UCLA Health

New Immunotherapeutic for Advanced Melanoma Represents a Major Advance

Dr. Antoni Ribas (right) with Tom Stutz, whose health improved dramatically after treatment with the newly approved drug.

A novel immunotherapy drug that was tested at UCLA and 11 other sites has gained U.S. Food and Drug Administration approval for use in patients with advanced melanoma. The drug, pembrolizumab (brand name Keytruda), is an antibody that inhibits the programmed death-1 receptor, or PD-1, to help expose cancer cells to a patient's immune system. The medication represents the first in a new class of immune system modulators that are expected to dramatically improve survival in patients with unresectable or advanced disease.

Rates of melanoma have been rising for more than three decades. The disease now accounts for more than 9,700 deaths annually in the United States. Melanoma that has metastasized presents a particular challenge, with five-year survival rates of 15 to 20 percent among patients with stage IV disease. Immunotherapeutic agents such as interleukin-2 have produced responses in patients with melanoma, however at extremely low response rates. Pembrolizumab produces a dramatically high, durable response rate that represents a significant treatment advance.

Releasing the immune response

Immunologic checkpoints such as the PD-1 pathway play an essential role in immune system function by preventing excessive immune response. However, some tumors exploit these checkpoints.

A pivotal advance in melanoma treatment

For several decades, physicians have had little to offer patients with advanced melanoma. However, recent advances in understanding the biological mechanisms of the disease as well as a deepening knowledge of immune regulatory checkpoints has ushered in a new era of targeted drug development.

Pembrolizumab overcomes the natural tendency of cancer cells to shield themselves from immune cells by expressing the ligand to PD-1 (known as PD-L1), thus overcoming a major obstacle in the evolution of effective cancer immunotherapeutics, says Antoni Ribas, MD, PhD, a principal investigator of the phase 1, fast-track trial of pembrolizumab.

"This drug is a game changer, a very significant advance in the treatment of melanoma," says Dr. Ribas, a professor of medicine in the division of hematology/oncology at the David Geffen School of Medicine at UCLA. "For patients who have not responded to prior therapies, this drug now provides a very real chance to shrink their tumors and the hope of a lasting response to treatment."

The PD-1 immunoreceptor protein tamps down the immune response by preventing T cells from identifying and attacking cancer cells. This mechanism has hampered efforts to use immunotherapeutics to combat advanced melanoma and other types of cancer.

Pembrolizumab, previously known as MK-3475 (and transiently known as lambrolizumab), overcomes immune resistance by targeting PD-1 to allow T-cell infiltration into tumors, bolstering the anticancer immune response. In a phase 1 investigation led by UCLA researchers — one of the largest phase 1 oncology trials to date — pembrolizumab therapy was associated with a one-year survival rate of 69 percent and an 18-month survival rate of 62 percent among 411 patients with advanced melanoma. The study participants included 221 patients with prior ipilimumab treatment and 190 patients who had not previously received ipilimumab.

Any degree of tumor regression from baseline was observed in 72 percent of patients. Moreover, tumors responded in patients from all the different dosing regimens and in various patient subgroups, including those whose cancers had worsened after having received ipilimumab. Previously, there were no treatment options with proven activity for those patients.

Overall, 34 percent of patients experienced objective responses to pembrolizumab — defined by tumor shrinkage of more than 30 percent following RECIST criteria with independent central radiology review. A complete response was observed in 5 percent of patients, including 8 percent in the group that had no prior treatment with ipilimumab and 2 percent with prior ipilimumab treatment.

Based on this early-stage clinical trial, the FDA granted breakthrough therapy designation to pembrolizumab for unresectable or metastatic melanoma in April 2013 under its Accelerated Approval program. On September 4, 2014, pembrolizumab, manufactured by Merck & Co., was approved for use in patients with advanced or unresectable melanoma who are no longer responding to other drugs, in particular ipilimumab. For patients whose tumors express the BRAF V600 gene mutation, pembrolizumab is intended for use after treatment with ipilimumab and a BRAF inhibitor.

Manageable safety profile

Pembrolizumab is delivered by infusion every three weeks. The drug produces a remarkably low rate of toxicity, possibly related to its distinct mechanism of action that exclusively targets tumor-specific T cells. A majority of patients experienced only mild and reversible side effects such as fatigue, rash, pruritus and diarrhea. Eight percent of patients had serious side effects, including inflammation of the lung or kidney, that were typically managed with a reduction in dosage or temporary suspension of treatment.

The immunotherapeutic approach utilizing PD-1 blockade offers the first opportunity for effective treatment for a majority of patients with advanced melanoma. Additional research is under way to explore the effects of pembrolizumab on cancers of the lung, bladder, head and neck.

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