Next-Generation Treatments for Melanomas

Researchers are hard at work developing meaningful improvements through next-generation treatments that could improve patient outcomes.

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By Marc Hurlbert, PhD, MRA Chief Science Officer

If you were going to purchase a new smartphone today, you would likely be exploring the iPhone 11, Samsung Galaxy S10 or Pixel 4 – you may even be coveting the 'next best thing' rumored online! The first iPhone was released in 2007; you can think of that first iPhone as an altogether different class of phone, while the iPhone 11 is the eleventh-generation with major improvements. Similarly, the first Pixel was released in 2016, a completely new class of phone, and the fifth generation Pixel is expected to be released next year.

Second-generation medicines

Just like for smartphones, improving upon the first treatments in a new class of drug – so-called 'second generation' treatments – is common in medicine. In diabetes, for example, patients used first-generation insulin created from pigs from its discovery in 1922 through the early 1980s. The second-generation insulin is derived from humans and was approved in 1982. More recently, diabetes care has improved with new generations of human insulin that are longer-lasting or that can be inhaled – so called 'next gen' therapy. Similarly, scientists have rapidly improved treatments for HIV since the 1990s. Today, the 3rd generation of HIV antiretroviral therapy combines three drugs into a single pill. In addition to more effectively treating HIV, newer medications also have far fewer side effects. Treatments with improved outcomes or that are more easily administered or given in combination are all examples of next-gen therapies.

It's exciting to know that in melanoma, the "next generation" of drugs are actively being developed.

Next-generation melanoma treatments

Improvements in survival over the last decade for patients diagnosed with advanced melanoma is largely due to the development of ground-breaking novel treatments, such as the first BRAF inhibitor (vemurafenib in 2011) specifically designed to target tumors with BRAF mutations, the first checkpoint immunotherapies, including the CTLA-4 blocking antibody ipilimumab in 2011, and

the first PD1 blocking antibodies pembrolizumab and nivolumab in 2014.

Building on the success of these new treatment approaches, researchers are hard at work developing meaningful improvements through next-generation treatments that could improve patient outcomes. MRA has funded research into more than 100 new treatments through 339 grant awards exploring new targets in melanoma, and highlighted many of the exciting new classes of treatments in clinical development at biotechnology and pharmaceutical companies. Here, is a snapshot of some of the recent advances in next-generation melanoma treatments.

Next-generation BRAF-MEK inhibitors for melanoma:

We are already seeing newer and different BRAF and MEK inhibitors evaluated in combination for melanoma. Over the last decade, three sets of combination BRAF-MEK targeted therapies have been approved. The first such combination included dabrafenib+trametinib, which was approved for use in metastatic melanoma in 2013, with the combination vemurafenib+cobimetinib approved the following year. In 2018, the encorafenib+binimetinib combination was approved. One of the benefits of having such a diversity of inhbitors is that not every treatment works the same way for each patient and different drugs with different profiles provide choices for patients and their doctors.

Many patients with BRAF mutant melanoma have robust responses to treatment with combination BRAF+MEK inhibition. Unfortunately, in the majority of cases, with time, tumors develop resistance to these therapies.

Many MRA-funded investigators, like Neal Rosen, MD, PhD, (Memorial Sloan-Kettering Cancer Center), Evris Gavathiotis, PhD, (Albert Einstein College of Medicine), and Poulikos Poulikakos, PhD, (Icahn School of Medicine at Mount Sinai), and others, are conducting research to develop future generations of BRAF and MEK inhibitors that are able to produce more durable responses for patients facing advanced melanoma.

Next-generation checkpoint immunotherapies for melanoma:

Researchers, including those funded by MRA and those in the pharmaceutical industry, are working hard to improve upon existing checkpoint immunotherapies. For example, MRA-funded investigators Pan Zheng, MD, PhD, (University of Maryland) and Erica Stone, PhD, (formerly at the Wistar Institute), have identified features of the anti-CTLA4 blocking antibodies that target the tumor cells versus interacting with healthy cells and tissues. Both have developed next-generation CTLA4 blocking antibodies with the goal of improved efficacy with fewer immune-related adverse events for patients. However, these agents are still being studied in the laboratory and will need to be extensively tested through clinical trials. In addition, the manufacturer of ipilimumab has already advanced its own second-generation CTLA-4 blocking antibodies into early stage clinical trials (BMS-986218 and BMS-986249).

In addition to exploring next-generation improvements on currently approved immunotherapies, scientists are actively exploring novel immunotherapy agents, including agents focused on TIM-3, LAG-3, VISTA, and KIR. Still other approaches hope to stimulate the anti-tumor immune response

by interacting with targets like CD40, GITR, OX40, CD137 and ICOS. Many of these are being explored in combinations with currently available checkpoint immunotherapies (CTLA4, PD1) and targeted therapies.

The Future:

MRA is investing heavily into research to help those patients whose melanoma either does not respond to currently available treatments or who experience a relapse. Whether that is through identifying new drug targets in melanoma cells and making altogether new classes of treatments, developing the next-generation of the currently available treatments, testing novel combinations of treatments, or bringing treatments approved in metastatic melanoma to earlier stages of disease, MRA-funded scientists are working diligently to make advances to help all patients with melanoma.

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