 4 phototype typically has olive or moderate brown skin that tans easily and burns minimally. He explained that “Type 1 patients have about a six-to-seven-fold increased risk of developing melanoma than a patient with Type 4.” This means that people with very fair skin that burns easily have a much higher melanoma risk. Blistering sunburns — especially during childhood — increase melanoma risk, particularly for those with a history of more than five sunburns.

Age & Family History

As people age, their melanoma risk increases, too. Dr. Semenov noted that “the peak incidence of melanoma actually occurs among individuals 75 years [and] older.” Another major risk factor is having a close family member with melanoma, especially multiple relatives. He said, “if you have two or more first-degree relatives [with] melanoma... that person gets pretty close to 20 [times increased risk].” This suggests a genetic predisposition.

UV Exposure

As is widely known, exposure to UV radiation, like excessive sun exposure or tanning beds, also elevates risk. Experts believe that 90% of melanomas are caused by overexposure

to UV radiation. There’s “a 75% lifetime risk of melanoma among those who used tanning beds before age 35.” It is also important to point out that UV exposure is cumulative and that you can’t undo damage that has already occurred.

Personal History of Cancer and Other Conditions

Having a history of precancerous or cancerous conditions, such as leukemia, non-melanoma skin cancers like basal cell carcinoma or squamous cell carcinoma, actinic keratosis (precancerous skin lesions), or a previous melanoma, significantly increases an individual’s risk of developing melanoma in the future. Some other notable risk factors mentioned were having had childhood cancer and organ transplants that required immunosuppressive drugs. People living with HIV/AIDS are also at increased risk of melanoma.

Be sure to let your doctor or dermatologist know if you have a history of any of these conditions.

Occupational Risks

Certain occupational exposures increase risk, such as being a firefighter or a pilot. Firefighters’ increased risk “is thought to not be because they’re getting more sun, but they’re inhaling or coming in contact with carcinogens, and one of these is polychlorinated biphenyls (PCBs).” It has been reported that PCB exposure causes an increased risk of developing cutaneous melanoma. Pilots and airline cabin crew have increased risk because “at 9,000 meters, which is the average cruising altitude for airplanes, the exposure to UVA is about two-fold [higher than at ground level].”

Socioeconomic Status

People with lower socioeconomic status who develop melanoma have a higher risk of mortality due to factors like reduced access to health care and clinical information, which often is related to delayed diagnosis and poorer prognoses. “Ultimately these individuals tend to be diagnosed with more advanced-stage disease, when melanoma is harder to treat,” said Dr. Semenov.

Dr. Semenov closed by describing work about predicting an individual’s personalized melanoma risk using advanced computer modeling and specific risk factors. The goal is to “triage the right patient to be seen by the right provider early on” for melanoma screening and prevention.

Increasing Public Awareness

Later, during MRA's 2024 Scientific Retreat, Dr. Sancy Leachman, Oregon Health Sciences University, discussed a public health campaign she pioneered in Oregon aimed at increasing early detection of melanoma. The hypothesis for the campaign was that a statewide early detection educational program that tailors methods and content to both health care providers and the public more broadly could improve knowledge, attitudes, and behavior; ultimately reducing death and costs related to melanoma.

The War on Melanoma (www.ohsu.edu/war-on-melanoma) campaign is a comprehensive, multi-pronged effort to educate various populations in Oregon about melanoma and encourage regular skin checks. The main component was a campaign with videos, radio ads, TV commercials, billboards, and social media targeted at the 4.2 million Oregonians. "Melanoma is the deadliest form of skin cancer but has a 99% survival rate when caught and treated early, but that drops to 30% when caught late," said Dr. Leachman. "Melanoma stands out, it's the cancer you can spot and stop with your own eyes." The campaign delivered over 154 million media impressions across the state. Social media campaigns promoting self-skin examinations are most effective when they combine educational content with confidence-boosting activities that increase people's intentions to perform self-exams.

Separate educational efforts targeted distinct groups involved in melanoma detection and care. A curriculum was developed

for people in the skin service industry, such as hairdressers and tattoo artists, more than 1,200 of whom completed the training program. For primary care providers who diagnose most melanomas, newsletters were sent out, conferences held, and over 800 providers used the campaign toolkit. This included more than 100 rural health practices that will soon be expanded through a partnership with the Oregon Health Authority and Centers for Disease Control and Prevention.

For melanoma experts such as dermatologists, an imaging and technology center was created to train providers on advanced diagnostic tools and facilitate telemedicine for remote populations. Dr. Leachman's team developed an e-visit system that allows patients to send images of skin areas to their doctor for review, minimizing delays in scheduling or avoiding in-person visits (this was especially important during the height of the COVID-19 pandemic). The researchers deployed a new tool using a dermatoscope attachment on a smartphone that can provide higher-quality images for telemedicine, reducing the need for follow-up appointments by about 50%.

Dr. Leachman believes the War on Melanoma efforts are paying off, because data showed that Oregon went from having the 6th highest incidence of melanoma in the United States in 2012 to the 21st in 2019. More impressively, the state's mortality from melanoma ranking dropped from 11th to 31st over the same period. While these preliminary findings are exciting, the team continues to monitor the impact of the War on Melanoma campaign. One unexpected early



Data showed that Oregon went from having the 6th highest incidence of melanoma in the United States in 2012 to the 21st in 2019 and mortality from melanoma ranking dropped from 11th to 31st over the same period.

“One of the aspects of high-quality melanoma treatment is to never trust the diagnosis, try to reassess everything.”

DR. REINHARD DUMMER



Reinhard Dummer, MD — University Hospital Zurich

finding, however, was that the team observed costs of melanoma treatment in Oregon increased to \$128 million from 2012 to 2021, in part because of the high costs for immunotherapy drugs.

Dr. Leachman expressed optimism about innovative technologies on the horizon that combine imaging, molecular screening, and artificial intelligence to enhance early detection. She cited a patient quote as inspiration: “Together, we can eliminate melanoma as a cause of death.”

The Importance of Accurate Diagnosis

Dr. Reinhard Dummer, University Hospital Zurich, discussed the importance of accurate diagnosis and staging in melanoma treatment. He emphasized the need to question and reevaluate initial diagnoses, stating “one of the aspects of high-quality melanoma treatment is to never trust the diagnosis, try to reassess everything.” He provided an example of a suspicious lesion that initially appeared concerning but was determined to be benign after molecular testing.

Dr. Dummer highlighted the heterogeneity of melanocytic lesions, with some being benign despite carrying mutations in genes like BRAF, which can cause melanoma cells to grow and divide uncontrollably, making it an important target for certain treatments. He stressed the significance of obtaining the correct diagnosis because it guides appropriate treatment and follow-up. “If we have the right diagnosis, we have to do the right staging procedures. And after that, if a patient has a high-risk situation, we are able to deliver therapies that can have an impact on the outcome.”

Regarding prognostic tests that can help inform treatment decisions or monitor recurrence, Dr. Dummer expressed optimism about these prognostic tests in the future. However, he noted some current skepticism about their reliability for treatment decisions as the tests today still need additional prospective testing in clinical studies. “Unfortunately, these tests are not yet currently investigated in a prospective way that you really can trust.”

He acknowledged the potential value of biomarkers in predicting treatment outcomes but emphasized their limitations today in guiding treatment decisions. “These biomarkers are most of the time prognostic so may identify patients who are at higher risk of disease progression. There are hardly any that are predictive, and they are not yet mature to make treatment decisions,” stated Dr. Dummer. He encouraged further research to identify crucial and reliable biomarkers. Overall, he emphasized the importance of accurate diagnosis, appropriate staging, and the need for more research to develop reliable predictive biomarkers to guide personalized melanoma treatment decisions.



J.B. Ward, PhD — Melanoma Patient Advocate

Scanxiety: Understanding, Managing, & Thriving Beyond the Fear

Undergoing medical scans can be an incredibly stressful experience for patients and their loved ones. The anxiety surrounding these procedures, referred to as “scan anxiety,” or more often “scanxiety,” encompasses a range of worries and fears about the scanning process itself as well as the potential results and what they might mean for one’s health. This overwhelming sense of distress can manifest in various ways, both physical and psychological, impacting a person before, during, and after scans. By shedding light on this phenomenon from a patient’s perspective, J.B. Ward, a psychologist and melanoma survivor herself, delved into the multifaceted nature of scanxiety, offering insights into its triggers, coping strategies, and the importance of self-compassion and open communication in navigating this challenging experience.

Coping with “Scanxiety”: A Patient’s Perspective

“Some people describe it as a physical feeling of distress that can occur before, during, and after a scan,” said Dr. Ward. A recent study looked at all the different parts of scanxiety to better understand it and found that worries about the actual scan procedures themselves, such as unfamiliar equipment, claustrophobia, physical discomfort, and radiation exposure, are common. However, concerns about the scan results and what they might mean often loom larger, according

“Until you actually feel and allow yourself to have compassion for yourself and others, it can be very challenging to improve your experience.”

J.B. WARD



2024 MRA Patient Forum Participants

Having a plan before, during, and after your scan can help you better prepare for it emotionally, mentally, and socially.

to Dr. Ward: “It’s more about the results themselves, and the uncertainty and change that might come as a result of the findings.”

Importantly, it’s not just the patient who experiences scanxiety. As Dr. Ward pointed out, “It’s also caregivers, or really anybody in your life ... my family members experienced it.” Just the act of waiting and wondering can cause loved ones to feel anxious, too. Scanxiety can happen at any point — weeks or even a month before the scan, the day of, during the procedure itself, or even after getting the results. And it feels different for everyone. It’s “not just fear” but can involve physical symptoms such as increases in heart rate, psychological distress like nervousness, and racing thoughts. The important thing is recognizing your own personal experiences with scanxiety.

Tips and Tools to Manage Scanxiety

Dr. Ward highlighted that scanxiety is a valid experience that shouldn’t be dismissed. “Self-compassion” in accepting these feelings as normal is key: “Until you actually feel and allow yourself to have compassion for yourself and others, it can be very challenging to improve your experience.”

Reflecting on your own personal triggers and timing of anxiety can also help. “If you take a moment to self-reflect and ask

questions about what is particularly challenging for you, you may be able to use that to help inform a plan,” she advised. Quoting Dr. Leslie Waltke, oncology physical therapist and creator of patient resource the Recovery Room, Dr. Ward explained that the goal is to “make it suck less” through compassionate self-awareness and proactive coping.

Self-advocacy involves putting self-compassion into practice by taking steps to make positive changes for yourself, which can be extremely difficult, even though we often advocate for others. Dr. Ward shared that we’re good at helping others but doing things for ourselves can be really tough — even when those things would improve our well-being. Letting yourself take steps to make positive changes for your own sake may require overcoming major obstacles.

Strategies for Managing Scanxiety

Information about how to manage scanxiety is limited. However, from the available research, several themes emerge. Using multiple approaches like distraction and education may be more effective than one technique alone.

Dr. Ward outlined four key areas to focus on to feel more grounded: mind, body, existential/spiritual, and self-compassion. Each person may struggle in different domains. She said,

“Everybody’s different so you really need to look at your own experience to see what is challenging for you.”

“Self-advocacy involves actively managing your thoughts and finding what works best for you when dealing with medical issues. Writing things down can help get thoughts out and prepare for appointments.” Others find personal rituals or superstitions comforting, Dr. Ward said, “At a certain point, my husband was not allowed to come to my appointments anymore. My sister came, and ever since then, things were great.” Some patients prefer to access any test results in advance, using their electronic medical record before going to the doctor’s office, “so that they have time to process and come up with questions.” But others need to be right there in the room with their provider when they get those results, or else their panic is at an all-time high. “The key is knowing yourself and what works for you when advocating for your needs.”

Reinforcing social support, although difficult, can be beneficial: “Support comes from kind words ... or people offering to help around the house.” And “these people may also be experiencing [your] same scanxiety.” Self-reflection about physical changes, worries, and fears is important, too. Dr. Ward suggested that digging into and identifying these difficult feelings can help produce a plan, although the process can be tough.

Dr. Ward shared Dr. Leslie Waltke’s YouTube channel resource called “Recovery Room,” and a video called “Coping with Scanxiety.” The resource highlights “having a before-scan plan” to prepare physically, mentally, and socially, such as “scheduling lunch with your friend” or “a relaxing massage.” Then have “a distraction plan” right before the scan that includes things like “taking someone with you in the waiting room, walking the halls, using music and videos.” Finally, create a post-scan plan by asking the medical team how you will be getting your results and potentially making changes to it, such as walking over to a different room and picking up the results early. As Dr. Ward stated, the key is “making the plan around actually obtaining the results and knowing [the plan] ... so that you can advocate for something that would work best for you.”

Visualization can also be a helpful technique during medical scans or moments of intense anxiety. If you feel out of control in those situations, visualizing a particular scenario or outcome can provide a sense of control. Engaging the mind through visualization allows you to direct your thoughts in a positive way during the scan or when anxiety spikes.

Positive thinking is not just an attitude, but a discipline that requires consistent effort and continuous learning over time. It involves “work” and is an “active” process of diligently training your mindset, rather than just trying to passively adopt a positive attitude.

For some people, combining a mantra with spirituality can be beneficial. Mantras, which involve mentally repeating a phrase or thought, can be very helpful when experiencing recurring thoughts or anxiety. The practice of using a spiritual mantra works well in various situations and settings.

Communication with Friends and Family

Communication and planning on how to share information with family and friends are important for managing scanxiety. As Dr. Ward shared, “We had to come up with a game plan because people were texting me ... and it was actually upsetting to me when I was getting these texts while I was actively working to distract myself.” Having an open conversation helped everyone understand her needs and that she would let family know the specific day and time that she would get the results and then call them afterwards. “Just having that understanding of when and what the results are going to be like, and how those will be communicated was helpful for everybody.”

When to Seek Help

It’s important to know when to seek help from a professional or counseling support group. Dr. Ward recommended getting assistance “if you notice that scans are getting in the way of your life” or “if you’re having a hard time coming up with a plan to deal with it.” Help should also be sought “if you’re making decisions that might not be recommended for you to do based on your medical care” or “if you’re having concerns about the procedure itself that are problematic.” Many clinics have people on staff who can help with scanxiety. “Large medical centers will have easy referrals to professionals that they know who can help with these things.” Dr. Ward suggested a few online resources such as Findhelp (www.findhelp.org) and CancerCare (cancer.org). Another option is to check your health plan for mental health providers that are in-network. Local cancer organizations often have resources as well. “It’s great to have someone else to talk to and to help come up with an individual plan to manage scanxiety,” concluded Dr. Ward. ☺



(L to R): Chris White, Colleen Wittoesch, and Leah Adams — Melanoma Advocates

Breaking Barriers: Demystifying Clinical Trials

Clinical trials in melanoma are critical in testing new therapies and treatment combinations with the aim of improving outcomes for patients. At the Melanoma Research Alliance’s **2024 Melanoma > Exchange Patient Forum**, in a session moderated by Dr. Janice Mehnert of NYU Langone, patient advocates shed light on the risks and benefits associated with participating in clinical trials, underscoring the courage of patients who enroll and contribute to driving scientific progress.

Throughout their discussion, the panel addressed common concerns and barriers faced by patients, such as side effects, financial constraints, and accessibility issues. They also discussed motivating factors that inspire patients to participate in clinical trials, as well as strategies for overcoming misconceptions and advocating for oneself throughout a clinical trial journey.

The Transformative Power of Clinical Trials

To get the conversation going, Dr. Mehnert stated that research as a treatment option is no longer a last resort, and that now more than ever it should be discussed as part of a patient’s initial diagnosis. She noted, however, that financial toxicity as well as access to clinical trials were barriers for many patients. She also explained the different phases of clinical trials, noting that “Phase 1 trials have really changed over the years to actual studies that can help bring the drug to market.” She stated that

Research as a treatment option is no longer a last resort, and it should be discussed as part of a patient’s initial diagnosis.

Phase 2 studies look more closely at efficacy signals, and Phase 3 trials compare the novel treatment with standard of care.

When discussing risks and benefits of trials, Dr. Mehnert acknowledged “whenever you’re trying something new, there’s an element of risk.” She praised the “bravery” of patients who participate in clinical research, as their involvement moves science forward. Through several patient stories Dr. Mehnert illustrated how clinical trial access can be empowering and allow those who participate to have extra months or years with loved ones. However, there can be significant barriers for patients to enroll in clinical trials. She stressed that “timing, advocacy, and just the power of having someone who’s going to push that rock uphill” is often key in overcoming challenges, like insurance denials.

While clinical trials always have risks, they provide critical access to promising new therapies. As Dr. Mehnert concluded, behind every major research advancement is “a whole army” of doctors, research staff, and brave patients working together to drive progress.

Learning From the Patient Experience

“If there was no research, there would be no treatments,” said Leah Adams, melanoma patient advocate and caregiver. She was diagnosed with Stage 1 melanoma, and not long after, her father was diagnosed with metastatic melanoma. Because there was a known family history of melanoma on her father’s side, Adams and her father enrolled in a study at their cancer center to examine the role of genetics in melanoma. Recently her father enrolled in another study looking into brain necrosis (the death of cells in an organ or tissue) after radiation treatment for brain metastases, which sometimes is mistaken for disease progression on scans. Adams explained that she and her mother encouraged her father to participate because “if it weren’t for us participating in this clinical research, we wouldn’t get this profound data that is showing so much promise and hope, ultimately bringing us closer to a cure for melanoma.”

Colleen Wittoesch, also a patient advocate on the panel agreed: “I have faith in the researchers who dedicate decades to their studies ... and I’m sitting here today because of that.” She enrolled in a Phase 2 clinical trial to treat her brain metastases that had spread from melanoma of no known primary origin. She explained that she was motivated to participate not just to save her own life, but to advance research for future patients: “I



Janice Mehnert, MD — NYU Langone Health

knew if we could get through the clinical trial, that we’d have the data that the researchers could use.” Wittoesch formed a close relationship with her care team, seeing them as partners: “I’m helping them as they’re helping me.” Though she experienced toxicity due to the treatment, her brain metastases responded, allowing her to extend her participation in the trial. She encourages patients to view clinical trials as a valid treatment option rather than a last resort, noting that she had alternatives but chose the trial. Wittoesch advocated for improving accessibility, because few patients who are eligible actually enroll in a clinical trial due in part to barriers like cost and travel.

Chris White, a mucosal melanoma patient advocate, mentioned that self-advocating can also be important to get access to clinical trials. Because he had brain metastases, it was a struggle for him to enroll in a trial of tumor-infiltrating lymphocyte (TIL) therapy (TILs are a type of immune cell that can recognize and kill cancer cells). Patients with brain metastases are often excluded from clinical trials, a barrier that is slowly starting to change as more investigators and pharmaceutical companies recognize the clear unmet need facing these patients. White emphasized the need to ask questions throughout the cancer journey, even though you may not know all the right questions at the start: “You don’t know what you need to know, until you need to know it.” White shared that he learned over time to ask about costs, side effects, and clinical trial options up front. He encouraged patients to engage with their medical team early and often as partners.

Addressing Questions and Concerns

“When I went in to discuss the trial, the first thing I asked about was, of course, finances — what was going to be covered, and



(L to R): Leah Adams, Janice Mehnert, MD, Colleen Wittoesch, and Chris White

“I have faith in the researchers who dedicate decades to their studies ... and I’m sitting here today because of that.”

COLLEEN WITTOESCH

what was not,” stated Wittoesch. She shared that the biggest barrier to participating was getting insurance coverage. Other concerns, such as side effects, were discussed with her care team and they reassured her they had options to manage them should they arise. “I was open and ready to use any type of research that was out there, because I knew my diagnosis was pretty bad. So, I was ready to take the risk.” For Wittoesch, a clinical trial was the only way to access new drugs to treat her disease that were not publicly available.

White shared that one of his concerns was about how this new type of T cell immunotherapy — TIL therapy — works. His doctor’s simple explanation about the way cells from his tumor would be harvested and used to fight his melanoma helped him understand the treatment protocol. Other concerns were about insurance, trial location and travel, length of hospital stay, and logistics of getting the therapy. White said he asked his doctors “anything that you could possibly think of when you have to leave town for a month” to prepare for the treatment and hospital stay. He also asked about other survivors’ experiences and their specific melanoma subtype to learn about what to expect. He wanted to know specifics about what kinds of clothes to pack, and if he could bring items from home, like blankets and pillows, to make his hospital stay more comfortable.

Overcoming Misconceptions About Clinical Trials

Wittoesch said that there are misconceptions about clinical trials being just for the drug companies’ benefit, but they are really focused on helping patients. It’s important for patients to

advocate for themselves and not be afraid to ask questions: “You have to be your own advocate, empower yourself,” she said. Her experience was that clinical trial staff were very responsive to questions or concerns: “I think there needs to be constant education, so that people aren’t always looking at this with fear.”

Dr. Mehnert commented that the patients enrolled in clinical trials receive a great deal of attention from trial care team members simply because of the need for frequent interactions, testing, and monitoring. As a result, there is more patient/doctor/clinical staff interaction and patients get extra attention, which is hugely beneficial for them. She also encouraged patients to seek a second opinion at a National Cancer Institute (NCI) designated cancer center from clinical experts who can provide additional advice and perspectives, so patients feel that they are making the most informed decisions.

Motivating Factors

All of the patients agreed that family was a huge motivating factor for participating in a clinical trial. White was in his 30s and had a strong will to live. “Every single FDA approved treatment at one point in time was first tested in clinical trials, it always has to start somewhere,” added Adams. Without volunteers, there would be no new treatments for melanoma, and it is important to contribute to the future so that every patient has access to the best treatment. “If not for brave individuals that are willing to put themselves out there and enroll in clinical research or clinical trials, we would not have come this far over the last 15 years,” she stated. ○



**Agendas, Participants,
and Sponsors**

2024 Scientific Retreat Agenda

FEBRUARY 21 – 24, WASHINGTON DC

Wednesday, February 21

- 7:30am-5:00pm Grant Review Committee Meeting (by invitation)
- 12:00-5:30pm **Melanoma Patients, Advocates & Foundations Forum**
Stephanie Kauffman, MRA President & Chief Operating Officer
Cody Barnett, MRA Senior Director of Communications and Engagement and MRA Patient, Advocates and Foundations Forum Chair
- 4:00-8:00pm Retreat Registration open
- 5:30-6:00pm Sponsor Toast/Reception
- 6:00-7:30pm Opening Reception

Thursday, February 22

- 6:30am-6:00pm Registration
- 7:30-8:45am General Breakfast
- 7:30-8:45am Young Investigators Breakfast (by invitation): **How to Work with Industry**
Gideon Bollag, Opna Bio
Crystina Bronk, Mural Oncology
J. Silvio Gutkind, UC San Diego
Clemens Krepler, Merck
Poulikos Poulikakos, Icahn School of Medicine at Mount Sinai
- 8:45-9:00am **Opening Remarks Day 1**
Marc Hurlbert, MRA CEO
Leah Adams, Patient Advocate
Kellie Cereceres, Patient Advocate
Joan Levy, MRA CSO
- 9:00-9:30am **Keynote Lecture 1: Patrick Hwu, Moffitt Cancer Center**
Next generation T cell therapy for melanoma
- 9:30-10:35am **Scientific Session 1: Adoptive Cell Therapies**
Chair: Leyuan Ma, University of Pennsylvania
- 9:30-9:55am Anusha Kalbasi, Stanford University
IL13Ra Chimeric Antigen Receptor (CAR) T cells for metastatic melanoma

- 9:33-10:15am Navin Varadarajan, University of Houston
Metabolic plasticity of T-cell therapies: multi-omic profiling of interacting human tumor-infiltrating lymphocytes and autologous tumor cells
- 10:15-10:35am **Cristina Puig-Saus, UCLA**
Engineering a potent T cell response against solid tumors
- 10:35-10:45am **Break**
- 10:45-11:50am **Scientific Session 2: Enhancing T cell Responses**
Chair: **Jamie Spangler, Johns Hopkins University**
- 10:45-11:10am **Linda Bradley, Sanford Burnham Prebys**
Advancing immune checkpoint inhibition of PSGL-1 for treatment of melanoma
- 11:10-11:30am **Vijay Kuchroo, Harvard University**
Checkpoint molecules, Tregs and induction of anti-tumor immunity
- 11:30-11:40am **Amie Bunker, Program Manager, Melanoma Research Program (MRP) CDMRP**
Congressionally Directed Medical Research Programs (CDMRP) Melanoma Research Program grant announcements
- 11:40-11:45am **Transition to lunch: Tanisha Jackson, MRA Scientific Program Director**
- 11:45pm-1:20pm **Networking Lunch and General Roundtables**
1. Acral + Mucosal Melanoma Patient Registry
 2. In transit melanoma
 3. Biomarkers — ‘liquid biopsy’ ctDNA, and tumor biomarkers
 4. irAE — understanding immune-related adverse events
 5. Brain metastasis, leptomeningeal disease, and tumor dormancy
 6. Microbiome
 7. Cell based therapy (CAR-T, NK cells, TILs)
 8. Neoadjuvant and adjuvant therapy
 9. Clinical trials — patient recruitment and decentralized trials
 10. Prevention (primary prevention)
 11. Diversity — Women & Underrepresented groups in melanoma research & care
 12. Targets & drug discovery for new treatments
 13. Early Detection & Diagnosis (AI, imaging, machine learning)
 14. Tumor microenvironment
 15. Genomics — Role of genetics, genomics & epigenetics; single cell technologies
 16. Uveal melanoma
 17. Vaccines and intralesional therapies
 18. Microbiome
- 1:20-2:45pm **Scientific Session 3: Metastatic Melanoma and In-Transit Disease**
Chair: **Zachary Buchwald, Emory University**
- 1:20-1:45pm **Michael Davies, University of Texas, MD Anderson Cancer Center**
Melanoma CNS metastases — Progress, challenges, and opportunities

- 1:45-2:05pm Georgia Beasley, Duke University
Findings from the in-transit metastatic melanoma consortium
- 2:05-2:25pm David Liu, Dana Farber Cancer Center
Tumor and immune evolution in in-transit melanomas
- 2:30-3:00pm Break
- 3:00-3:40pm **Scientific Session 4: Advances in Melanoma Detection and Diagnostics**
Moderator: Marc Hurlbert
- Sancy Leachman, Oregon Health Sciences University
 - Reinhard Dummer, University Hospital Zurich
- 3:45-5:00pm **Scientific Session 5: Highlighting MRA Young Investigator Awardees**
Chair: Vito Rebecca, Johns Hopkins University
- Rare Melanomas
- 3:45-4:00pm Priya Nagarajan, The University of Texas, MD Anderson Cancer Center
Male genitourinary melanoma: Pilot analysis of clinicopathologic, genomic, transcriptomic features and tumor-infiltrating lymphocytic infiltrate
- 4:00-4:15pm Kasey Coutts, University of Colorado
Epigenetic regulation of mucosal melanoma immunity
- Novel Therapies
- 4:15-4:30pm Liron Bar-Peled, Massachusetts General Hospital
An 'omics approach to melanoma drug discovery
- 4:30-4:45pm Teresa Davoli, New York University
Investigating the role of copy number alterations in cancer immune evasion
- 4:45-5:00pm Jeffrey Ishizuka, Yale School of Medicine
Activating dsRNA sensing in melanoma to overcome immunotherapy resistance
- 5:00-5:05pm **Closing Remarks Day 1:** Nicholas Starink, MRA Senior Associate, Registry and Grants Program
- 5:15-6:45pm **Poster Session Reception** (Dermatology Fellows, Young Investigators, Pilots and Sponsors)
Light refreshments; all retreat attendees encouraged to attend
- 7:00-10:00pm **Dinner** Succotash, 915 F St. NW, Washington, DC 20004 (*Pre-registration and ticket required*)

Friday, February 23

- 6:30-10:00am Registration open
- 7:30-9:00am General Breakfast
- 7:00-8:50am **Industry Roundtable Breakfast** (by invitation only)
- 9:00-9:05am **Opening Remarks Day 2:** Tanisha Jackson, MRA Scientific Program Director
- 9:05-9:35am **Keynote Lecture 2:** Yardena Samuels, The Weizmann Institute of Science
Revisiting the neoantigen approach to cancer immunotherapy

- 9:35-11:20am Scientific Session 6: The Tumor Microenvironment**
Chair: **Feng Liu-Smith**, University of Tennessee Health Science Center
- 9:35-10:00am** **Yochai Wolf**, The Sheba Fund for Health Service and Research
mRNA-based re-programming of terminally differentiated TILs
- 10:00-10:20am** **Andrew White**, Cornell University
Ccr2+ monocyte-derived macrophages influence trajectories of acquired therapy resistance
- 10:20-10:40am Break**
- 10:40-11:00am** **Emily Bernstein**, Icahn School of Medicine at Mount Sinai
Histone variant regulation of the melanoma microenvironment
- 11:00-11:20am** **Victor Engelhard**, University of Virginia
Formation and function of tertiary lymphoid structures in melanoma
- 11:20-11:25am** **Introduction of Closing Panel:** **Joan Levy**, MRA Chief Scientific Officer
- 11:25-12:30pm** **Closing Panel: Disease Management Across the Continuum: Dermatology, Surgery, Oncology, and Survivorship**
Moderator: **Omid Hamid**, Cedars-Sinai, The Angeles Clinic and Research Institute
- Dermatologist: **Rajan Kulkarni**, Oregon Health and Science University
 - Surgery: **Charlotte Ariyan**, Memorial Sloan Kettering Cancer Center
 - Oncology: **Harriet Kluger**, Yale School of Medicine
 - Survivorship: **Rachel Vogel**, University of Minnesota
- 12:30-12:35pm** **Closing Remarks:** **Stephanie Kauffman**, MRA President and COO
- 12:35-1:30pm** **Lunch and Departures**

Melanoma > Exchange

Patient & Advocate Forum Agenda

FEBRUARY 21, 2024

- 11:30-11:45 am **Registration & Check In***
- 11:45-1:00 pm **Networking Roundtables with Lunch***
- 1:00-1:10 pm **Welcome Remarks**
Stephanie Kauffman – President & COO, Melanoma Research Alliance, MRA
Cody Barnett, MPH – Senior Director of Comms & Patient Engagement, MRA
- 1:10-1:55 pm **The Melanoma Standard of Care & Emerging Research**
The melanoma treatment landscape has dramatically changed in the last decade. This talk will give participants a shared foundation and will ground the full program.
Sapna Patel, MD – MD Anderson Cancer Center
- 1:55-2:50pm **Leaving No Patient Behind: Current Research Challenges**
We’re making incredible progress in melanoma research, but it isn’t all smooth sailing. Hear from experts in the field about key challenges facing patients, clinicians, & researchers alike.
Alex Shoustari, MD – Memorial Sloan Kettering Cancer Center
Janice Mehnert, MD – New York University Perlmutter Cancer Center
Michael Davies, MD – MD Anderson Cancer Center
Moderator: Sapna Patel, MD – MD Anderson Cancer Center
- 2:50-3:20pm **Scanxiety: Understanding, Managing, & Thriving Beyond the Fear**
Learn tips and strategies to mitigate and manage the emotional and psychological impacts of upcoming exams, scans, or other anxiety inducing hurdles that are all too often part of a melanoma journey.
J.B. Ward, PhD – Patient Advocate, Psychologist, & Fine Artist
- 3:20-4:20pm **Breaking Barriers: Demystifying Clinical Trials**
Gain valuable first-hand insight into what clinical trials are, how they operate, and possible benefits and risks from this enlightening panel.
Leah Adams – Patient Advocate
Chris White – Patient Advocate
Colleen Wittoesch – Patient Advocate
Moderator: Janice Mehnert, MD – New York University Perlmutter Cancer Center

- 4:20-4:50pm **Understanding Melanoma Risk: Going Beyond UV**
We know that about 90% of melanomas are caused by UV exposure, but what about those other 10%?
Are there genetic risk factors to consider too?
Eugene Semenov, MD – Massachusetts General Hospital
- 4:50-5:50pm **Panel Discussion: Living with Melanoma**
Get tips and strategies from this diverse panel of people who have all been impacted by melanoma.
Trena Brown – Patient Advocate
Camille Price – Patient Advocate
Elizabeth McGowan – Patient Advocate
James Skelton – Patient Advocate
Moderator: Cody Barnett, MPH – Melanoma Research Alliance
- 5:50-6:00pm **Closing & Wrap-up**
- 6:00-7:30pm **Patient, Advocate, & Researcher Reception***

Download Meeting Materials:



Scan the QR code or visit
CureMelanoma.org/Forum-Materials

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