Targeted Therapy Advance: Vemurafenib

Pivotal data from the phase three trial of vemurafenib was presented by principal investigator Paul Chapman, a medical oncologist on the Melanoma and Sarcoma Service. The international, multicenter study of 675 patients has concluded that treatment with the new targeted therapy resulted in a 63 percent decrease in risk of death, compared to those who received the standard chemotherapy, dacarbazine. Treatment with vemurafenib resulted in significant tumor shrinkage in 48 percent of patients.

“This is the beginning of personalized medicine in melanoma,” said Dr. Chapman. We have seen tumors shrink rapidly, and in some patients, quality of life improved dramatically. It has been a very exciting year.”

Half of melanomas have been found to be associated with a mutated gene called *BRAF*. Vemurafenib inhibits *BRAF* and shuts off these tumors by targeting and blocking the mutated *BRAF* protein at the cellular level. The drug is an oral medication taken twice daily.

Dr. Chapman was the principal investigator of the trial, which included the work of collaborating investigators from 103 other centers around the world.

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Immunotherapy Advance: Ipilimumab

Jedd Wolchok , a medical oncologist in the Melanoma and Sarcoma Service with a joint appointment in the Sloan Kettering Institute’s Immunology Program, presented data from an international, multicenter study of the immunotherapy ipilimumab (trade name Yervoy ™) as a first-line treatment option in advanced melanoma patients. In March of 2011, ipilimumab was approved by the FDA as a treatment for patients with advanced melanoma.

The double-blind, randomized trial of 502 patients examined the response of newly diagnosed patients who had not had any prior treatment for their disease. Patients were divided into two groups. One group received the standard chemotherapy, dacarbazine. The other group received the same chemotherapy along with ipilimumab. The results show that the patients who received ipilimumab in addition to chemotherapy lived approximately two months longer than the patients who received chemotherapy alone. There was a significant survival benefit in the ipilimumab group: Approximately twice as many patients in this group were alive two and three years after beginning treatment .

“Ipilimumab blocks a very critical brake that the immune system uses to hold itself back from attacking normal tissues,” explained Dr. Wolchok. “By temporarily blocking this brake, ipilimumab allows the immune system to become more robustly activated than it otherwise would and ,therefore, in some people causes the production of antibodies and T-cells that can recognize melanoma leading to control of the disease,” explained Dr. Wolchok.

The therapy, originally known as anti-CTLA-4, was developed by James Allison, PhD, Chair of the Sloan Kettering Institute's Immunology Program. For more that 20 years, Dr. Allison's research has focused on the mechanisms that regulate the immunologic responses of T lymphocytes — commonly referred to as T cells — with an emphasis on manipulating T cell response in order to develop novel tumor immunotherapy approaches.

"The past decade has brought us significant insights into two areas of melanoma biology that have now led to successful drug development," said Dr. Wolchok. "The first is a better understanding of what genetic errors are contained inside a melanoma cell, and that has allowed for the development of drugs that target those erroneously activated pathways. The second is a better understanding of how the immune system can recognize cancers like melanoma and how to activate the immune system more potently to cause a more vigorous response against melanoma," he added.

> We've worked together to make a very significant impact on these two pivotal clinical trials which are poised to change the way physicians take care of people with melanoma.
>
> Jedd Wolchok MD, PhD, one of the lead authors on the studies and member of Memorial Sloan Kettering Cancer Center's Melanoma and Sarcoma service

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Collaboration And Translational Research

Memorial-Sloan Kettering's commitment to translational research is evident in the work presented at the plenary session of ASCO. Drs. Chapman and Wolchok were each others' co- principal investigators on their respective clinical trials, and the collaboration with other members of the Melanoma and Sarcoma Service, along with colleagues across departments at Memorial Sloan Kettering, contributed greatly to these studies. In addition, the significant work of investigators and staff at the more than 100 participating cancer center trial sites worldwide was critical to the advancement of this research.

"This really speaks to the dedication of all the teams of people here at Memorial Sloan Kettering, working with colleagues around the world with the goal of developing new and effective treatments for melanoma," said Dr. Chapman.

Dr. Wolchok added that, "we've worked together to make a very significant impact on these two pivotal clinical trials which are poised to change the way physicians take care of people with melanoma."

These important individual advances in the treatment of melanoma could lead to a combination approach in the future. Both Drs. Wolchok and Chapman agree that the next steps in this work are to investigate combinations of ipilimumab with more recently developed agents that have greater response rate than the current standard of care. Given the impressive results demonstrated using vemurafinib in patients with BRAF mutated melanoma, combining ipilimumab with that or other targeted pathway inhibitors is of great interest looking forward.

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