TEN YEARS OF ACCELERATING CURES:
Highlights from the Melanoma Research Alliance 10th Annual Scientific Retreat
# CONTENTS

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Letter from Chief Science Officer and Scientific Program Director</td>
<td>02</td>
</tr>
<tr>
<td>Future Challenges In Melanoma</td>
<td>03</td>
</tr>
<tr>
<td>Optimizing the Use of Immunotherapy</td>
<td>07</td>
</tr>
<tr>
<td>MRA Researchers Exploring a Diversity of Treatment Strategies</td>
<td>09</td>
</tr>
<tr>
<td>Tackling Brain Metastases</td>
<td>11</td>
</tr>
<tr>
<td>Applying Artificial Intelligence to Melanoma Detection</td>
<td>13</td>
</tr>
<tr>
<td>Maintaining the Pace of Melanoma Innovation in the Era of an Evolving Standard of Care</td>
<td>14</td>
</tr>
<tr>
<td>Agenda</td>
<td>15</td>
</tr>
<tr>
<td>Participant List</td>
<td>19</td>
</tr>
<tr>
<td>Retreat Sponsors</td>
<td>30</td>
</tr>
</tbody>
</table>
For the Melanoma Research Alliance (MRA), promoting collaboration and conversation among key stakeholders in the melanoma community is central to our mission. One way MRA achieves this is through our Annual Scientific Retreat, which this year was held February 28-March 2, 2018, in Washington, D.C, and marked the tenth anniversary of this important gathering. This invitation-only, think-tank style conference brings together nearly 300 academic investigators, pharmaceutical and biotech representatives, government officials, donors, and patient advocates.

At MRA's Tenth Annual Scientific Retreat, participants heard about the latest discoveries in melanoma prevention, diagnosis, and treatment, many of which are being made by MRA-funded investigators. They also learned firsthand from individuals personally affected by melanoma and discussed ways in which the different sectors of the melanoma community can work together to ensure the momentum of the past decade of discoveries and treatment approvals continues.

Presentations and panel discussions touched on a variety of topics, spanning early discovery research to the latest changes in clinical practice. Researchers provided new insights into how melanoma metastasizes, including identifying new therapeutic targets. They also discussed factors that may influence whether patients will respond to immunotherapy, which include such things as the composition of a patient's gut microbiome. Other highlights included recent practice changing results that emerged in the past year that impact patients with later stage, surgically removable melanoma. Together, the presentations highlighted the incredible progress of the past decade and illuminated the path forward so that all melanoma patients may have an effective therapy.

The Scientific Retreat also featured several satellite sessions, including the Young Investigators' Breakfast and the Industry Roundtable, which engaged participants in conversations around effective collaboration and maintaining the rapid pace of progress in preventing, diagnosing, and treating melanoma, respectively. A group of melanoma patient advocates also gathered to learn from one another and to hear updates on the latest science from leading melanoma researchers.

We at MRA are delighted to host such important and productive conversations. We know they will spur the next wave of progress and lead to a day when suffering and death from melanoma will be a thing of the past.

Sincerely,

Louise M. Perkins, Ph.D.  
Chief Science Officer

Kristen L. Mueller, Ph.D.  
Scientific Program Director
FUTURE CHALLENGES IN MELANOMA
Ten years ago when Samantha Stinchcomb’s father was diagnosed with advanced melanoma, his doctor told his family there was little that they could do to save his life. He died a few years later. “Fewer patients and their families are being told that anymore,” Samantha told the audience at the 10th Annual Melanoma Research Alliance Scientific Retreat held in Washington, DC, February 28-March 2, 2018.

This theme of progress against the backdrop of future challenges echoed throughout the 10th Annual Retreat. From the opening lecture by Dr. Suzanne Topalian on “A Decade of Progress in Melanoma” to the Industry Roundtable that focused on “Maintaining the Pace of Melanoma Innovation in the Era of an Evolving Standard of Care” – successes and remaining challenges were put in focus.

In the opening lecture, Topalian, of Johns Hopkins University, summed up the advancements saying “this is head-spinning progress.” Ten years ago, advanced melanoma patients only had three treatment options, and none of them were that effective. Now, in contrast, there are 11 FDA-approved therapies for this same group of patients and about half of these people experience substantial benefit.

But Topalian and several other clinicians were quick to point out, that while the glass is half full, it is also half empty. In short – too many patients with metastatic melanoma still die from this cancer. Over half of patients with cutaneous melanoma either fail to respond or relapse early, despite receiving the latest treatments. Moreover it is still particularly dangerous for patients with ocular, acral, or other rare forms of melanoma, for whom current treatments are not usually as effective as they are for the more common cutaneous melanomas that arise on sun-exposed parts of the skin. “There are still pockets of need that have to be addressed,” noted Dr. Jedd Wolchok of Memorial Sloan Kettering Cancer Center.

At this gathering of 300 of the best and brightest melanoma clinicians, researchers, advocates and other keys stakeholders, much of the discussion focused on what needs to be done next to cure melanoma and “put MRA out of business as soon as possible,” as MRA co-founder Debra Black succinctly puts it. Ideas were plentiful; including furthering our understanding of the biology of rare, hard-to-treat melanoma subtypes and the tumor microenvironment, which contains a variety of cell types that can impact on whether a therapy will work, as well as developing better ways to predict which patients are likely to respond to which treatments. Improving the understanding and treatment of drug resistance also continues to be a major focus of research, along with determining which drugs to combine to best treat melanoma patients.

Participants also stressed the importance of pursuing earlier-stage treatment avenues that are currently gaining momentum in the clinic. One is treating patients with high risk, but surgically removable melanomas, with various therapies to reduce the risk of melanoma coming back (adjuvant therapy). Some therapies, such as interferon, ipilimumab, nivolumab and combination Dabrafenib and Trametinib, are already approved in the adjuvant setting, and other treatments have shown promising results in recent clinical trials. A second, related strategy, called neoadjuvant therapy, involves treating melanoma patients to reduce the presence of cancer prior to removing their tumors surgically.
Early clinical results for neoadjuvant therapy show real promise; however, no neoadjuvant therapies are currently FDA-approved. Given the game-changing nature of these approaches, experts stressed the importance of designing clinical trials and studies in a way that reveal how the drugs are working in melanoma and the surrounding cellular environments. This could be critical information to improve the way we treat melanoma for all patients.

**When Should Patients Stop Treatment?**

Another concept that generated buzz among participants was when and how to stop drug therapy for melanoma patients. For example, the immunotherapy drugs nivolumab and pembrolizumab are given to patients until disease progression or unacceptable side effects develop. With infusions required every 2-4 weeks depending on the dose and drug, this is a substantial burden, especially for those patients who respond long-term. Put bluntly, researchers just don’t know how long these drugs need to be taken to be most effective. Dr. Patrick Hwu of the MD Anderson Cancer Center stressed that stopping such treatments should be accompanied by surveillance for early recurrence of melanoma, but also noted that we need better, noninvasive methods to detect recurrence. One promising way to do this might be to use a test for melanoma tumor DNA circulating in the blood, known as liquid biopsies. An early clinical test of this in colon cancer enabled doctors to detect a recurrence up to 6 months prior to the cancer being seen in a scan. In addition, Topalian, Wolchok, and Dr. Georgina Long of the University of Sydney stressed the need to research whether periodic ‘booster’ treatments would improve the long-term effectiveness of melanoma drugs, particularly within the context of immunotherapies.

**Aligning Basic and Clinical Research**

Dr. Richard Marais of Cancer Research UK Manchester Institute pointed out that the fast pace of melanoma research requires frequent interaction between basic and clinical researchers. He noted that the laboratory work delineating the molecular pathways that drive melanoma led us to targeted therapies known as BRAF and MEK inhibitors and immunotherapies, and suggest ways to overcome treatment resistance. Marais stressed the continued need to understand the basic biology of melanoma and its treatments, and for basic biology researchers to explore answers to questions that are relevant to clinicians. “An amazing MRA achievement has been to create a community where basic and clinical researchers can meet. The discussions we’ve had here will continue at other meetings,” Marais said. As MRA President and CEO Michael Kaplan stressed in his closing statement at the retreat, “We take seriously the word ‘Alliance’ in MRA’s name.”

**Collaborating for Success**

The need for ever more collaboration among multiple sectors was stressed by all types of stakeholders, including representatives from industry and the federal government, as well as by academic researchers and patients. Drs. Richard Pazdur and Marc Theoret of the FDA noted the collaborations their agency fostered so that several cancer biomarkers or drugs from multiple companies can be tested concurrently in the same clinical study. The FDA has also begun interacting with drug companies earlier in the drug development process to ensure drug sponsors collect the information needed for regulatory decisions.

Several industry participants noted the numerous studies already underway in which drug companies are collaborating with each other to clinically test combination therapies, and Dr. Elad Sharon from the National Cancer Institute (NCI) noted that his agency works closely with the FDA and pharmaceutical companies to make sure government-sponsored trials are innovative and not duplicating what industry can do on its own. “There is an unprecedented level of collaboration now,” Pazdur noted, but added “everyone has their own favorite drug that they want to test.” He suggested NCI could help ensure that the most promising combinations are entering clinical trials.

“We need to break down the commercial barriers so we can get the molecules together that will give us the best outcome,” said Long, and she along with Dr. Caroline Robert of Institut Gustave Roussy added the importance of sharing data in order to streamline the development of drugs and biomarker tests that would help physicians give the right treatment to the right patient.
Designing Clinical Trials of the Future

The FDA along with academic and industry scientists are working hand-in-hand to ensure that clinical trials are producing the highest quality data possible while balancing the need to get lifesaving treatments to the people who need them the most as quickly as possible. The FDA has demonstrated its willingness to be flexible in the types of data and studies it will accept for its approval of new cancer drugs so as to speed the entry of new effective treatments into the clinic. According to Pazdur: “It used to be that you had to present data from a randomized, controlled trial or go home, but that’s no longer the case.”

In clinical trials, an endpoint is the primary outcome that is being measured. In oncology, this is often a comparison of the duration of patient survival or length of time before progression using the experimental therapy compared to those using the standard of care. Several researchers advocated for the need to develop additional endpoints in clinical trials to determine if a treatment is effective. These could be patient-reported outcomes, circulating tumor markers or a measure of tumor cells in tissue samples removed during surgery or biopsy. Such expanded definitions of success will further accelerate the development of new melanoma treatments.

Most clinical trials set strict eligibility criteria in order to minimize the effect of other factors that could obscure the effect of the experimental drug. However, strict criteria restrict patient enrollment, limit access to the experimental therapy, and may make trial results less generalizable to real-world patient populations. For example, about half of late-stage melanoma patients have brain metastases however people with brain metastases have been historically excluded from most studies. Several researchers advocated for adopting modernized clinical trial eligibility criteria to include these groups and others to both speed drug development and provide better insight into efficacy and side-effects earlier.

Bringing Research Home

When Samantha Stinchcomb’s father died in 2010, she thought the chapter of her life that intersected with melanoma was over. Sadly, that has not been the case. Far too often, said Stinchcomb, she leaves her dermatologist’s office in tears because of the numerous precancerous moles detected on her skin that will later need to be removed. She is comforted by the incredible progress being made in the treatment of late-stage disease, but knows that more work is needed to ensure the end of suffering and death due to melanoma once and for all. “Research to end melanoma sounds good to me. Your work means more tomorrows,” said Stinchcomb.

“Research to end melanoma sounds good to me. Your work means more tomorrows”
Perhaps the decade’s greatest achievement in melanoma treatment has been the FDA approval of cancer immunotherapy treatments called checkpoint inhibitors. This class of drugs include ipilimumab, nivolumab and pembrolizumab. These therapies harness the power of the immune system to fend off disease – including melanoma. Many patients treated with these drugs experience durable responses, and in a fraction of patients experts suspect the drugs are curative.

Predicting Response and Recurrence

While immunotherapy has been an incredible advance, there is still room for improvement. For example, only about half of patients with advanced melanoma respond to these treatments, and in some cases, patients may not see their tumors start to shrink until several months after starting therapy. This is problematic because some patients with advanced disease have widespread and bulky tumors. In addition, immunotherapy can sometimes trigger serious, and at times irreversible, autoimmune conditions such as thyroid dysfunction or diabetes. Researchers do not yet understand why some people develop these side effects and others do not. This is especially important as physicians increasingly turn to adjuvant immunotherapy for early-stage melanoma patients, where a substantial fraction of patients may never experience a recurrence after their primary melanoma is removed.

“We’ve made tremendous progress in the treatment of cancer with immunotherapy, but responses aren’t universal and not always durable, so we need [better predictive] markers of response,” stressed Dr. Jennifer Wargo of MD Anderson Cancer Center.

To help understand which patients with advanced melanoma will benefit from immunotherapy, researchers are trying to identify molecular features – called biomarkers – in tumors or in the patient’s immune cells that can predict an effective response to treatment. For patients with early-stage melanoma, researchers are searching for biomarkers that indicate high recurrence risk. Several MRA-funded researchers reported on their groundbreaking efforts to find these biomarkers at the latest MRA scientific retreat.

To try to identify biomarkers that can predict risk of recurrence in Stage 2 or 3 surgically removable melanoma, Dr. Yvonne Saenger of Columbia University in New York City examined patients’ tumor samples. She discovered that a particular pattern of gene expression, as well as the presence of one type of immune cell, called a ‘killer’ T cell, and the absence of another, called a macrophage, were correlated with a greater likelihood of long-term survival. “We hope this will help patients decide whether they should get [adjuvant] immunotherapy after surgery,” Saenger said.

Melanoma at Single Cell Resolution

Dr. Ido Amit of the Weizmann Institute of Science in Israel presented his work using powerful new single cell sequencing and imaging technologies he developed to determine in fine detail the different immune cell subtypes within and surrounding tumors. “When we wanted to identify biomarkers of responders versus non-responders to treatment, we saw a complex zoo of many different types of immune cells and functions in tumor samples that current markers couldn’t describe,” he said when explaining why he developed these techniques. “The tumor microenvironment is extremely complex, yet understanding these cells and how
they change in patients is critical to identify new markers for rapid and effective tumor characterization, and identification of novel immune modulatory pathways.”

One of Amit’s technologies called ‘single cell RNA sequencing’ essentially provides a snapshot of all the genes expressed by an individual cell plucked from a tumor. The advantage of this technology is that it gives researchers a much more complete picture of the complex network of cells that make up a tumor and its surrounding tissue. So far, Amit has used his technique on tumor samples from 26 patients with melanoma and has uncovered “very dramatic differences between patients in the types of T cells seen in their tumors,” he said. His research identified specific populations of immune cells, some of which kill tumors and others that block the anti-tumor immune response. “Our single-cell technologies provide unprecedented opportunities to draw a more accurate picture of the various cell types and underlying tumor-immune interactions and response to therapies.”

Can the Microbiome Predict the Effectiveness of Immunotherapy?

Other promising treatment response biomarkers are not found on patients’ tumor or immune cells, but rather in the more than 100 trillion microbes that inhabit their bodies, especially those that reside in the gut. This ecosystem of microbes, collectively known as the human microbiome, has become a major focus of cancer research, as mounting evidence reveals it may alter our risk of developing various cancers and how a patient may respond to immunotherapies like pembrolizumab, nivolumab, and ipilimumab.

Dr. Thomas Gajewski of the University of Chicago found that certain bacteria living in the gut of melanoma patients were linked to patients’ ability to respond to immunotherapy targeting the PD-1 molecule. Could gut bacteria be a biomarker for response to immunotherapy in melanoma patients? “It’s certainly on par with other biomarkers enriching for responders,” Gajewski said, but added that, “The microbiome isn’t everything. Tumor mutation factors matter, and germline polymorphisms are also likely important. But it could be a better biomarker than mutational load and should be explored further and integrated with others.”

In mouse models, Gajewski found transferring the immune response-promoting bacteria to mice with melanoma via stool transplants improved their response to immunotherapy. This suggests that the microbiome may not only serve as a response biomarker, but that one day probiotics designed to contain ‘good’ bacteria may improve the treatment of patients who lack inflamed tumors.

In an independent set of related studies, Wargo found that the microbiome of patients with melanoma who responded to PD-1-targeting immunotherapy differed from those who did not. Like Gajewski, she also found that an abundance of certain bacteria in the gut correlated with a “hot” immune response to tumors, while a high abundance of other species linked to a “cold” response. Abundant Bifidobacterium species did not surface as a major indicator of response in Wargo’s studies, as it did in Gajewski’s research. But the microbial signature Wargo found that indicated an effective response to immunotherapy has also been reported by researchers studying patients with lung and kidney cancer treated with checkpoint inhibitors, Wargo noted. She and others are currently testing a number of strategies to see if they can improve responses to immunotherapies in melanoma and other cancer patients.

“Can we modulate the gut microbiome to enhance responses to immunotherapy? Yes! But that needs to be tested within a clinical trial,” Wargo stressed.
MRA RESEARCHERS EXPLORING A DIVERSITY OF TREATMENT STRATEGIES

Over the past 10 years, we have made tremendous strides in the treatment of melanoma, with 11 new treatments earning FDA approval. But less than half of patients respond to these treatments, meaning that the battle against melanoma is far from over and more treatments are desperately needed. MRA-funded researchers are pursuing promising new strategies - like blocking melanoma metastasis; finding new drug targets; or putting an old diabetes drug to work against melanoma – to better treat and ultimately cure melanoma.

Preventing Melanoma Spread

Dr. Marisol Soengas of the Spanish National Cancer Research Center is working on better understanding why some patients with melanoma see their cancer spread rapidly following surgery, while others don’t. Using genetically engineered mouse and zebrafish models, which enable live imaging of the early metastatic process as it unfolds, Soengas’ team discovered a protein called Midkine, which melanoma cells produce before they spread throughout the body. Midkine helps to roll out the welcome mat for metastatic tumor cells by making these sites ‘permissive’ locations where they can take up residence, essentially paving the way for metastasis. The more Midkine produced, the worse the prognosis for the patients.

Dr. Ashani Weeraratna of the Wistar Institute, a member of Soengas’ L’Oreal Paris – MRA team, explored the effects of aging on metastasis. To do this, she compared a type of skin cell called fibroblasts from people 25 to 35 years old with those from older individuals. She found that fibroblasts taken from older people produced an altered array of proteins that promoted metastasis. Proteins produced by these ‘aged’ fibroblasts instructed tumor cells to migrate to and colonize lymph nodes, and promoted the growth of blood vessels needed to support the growth of tumor cells at metastatic sites. Soengas and Weeraratna plan to test experimental drugs that target these and other metastasis-supporting molecules in clinical trials.

Blocking Tumor Escape

Dr. Kai Wucherpfennig of Dana-Farber Cancer Institute reported on his latest findings on MICA, a molecule found on the surface of stressed or damaged cells that signals to the immune system that these cells should be killed. Tumor cells are smart and shed MICA from their surface to evade death. In fact, patients who shed high amounts of MICA responded poorly to the immune checkpoint inhibitor ipilimumab, suggesting that shedding MICA helps melanoma evade the anti-tumor immune response. To overcome this, Wucherpfennig developed an antibody that inhibits MICA shedding by tumor cells. When Wucherpfennig tested the antibody in mice with melanoma, he found it reduced the number of lung and liver metastases. Wucherpfennig plans to start testing the antibody in patients with cancer within the next year, with the hopes it will enhance tumor killing by the immune system.

Adding Radiation Therapy to Enhance Checkpoint Blockade

Dr. Robert Vonderheide of the University of Pennsylvania’s Abramson Cancer Center explored a potential synergistic combination treatment for melanoma—radiation therapy followed by treatment with immunotherapy. Vonderheide was prompted to explore if radiation could jumpstart an immune response after a patient with advanced melanoma who did not respond to two different immunotherapy agents was given radiation therapy to relieve pain he was experiencing from a tumor in his chest. Strikingly, the patient entered a nearly complete remission, which is still ongoing more than 7 years later. Moreover, a small subset of patients experienced tumor regression in an early stage clinical trial testing the combination of radiotherapy and the FDA-approved immunotherapy ipilimumab, suggesting the promise of this combined approach.

Vonderheide and his colleagues next turned to mouse models to better understand how radiation therapy and immunotherapy synergize, and reveal potential causes of why this approach doesn’t work in all patients. For instance, when the researchers compared tumors that responded to the combination of radiotherapy and the CTLA-4 inhibitor ipilimumab to those that did not, they found high levels of a molecule called PD-L1 on the surface of non-responding tumor cells. Adding a PD-1 inhibitor, similar to nivolumab or pembrolizumab to ipilimumab and radiotherapy improved responses in mice. This suggests that a three-part combination may lead to improved responses in patients. "The bottom line is that three treatments—an anti-CTLA-4 drug, an anti-PD-L1 drug, and radiation all have different mechanisms of action so should be synergistic when combined," Vonderheide said. He and his colleagues are currently testing such combinations in multiple clinical trials.
Beyond BRAF Mutations

MRA-funded researchers are also actively pursuing new treatment strategies that focus on genetic changes in melanoma itself that go beyond BRAF genetic mutations. For example, another tumor-fueling alteration involves molecules that instead are involved in regulating gene activity and the production of proteins that affect tumor growth. There is mounting evidence that these gene-regulating “epigenetic” factors can play a major role in fomenting cancers and thus could be effective drug targets for melanoma.

Dr. Emily Bernstein of the Icahn School of Medicine at Mount Sinai reported on a new method for detecting epigenetic changes that promote tumors. Using this method, she discovered a protein called AMIGO2 that could serve as a novel drug target. Unlike BRAF and other genetic flaws that drive tumor growth, no mutations are found in the gene encoding AMIGO2 in melanoma. Instead, melanoma cells contain much higher amounts of the AMIGO2 protein compared to normal cells and this increased expression is essential for melanoma cell survival. AMIGO2 is a target of a group of experimental drugs called BET inhibitors that are currently being tested in clinical trials. “The epigenome is an important new area of biology and cancer that is very exciting and experimental drugs targeting it are rapidly moving into the clinic,” stressed Bernstein.

Reviving an Old Drug to Treat Melanoma

In contrast to Bernstein’s reports on newly devised drugs, Lewis Cantley of Weill Cornell Medical School reported on an old drug that may be put to a new use fighting melanoma. The drug phenformin was developed as a diabetes treatment and was abandoned after it proved too toxic in a small subgroup of patients. Recognizing that the molecular actions of phenformin might be useful in the treatment of melanoma, Cantley tested it in combination with FDA-approved targeted therapies for melanoma. He found the combination of phenformin and the BRAF inhibitor vemurafenib was synergistic in a BRAF mutant melanoma mouse model. Further, Cantley found that phenformin effectively killed melanoma cells with NRAS mutations in culture when it was combined with the FDA-approved MEK inhibitor trametinib. This is important because no therapies targeting NRAS-mutant melanoma have been FDA approved. Cantley also discovered that phenformin enhances PD1-targeting immunotherapies for melanoma in mouse models.

Cantley and colleagues Dr. Paul Chapman (Memorial Sloan Kettering), Dr. Jonathan Zippin (Weill Cornell Medicine) and Dr. Bin Zheng (Massachusetts General Hospital) are currently testing the safety of phenformin in combination with dabrafenib and trametinib in patients with melanoma. So far this study suggests phenformin can be safely given to patients at doses likely to be active in fighting their tumors. Cantley’s future analyses will assess the effects of phenformin on melanoma tumor biology and immune cell dynamics in patients with melanoma.

Collectively, these studies highlight how researchers are attacking melanoma on multiple fronts. By funding such groundbreaking work, MRA is driving critical discoveries toward the next generation of melanoma treatments.
Brain metastases (mets) are a frequent and often deadly problem in patients with advanced melanoma. Nearly 40% of patients with metastatic melanoma have brain mets at diagnosis, with an average survival of only 4 months, suggesting a crucial need for treatments that can rid the brain of these tumors.\textsuperscript{1,2} But new cancer treatments are rarely tested in patients with active brain mets. This is largely due to concerns about whether these patients will have side effects unique to brain mets, and poorer outcomes that may negatively weigh against otherwise positive clinical benefits. Another potential concern is whether the drugs will even penetrate the brain, which has a fortress-like ability to keep substances from entering it.

Fortunately, MRA-funded researchers are making headway in understanding brain mets and how to best treat them. Reporting from this exciting research frontier, three investigators at the 2018 MRA Scientific Retreat presented their findings on how the unique biology of the brain supports brain mets, what predicts whether brain mets will respond to treatment, and what new therapies might be especially effective at destroying these tumors.

Evaluating the Effectiveness of FDA-Approved Therapies in Treating Brain Mets

Because patients with brain mets are frequently excluded from clinical trials, clinicians do not fully understand how patients with brain mets respond to even FDA-approved drugs. To help overcome this, Dr. Michael Davies of the University of Texas MD Anderson Cancer Center studied the response of melanoma patients with brain mets to treatment with dabrafenib plus trametinib. This targeted therapy combination blocks specific proteins that fuel the growth of the approximately 50% of melanomas that contain mutations in the BRAF enzyme. The average progression-free survival of patients in the study was 11 months, approximately half the time of what patients without brain mets can expect who are given the same treatment. Notably, tumors in patients’ brains often progressed, while tumors outside the brain did not. “The treatment didn’t work as well in the brain as outside the brain,” stressed Davies, who was puzzled by this finding, and conducted two additional studies to find out why this was so.

These follow-up studies compared tumor biopsies taken from a patient’s brain mets and compared them to other tumor samples from the same patient. The research suggests that brain mets tend to have an overactive tumor-fueling growth pathway that is not directly targeted by dabrafenib and trametinib. Moreover, immune system profiling indicated weakened anti-tumor immunity in brain mets compared to those in other sites, suggesting that cancer immunotherapies may also be less effective in the brain. Altogether, Davies’ studies highlight the need for continued research to evaluate the effectiveness of already approved therapies in treating brain mets and reveal potential therapeutic vulnerabilities.

Whether immunotherapies can shrink melanoma brain mets, and what biomarkers relate to such an effect, is also an under-explored territory. In a small study reported by Dr. Lucia Jilaveanu of Yale University, pembrolizumab reduced the size of brain mets in approximately 25% of melanoma patients treated. This quarter of patients also experienced significant shrinkage in tumors located outside of the brain. Jilaveanu suspects that using combinations of treatments might improve the relatively low response rate, and that biomarkers may predict which patients will respond, allowing clinicians to target treatments to those patients.
Jilaveanu’s team then examined brain met samples removed from patients prior to treatment with pembrolizumab. Compared to patients whose disease progressed while on treatment, responders’s brain mets had higher numbers of tumor-fighting T cells, and their brain mets also produced more PD-L1 molecules, which is part of the molecular pathway targeted by pembrolizumab. She also found that patients with brain mets who responded to pembrolizumab experienced a reduction in the amount of edema, or excess fluid accumulating in their brains. Edema can be disruptive, and at times deadly, for patients with brain mets, and there was concern that immunotherapies might aggravate it. But at least in Jilaveanu’s study, this proved not to be the case. “This should lessen concerns of using these treatments in these patients,” she said.

Probing the Biology of Melanoma Brain Mets

Dr. Manuel Valiente of the Spanish National Cancer Research Center focuses his research on the cellular environment surrounding brain mets in an effort to understand how this ‘tumor microenvironment’ allows brain mets to develop and progress. He soon realized that though many tumor cells arrive in the brain, only some become metastatic tumors large enough to be detected on a scan. “Metastasis is not just a matter of getting there—the real picture is more complex,” Valiente said. He then set out to explore this complexity by studying both animal models of melanoma and brain met biopsies. This research uncovered that star-shaped brain cells called astrocytes are present in the tumor microenvironment of brain mets and secrete molecular signals that trigger tumor growth. When Valiente blocked this signaling in mice with melanoma or lung cancer, he found it reduced the number and size of brain mets. He then tested an experimental drug that inhibits the same molecular pathway in a small number of patients with brain mets. A majority of these patients experienced a reduction in the tumor burden in their brain, whereas no substantial reductions were seen in the size of tumors outside the brain, highlighting the likely different underlying biology of brain mets compared to other sites. “We are excited about these results and hope to start a clinical trial of the inhibitor soon in cancer patients,” Valiente said.

Because the studies conducted by Davies, Jilaveanu, and Valiente all included relatively small numbers of melanoma patients, their findings will need to be verified in larger cohorts of patients. But the glimmers of insight into brain mets should ultimately help treat patients with these tumors. “If we can identify molecular patterns in brain metastases, we can exploit them therapeutically,” Valiente stressed.

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It has been said that “melanoma writes its message on the skin with its own ink for all of us to see, so why is it so hard to detect?” asked Dr. Susan Swetter of Stanford University at the 2018 annual MRA retreat. Early detection saves lives, given the 95% ten-year survival rate for patients diagnosed with very early stage melanoma. However, that ink is hard to read. There are various visual clues that can indicate a cancerous skin lesion, but not all cancerous moles share these features and harmless moles can sometimes have similar clinical features. It’s easy to understand why misdiagnosis happens.

That may soon change, given the promising results of a new computer-based system for distinguishing malignant from benign moles or other non-cancerous skin conditions, such as psoriasis. With the advent of artificial intelligence combined with large image databases and “deep learning” algorithms, Swetter and her Stanford Dermatology and Computer Science colleagues were inspired to create a computer program that could learn the relevant patterns of various skin conditions and aid the diagnosis of early melanoma. “We figured if artificial intelligence can differentiate between hundreds of dog breeds in pictures, it could make a great contribution to dermatology,” Swetter said.

Initial results of the system the researchers created are promising. After being trained on a database of nearly 130,000 images spanning the breadth of skin diseases, the system performed at least as well as 21 board-certified dermatologists in distinguishing skin melanomas from benign moles. “This is an astounding result that a computer system trained over a matter of weeks could outperform human experts who had spent years in training,” Swetter said, adding that over time as the computer system continues learning, its diagnostic performance is also likely to improve.

But more tests need to be done to verify the accuracy of the system. Swetter expects the computer program to be ready for large-scale clinical tests within another year, including an app version that can be used on a smart phone. This app may also enable early detection of melanoma and other skin cancers in remote, underserved populations, Swetter noted. But neither the app nor computer program are ready for mole surveillance, since they don’t yet look at sequential changes in moles, Swetter said.

She stressed that artificial intelligence systems, such as the one she helped to create, are decision support tools and won’t replace dermatologists in the diagnosis of melanoma. But she added “If AI can be demonstrated to perform robustly in prospective clinical settings, I am willing to incorporate its results into my medical decision-making.” She gave an example of an image of a patient’s mole whose features were ambiguous enough that her research colleague was on the fence about whether to biopsy it. “Our computer system weighed in on the side of malignancy (as did the clinician), and low and behold it was a subtle early melanoma, so the proof is in the pudding,” Swetter said.

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APPLYING ARTIFICIAL INTELLIGENCE TO MELANOMA DETECTION

Susan Swetter

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MAINTAINING THE PACE OF MELANOMA INNOVATION IN THE ERA OF AN EVOLVING STANDARD OF CARE

There is no doubt that treatments for metastatic melanoma have changed dramatically in the decade since MRA’s founding in 2007. Targeted therapy and immunotherapy have become mainstays of treatment and have extended patient lives. In addition, new approaches to the diagnostic workup for patients have been recently announced and multiple treatments to keep melanoma from returning after surgery are now available. Specifically:

- Eleven treatments for patients with metastatic melanoma garnered FDA approval since 2011 including: a) targeted drugs for BRAF and MEK; and, b) immunotherapy with checkpoint blockade, cytokines or oncolytic viral therapy. Over 400 melanoma interventional trials are recruiting patients on www.clinicaltrials.gov.
- Treatment continues to evolve with the late 2017 approval of nivolumab for melanoma adjuvant therapy, the April 30, 2018, approval of adjuvant dabrafenib and trametinib, and encouraging data for other drugs.
- New melanoma staging guidelines and recommendations on complete lymph node dissection (CLND) have recently been published.
- Companion diagnostics for both targeted and immunotherapy have gained approval and biomarker development remains a top priority.

Louise Perkins and Antoni Ribas

These changes in the standard of care for melanoma bring with them the need to consider what their impact is on how even newer treatments are developed from the standpoint of academic and government researchers, biopharma scientists and regulators.

Over 50 thought leaders came together at an annual, invitation-only Industry Roundtable to identify and discuss cross-cutting issues facing melanoma treatment and diagnostic development. Participants included representatives from academia, FDA, industry, NCI and MRA. The session was moderated by Dr. Antoni (Toni) Ribas and MRA Chief Science Officer, Dr. Louise Perkins. Among the topics discussed were a) clinical trials; b) endpoints; and, c) biomarkers.

Ribas asked a provocative question to kick off discussion, “Are there too many clinical trials being conducted in melanoma?” Given the need for improved outcomes and the rationale supporting most trials, the overwhelming majority of participants felt that the answer was a resounding “No, there are not too many trials.” What followed was a nuanced discussion that explored both efficiency improvements and mobilizing the precious resource of patients who are able and willing to participate in such trials. MRA, along with external partners, recently launched Melanoma > Exchange to bolster education about clinical trials and an online platform that makes it easier for patients to find a trial.

One way to improve the efficiency of melanoma clinical trials would be the development of endpoints to more accurately predict whether treatments are working as compared to those in common use today. For example, tumor shrinkage, progression after treatment and overall survival are common endpoints. But what if a blood test, an imaging endpoint or a pathology measurement could accurately shed light on whether your treatment is working or is failing earlier than current technologies can determine? There is great interest in this area and its potential to more rapidly and accurately inform drug development.

Biomarker development is a related subject that attempts to measure things like proteins or cell types to help identify which patients will benefit from which treatment. A great deal of effort in research is being invested to develop these biomarkers for melanoma and to use them to identify which patients are in need of more aggressive or earlier therapy compared to those who will do fine with standard surgery or existing drugs.

Another topic that was discussed related to bringing potentially life-saving treatments to patients more quickly by including patients in trials who are typically excluded. For example, patients with brain metastases have historically been excluded from clinical trials even though around 15% of newly diagnosed melanoma patients have existing brain mets. Recent work by a multi-stakeholder group made the case for modernizing clinical trial eligibility, including treating certain patients with brain mets, to achieve several objectives including understanding the safety and efficacy in real-world populations and also to potentially enroll more patients on trials more quickly.

In conclusion, the rapidity of change in melanoma since the first wave of new treatments came to market in 2011 has been astounding. Through dialogue among experts such as at this Industry Roundtable, problems and solutions can emerge that address problems that now exist due to the relative success in the field.

[14]
AGENDA
Wednesday, February 28th

1:30-5:30 pm  Melanoma Advocates & Foundations Forum (invitation only) ........................................... Salon II
4:00-8:00 pm  Registration open .......................................................... Foyer of Salon III
6:00-7:30 pm  Opening Reception ........................................................ Salon III

Thursday, March 1st

6:30 am-6:00 pm  Registration ................................................................. Outside of Salon Ballroom
7:00-8:15 am  General Breakfast ........................................................... Salon III
7:00-8:15 am  Young Investigators Breakfast (by invitation only) ........ Plaza Ballroom
8:30-8:45 am  Opening Remarks Day 1 ....................................................... Salon I & II
  Michael Kaplan, MRA President & CEO
  Louise Perkins, MRA Chief Science Officer
  Samantha Stinchcomb, Wayne Stinchcomb Big Orange Foundation

8:45-9:15 am  Lecture
  Suzanne Topalian, Johns Hopkins University: A decade of progress in melanoma

9:15-11:10 am  Session 1: New approaches and tools for predicting efficacy: immunotherapy and beyond
  Chair: Jennifer Wargo
  Kai Wucherpfennig, Dana-Farber Cancer Institute: Human anti-MICA monoclonal antibodies for melanoma immunotherapy
  Marisol Soengas, Spanish National Cancer Research Center (CNIO): Imaging and targeting dormant and pro-metastatic melanoma lesions in vivo
  Iwei Yeh, University of California, San Francisco: Activating β-catenin mutations cooperate with BRAFV600E to promote invasion
  Break
  Yvonne Saenger, Columbia University: Combination immunotherapy leads to decreased tumor growth, improved survival and intratumoral immune infiltration in transgenic murine model of melanoma

11:10 am-12:00 pm  Session 2: Microbial influences on immunotherapy efficacy
  Chair: Marisol Soengas
  Tom Gajewski, University of Chicago: The commensal microbiota as a new variable impacting cancer immunotherapy
  Jennifer Wargo, MD Anderson Cancer Center: Profiling the microbiome to predict immunotherapy efficacy
AGENDA

12:00-12:10 pm  Transition to lunch
12:10-1:15 pm  Lunch and Panel Discussion……………………………………………………………………………… Salon III
   The changing landscape of melanoma
   Moderator: Elliott Sigal, MRA Board of Directors
   Panelist: Richard Pazdur, Oncology Center of Excellence, FDA
   Panelist: Marc Theoret, Oncology Center of Excellence, FDA
   Panelist: Nageatte Ibrahim, Merck
   Panelist: David Feltquate, Bristol-Myers Squibb
   Panelist: Caroline Robert, Institut Gustave Roussy
1:15-1:30 pm  Transition to room
1:30-3:00 pm  Session 3: Melanoma metastasis………………………………………………………………………… Salon I & II
   Chair: Robert Vonderheide
   1:30-1:55  Michael Davies, MD Anderson Cancer Center: Targeting BRAF mutant brain metastases
   1:55-2:15  Manuel Valiente, Spanish National Cancer Research Center (CNIO): Blocking brain metastasis by targeting the microenvironment
   2:15-2:35  Lucia Jilaveanu, Yale University: Response to PD-1 inhibitors in melanoma patients with brain metastases
   2:35-3:00  Robert Vonderheide, University of Pennsylvania: Radiation and immune checkpoint blockade from mechanism to patients
   3:00-3:20 pm  Break
3:20-5:00 pm  Session 4: New targets for melanoma…………………………………………………………………… Salon I & II
   Chair: Ido Amit
   3:20-3:45  F. Stephen Hodi, Dana-Farber Cancer Institute: Combined CTLA-4 and angiopoietin-2 blockade in advanced melanoma patients
   3:45-4:05  Niroshana Anandasabapathy, Weill Cornell Medical School: Tissue immune differentiation reveals new pathways of melanoma escape
   4:05-4:30  Michal Lotem, Hadassah Medical Organization: Mechanism of action of SLAMF6 and its potential role in immunotherapy
   4:30-4:55  Ido Amit, Weizmann Institute of Science: Single cell analysis and perturbation of the tumor-immune ecosystem
   4:55-5:00  Closing Remarks Day 1
   Kristen Mueller, MRA Scientific Program Director
6:30-9:00 pm  Reception and Dinner………………………………………………………………………Teddy & the Bully Bar*
   Dress: Casual 1200 19th Street, NW, (202) 872-8700
   Reception: 6:30-7:00 pm; Dinner: 7:15 pm

*6:15-7:00 pm: Transportation provided to Teddy & Bully Bar; Shuttles will depart from the circular drive outside the hotel lobby. Upon exiting the hotel, bear to your right and shuttles will be stationed in the breezeway between the hotel and art gallery on the property.
Friday, March 2nd

6:30-10:00 am  Registration open………………………………………………………………………..Outside Salon Ballroom
7:00-8:30 am  General Breakfast…………………………………………………………………………..Salon III
7:00-8:30 am  Industry Roundtable Breakfast (by invitation only)………………………………Plaza Ballroom
8:40-8:45 am  Opening Remarks Day 2 ………………………………………………………………..Salon I & II

Kristen Mueller, MRA Scientific Program Director

8:45-11:25 am  Session 5: New strategies in preventing and treating melanoma

Chair: Lewis Cantley

8:45-9:10  Georgina Long, Melanoma Institute Australia, University of Sydney: Adjuvant therapy for melanoma

9:10-9:30  Steve Barthel, Brigham and Women’s Hospital: Melanoma cell-intrinsic Tim-3: An unexpected variable in cancer immunotherapy?

9:30-9:50  Amanda Lund, Oregon Health & Science University: Lymphatic vessels and T cell-inflammation in melanoma

9:50-10:15  Boris Bastian, University of California, San Francisco: Structure and expression level of BRAF fusion kinases affect drug response

10:15-10:35 am  Break

10:35-11:00  Susan Swetter, Stanford University: Artificial intelligence (AI) for cutaneous melanoma detection

11:00-11:25  Emily Bernstein, Icahn School of Medicine at Mount Sinai: Harnessing the epigenome for melanoma oncogene discovery

11:25-11:55  Lecture

Lewis Cantley, Weill Cornell Medical School: Development of AMPK activators for treatment of melanoma

11:55-12:35 pm  Panel Discussion

A decade of MRA: Funding for the future
Moderator: Margaret Anderson, MRA Board of Directors
Panelist: Debra Black, MRA Board Chair and Co-founder
Panelist: Georgina Long, Melanoma Institute Australia, University of Sydney
Panelist: Richard Marais, Cancer Research UK Manchester Institute
Panelist: Suzanne Topalian, Johns Hopkins University, MRA Board of Directors
Panelist: Jedd Wolchok, Memorial Sloan Kettering Cancer Center

12:35-12:45 pm  Closing Remarks

Michael Kaplan, MRA President and CEO
Louise Perkins, MRA Chief Science Officer

12:45-2:00 pm  Lunch and Departures………………………………………………………………………………Salon III
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