

Radiation plus immunotherapy combo revs up immune system to better attack melanoma, study suggests

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Melanoma in skin biopsy with H&E stain—this case may represent superficial spreading melanoma. Credit: Wikipedia/CC BY-SA 3.0

Treating metastatic melanoma with a triple threat—including radiation therapy and two immunotherapies that target the CTLA4 and PD-1

pathways—could elicit an optimal response in more patients, one that will boost the immune system's attack on the disease, suggests a new study from a multidisciplinary team of researchers from Penn's Abramson Cancer Center published today in *Nature*.

The study, led by senior authors Andy J. Minn, MD, PhD, assistant professor of Radiation Oncology, Robert Vonderheide, MD, DPhil, the Hanna Wise Professor in Cancer Research, Amit Maity, MD, PhD, professor of Radiation Oncology, and E. John Wherry, PhD, professor of Microbiology and director of the Institute for Immunology at the Perelman School of Medicine at the University of Pennsylvania, reports for the first time on the response and resistance to radiation combined with ipilimumab (an antibody against CTLA4) in both patients and mice.

In the phase I clinical study, known as the "RadVax" trial, the team found that combining ipilimumab with radiation was safe and shrank tumors in a subset of 22 [metastatic melanoma](#) patients (18 percent). The concurrent mouse study shed light on a mechanism of resistance, known as the PD-L1 pathway, found in many patients whose cancers progressed, suggesting that an antibody against PD-L1 or its partner PD-1 is an ideal third treatment to improve response and immunity.

"These new immunotherapies are potent treatment options that have generated a lot of excitement in the past few years, but we know that many patients fail to respond, underscoring the need to further improve the drugs' abilities," Minn said. "Anecdotally, we know that combining radiation with immunotherapy can be powerful, so we were very motivated to move forward with both a clinical trial to demonstrate that this combination is a promising route to pursue and with laboratory studies to understand why response happens and why it does not."

Ipilimumab is an FDA-approved, anti-CTLA4 antibody that serves to lift a break on the immune system, allowing T cells to infiltrate and attack

[tumor cells](#). Antibodies that block the PD-L1 pathway, which cancer cells use to hide from the immune system, include pembrolizumab or nivolumab, anti-PD-1 immunotherapies approved by the FDA recently.

It is believed that adding radiation results in a synergistic attack, turning the destroyed tumor cells as a vaccine against the cancer. Irradiated tumor cells are believed to release antigens that help train the immune system to fight other tumors in the body. The treatment has earned the name "RadVax" because of its vaccine-like qualities.

The impetus for the Penn phase I clinical study was a metastatic melanoma patient in his early 50s who was treated with an anti-CTLA4 antibody at Penn Medicine by co-author Lynn M. Schuchter, MD, chief of Hematology/Oncology at Penn's Abramson Cancer Center. While on an anti-CTLA4 antibody, the patient's condition worsened, and he required palliative [radiation therapy](#). Over the course of many months after both modalities and no further treatment, however, his metastatic cancer started to resolve, and he was eventually deemed nearly cancer free.

Attempting to mirror his treatment experience, the researchers recruited 22 previously treated and untreated stage IV melanoma patients for a phase I clinical trial that investigated the use of both modalities. The group received stereotactic body radiation therapy (SBRT) to a single tumor followed three to five days later with ipilimumab every three weeks for four cycles.

The team found that 18 percent of patients had partial response in unirradiated tumors, 18 percent had stable disease and 64 percent had progressive disease. The median progression free survival and overall survival for patients was 3.8 months and 10.7 months with a median follow up of 18.4 and 21.3 months, respectively. The group's overall survival rate was 35 percent. A past, phase III study showed an overall

survival rate of 20 percent in patients on ipilimumab alone.

"This approach is changing the way we view radiation—from strictly a local form of therapy to one that may augment a systemic response when given with immunotherapy," Maity said.

The response in mice was met with similar results: 17 percent of mice responded to the combination of radiation therapy and an anti-CTLA4 antibody.

To better understand the mechanism of resistance observed in many of the patients, the researchers turned to the mice. Mouse tumors that relapsed after radiation and anti-CTLA4 revealed that PD-L1, known to inhibit the activation of T cells, was among the top upregulated genes that made up a "resistance gene signature," the authors reported. Indeed, mice with tumors showing high PD-L1 had disabled T cells and all failed treatment.

In mice, inhibiting PD-L1 restored both T cell function and tumor response to radiation therapy and anti-CTLA4, increasing survival to 60 percent. Going full circle back to the clinical trial, those patients with tumors showing high PD-L1 also had disabled T cells and all failed treatment, but patients with low PD-L1 tumors had 50 percent survival. The authors conclude that PD-L1 on tumor cells can be a dominant resistance mechanism to radiation therapy and ipilimumab.

"Understanding resistance is very important. Although outcome can be improved when more therapies are combined, risk of side effects can increase. Precision medicine requires knowing when to give more and what to give," said Minn. His lab focuses on cancer therapy resistance and recently published another [report in Cell](#) on the subject.

"These results are extremely encouraging and will allow us to propel the

work further, into bigger clinical studies investigating the triple threat," said Vonderheide, who is working with the team to start the clinical trials in other tumors, including pancreatic, lung and breast. "Once again, we are extending the reach of the [immune system](#), and breaking the ceiling on what these drugs can do for our [patients](#)."

More information: Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer, [DOI: 10.1038/nature14292](#)

Provided by University of Pennsylvania School of Medicine

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