Melanoma Research Alliance

Treatment

The Melanoma Research Alliance (MRA) has invested almost $32 million in research funding to improve melanoma treatment – more than 80 percent of total funding awarded to date. If caught early, melanoma can be successfully treated by surgery. In contrast, those diagnosed with widespread metastatic disease (Stage IV) have a median survival of less than one year. Clearly, new treatments are needed to transform the outlook for patients. In 2011, clinical advances ushered in a new era in the fight against metastatic melanoma with two new agents coming onto the market. MRA is accelerating this remarkable progress by supporting research to improve these therapies as well as develop new immunotherapy, molecularly targeted therapy, and combination therapy treatment approaches.

Immunotherapy

Melanoma is one of the most immunogenic cancer types, meaning that patients' immune systems respond and try and attack the cancer. While this is insufficient on its own, researchers and clinicians aim to take advantage of this by developing drugs – immunotherapies - that will boost the immune system to fight the cancer more effectively.

One approach is to block the natural brakes on the immune system (called inhibitory checkpoints). MRA has committed nearly $6.7 million to advancing immune checkpoint blockade, which includes research on ipilimumab, one of the new melanoma drugs that were approved in 2011, as well as next generation blockers, such as anti-PD-1. While effective for some patients, researchers are trying to understand the reasons why it does not work for others to improve its effectiveness and identify biomarkers for patient selection.

Increasing the population of white blood cells that fight melanoma through a procedure called adoptive T cell transfer has shown promising results, but this method needs to be further validated and expanded. MRA-funded research is aimed at improving the protocols through enhancing the survival of the white blood cells, improving their function through genetic engineering, and developing better ways to monitor them during treatment. For example, MRA is funding a project that developed a complex nanotechnology based chip that enables researchers to assess the functionality of single white blood cells of patients undergoing adoptive cell transfer therapy in melanoma trials for the first time.

MRA investigators are working on other ways to stimulate tumor specific T cells to attack and kill melanoma tumors. One way is through therapeutic melanoma vaccine strategies by testing different ways to induce the immune response against proteins on melanoma cells (antigens) and studying the importance of different immune cell types in the response to vaccination. Another way to enhance the activity of tumor killing T cells is to manipulate stimulatory molecules that activate them and attract them to the tumor site.

Molecularly Targeted Therapy

Genes and proteins, working in complex molecular systems, are ultimately responsible for the initiation, survival, growth, and metastasis of cancer. Alterations in intracellular signaling pathways have been identified in subsets of melanomas, and researchers are working to develop drugs based on these discoveries. MRA is funding research on therapies directed at a wide variety of molecular targets in melanoma including abnormal cell growth signaling pathways, targets on specific melanoma cell populations, and cell death pathways.

A mutation in a gene called BRAF is involved in about half of melanomas, and a drug that blocks the abnormal protein was recently approved. This BRAF inhibitor is called vemurafenib, and other similar drugs are in development. They have shown dramatic results; however, most patients develop drug resistance and relapse. MRA has committed over $7 million to further progress of selective BRAF inhibition by identifying mechanisms of resistance and combining them with other agents. For example, a team representing several institutions across the country is working to share biopsy specimens to address this critical challenge. Together, they have found several new mechanisms of resistance with near-term implications for clinical application.

Because about half of melanoma patients do not have mutant BRAF, MRA has invested more than $6 million to develop new drugs against other targets on melanoma cells. This includes the Stand Up to Cancer-MRA Melanoma Dream Team, a $6 million award that will identify and test molecularly targeted agents in patients with BRAF-wild type

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melanoma. MRA researchers are identifying and testing new targets in melanomas of the skin and eye based on genetic mutations in the cancers as well as targets on specific subpopulations of melanoma cells (sometimes called “stem cells”), and specialized targets in melanoma cells that metastasize to the brain.

Combination Therapy

Cancers are dependent on a number of altered molecular pathways and can develop resistance to single agent therapy, thus combination of therapeutic approaches may be necessary to provide durable control and cures for patients. MRA-funded studies in this area include testing both approved agents and investigational agents. MRA-supported combination therapy clinical trials include a phase 1 study of bevacizumab and ipilimumab, a phase 2 trial of vemurafenib plus leflunomide, and a phase 1 trial of radiation and ipilimumab.

Other MRA investigators are pursuing translational studies to set the stage for clinical testing of combinatorial regimens. These approaches include testing different agents that target multiple proteins along the same cell signaling pathway and parallel pathways to more completely block growth signals driving the cancer and to overcome drug resistance. Researchers are studying the best ways to combine immune checkpoint inhibitors (anti-CTLA-4 and anti-PD-1) with other therapies including BRAF inhibitors.