On Cancer

A Changing Melanoma Landscape: How Research Has Improved the Outlook for People with Advanced Disease

By Julie Grisham, **Monday, May 4, 2020**

Medical oncologist Paul Chapman specializes in treating advanced forms of melanoma.

Summary

Thanks to new drugs, many of them developed at Memorial Sloan Kettering, people with advanced melanoma now have many treatment options.

Editor's note: According to medical oncologist Paul Chapman, "In these unprecedented times of the COVID-19 pandemic, we have had to put our clinical trials on pause while we shift our attention entirely to fighting COVID-19 and ensuring the safety and health of our patients and staff. Once it is safe to do so, we will reopen our clinical trials." Go to MSK's **information page** on the COVID-19 pandemic to learn more, or speak with your doctor or nurse.

In recent years, advanced **melanoma** has been transformed from a disease that was almost always fatal to one that often can be brought under control for years or even cured. Thanks to new drugs, people with advanced disease now have a five-year survival rate of about 50%.

"The landscape for melanoma has changed dramatically," says Memorial Sloan Kettering medical oncologist **Paul Chapman**, who specializes in treating advanced forms of the disease. "Here at Memorial, because we were involved in the early trials, outcomes started to really improve in 2006 or 2007. For the rest of the world, they changed in the early 2010s, after these new drugs were approved and went into wider use."

Treatments for melanoma have advanced on two fronts: **immunotherapy** and **targeted therapy** — both of which have contributed to the remarkable changes that have occurred. But some patients don't do as well with those drugs, so researchers continue to focus on new therapies and treatment combinations.

Harnessing the Immune System to Fight Cancer

In the area of immunotherapy, the first drug to show significant promise was **ipilimumab (Yervoy®)**. The drug works by exploiting the ability of the body's own immune system to attack cancer. Specifically, it blocks the activity of a protein called CTLA-4. This takes the brakes off the immune system and enables immune cells called T cells to go after cancer.

Ipilimumab was developed in 1996 by immunologist James Allison, who served as Chair of the Sloan Kettering Institute Immunology Program between 2004 and 2012. Dr. Allison later won a **Nobel Prize** for this work. MSK physician-scientist **Jedd Wolchok** led the clinical trials that resulted in the drug's **approval by the US Food and Drug Administration** in 2011.

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Paul B. Chapman
medical oncologist

Additional immunotherapy drugs for melanoma, including **pembrolizumab (Keytruda®)** and **nivolumab (Opdivo®)**, soon followed. They work in a similar way but block a different protein, called PD-1. (Still more immunotherapy drugs that block a related protein called PD-L1 have also been approved.)

Research led by Dr. Wolchok and **presented in 2015** showed that, for many people, the combination of ipilimumab and nivolumab was safe and worked better than either drug on its own. That therapy is now standard for many people with metastatic melanoma.

Since the approval of these immunotherapy drugs for melanoma, they have also become a standard treatment for several other types of cancer, including **lung cancer**, **bladder cancer**, and **head and neck cancers**. Investigators are continuing to study how these drugs work in order to optimize their use and extend these treatments to more people with cancer.

Targeting the Factors that Drive Cancer

The first-ever targeted drug for melanoma to show a profound effect was **vemurafenib (Zelboraf®)**. It targets a specific mutation in a gene called *BRAF* and blocks its cancer-causing actions. The mutation is found in about half of all melanomas.

“The drug was designed specifically for people whose cancer contained this mutation,” says Dr. Chapman, who **led the phase III trial** that resulted in the FDA’s approval of the drug in 2011. “When we saw how well vemurafenib was working, it was a very exciting time.”

Since it was approved for melanoma, vemurafenib has also **been approved** for cases of a rare blood disorder called Erdheim-Chester disease that have the same *BRAF* mutation. Other drugs that block the BRAF protein have also been approved.

Another class of targeted therapy for melanoma is called a MEK inhibitor. These drugs block the activity of a growth pathway that is often overactive in melanoma and other cancers. They may be used alone or in combination with BRAF inhibitors.

“Unfortunately, the data show that about 80% of people will eventually develop resistance to BRAF and MEK inhibitors,” Dr. Chapman says. “We’re now looking at new strategies for delivering these drugs.”

Melanoma

Learn more about melanoma, including skin melanoma and eye (ocular) melanoma, and find out how MSK is improving the outlook for people with these cancers.

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Research Aims at Further Gains

“It turns out that melanoma is one of the most responsive cancers to both immunotherapy and targeted therapy,” Dr. Chapman says. “The challenge is to learn more about how to treat the 50% of people whose tumors don’t respond to these treatments.”

Research from MSK and other institutions **published in 2013** found that the combination of vemurafenib and ipilimumab led to significant side effects, and therefore the drugs should not be used together. But since then, investigators at MSK and elsewhere have been studying new combinations with different kinds of drugs.

“We’re trying to figure out what’s different about these tumors and if there is some way that we can convert a nonresponsive tumor to a responsive one,” Dr. Chapman adds. “One strategy involves introducing inflammatory molecules to the tumor to see if we can convert it to an environment that’s more receptive to T cell activity.”

Another important aspect of current research is to figure out the smallest dose that can be given to people with cancer while still achieving beneficial effects. “Toxicity and side effects are always a concern when treating any kind of cancer,” Dr.

Chapman says. “Part of the history of oncology, whether you’re talking about chemotherapy or some of these more recent drugs, is looking at how much you can dial a treatment back and still cure people. This is an important area of research going forward.”

Dr. Chapman has stock and other ownership interests in Rgenix. He has advised or provided consulting to Genentech, Takeda, Cell Medica, Merck, Immunocore, and AstraZeneca and received research funding from Pfizer.

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