

# PV-10: A Melanoma Therapeutic in the Pipeline

Data for an intralesional therapy for melanoma are promising, as phase III trials near.

## A Q&A with Sanjiv S. Agarwala, MD

### How would you describe the current landscape for melanoma therapeutics?

When it comes to therapeutic advancements, "It's been a good year for melanoma—for advanced melanoma specifically," observes Sanjiv S. Agarwala, MD, Professor of Medicine at Temple University School of Medicine in Philadelphia and Chief, Oncology & Hematology at St. Luke's Cancer Center in Bethlehem, PA. The approvals of vemurafenib and ipilimumab offer new treatment options for patients with fairly widespread systemic disease, including melanoma that has metastasized to multiple organs. (For more on vemurafenib and ipilimumab see page 37 in this edition.)

The investigational agent PV-10 offers a potential therapy for patients with locally advanced melanoma. "It is an investigational agent that shows promise for a unique and quite important subset of patients with melanoma that has spread but is not yet widely disseminated," Dr. Agarwala says. This could include, for example, melanoma that has spread beyond resectable lymph nodes or multiple subcutaneous nodules.

### How does PV-10 work?

PV-10 is a chemoablative agent for intralesional injection. It is derived from Rose Bengal, "which for more than 100 years has been used as a cosmetic dye," Dr. Agarwala says. The agent has been used in medicine as a diagnostic imaging dye and was serendipitously discovered to have antitumor effects. Rose Bengal is a fluorescein derivative that

appears to selectively target tumor cells, Dr. Agarwala explains.

"When it is injected into a tumor it induces local necrosis," Dr. Agarwala says, leading to destruction of the injected tumor. It also appears to recruit immune cells to the injection site. There is some indication that these immune cells may circulate throughout the body and provide distant effects on metastases or micrometastases. However, "it remains to be determined how powerful the systemic effects of PV-10-induced immune response may be," according to Dr. Agarwala.

### What is the evidence for PV-10 thus far?

PV-10 has been investigated in Phase II trials and Provectus, the company developing the agent, is in talks with FDA to establish Phase III trial protocols.

**Take-Home Tips.** PV-10 is a chemoablative agent for intralesional injection. It has been used in medicine as a diagnostic imaging dye and was serendipitously discovered to have antitumor effects. PV-10 has shown a high response rate, with regression seen in 50 percent of injected tumors. Furthermore, about 50 percent of those who had a local response also demonstrated a distant response or regression in a tumor that had not been injected. PV-10 also appears to be very safe with a good side effect profile. Administering PV-10 does not require any specific oncology training. The dose is calculated based on tumor volume, and local injection can be performed by a physician or even a nurse. Unlike the therapies for advanced melanoma, PV-10 can be provided by the dermatologist or surgeon. ●

Dr. Agarwala says three key findings have emerged from the trials thus far. "PV-10 has shown a high response rate, with regression seen in 50 percent of injected tumors. Furthermore, about 50 percent of those who had a local response also demonstrated a distant response or regression in a tumor that had not been injected. Finally, PV-10 appears to be very safe with a good side effect profile."

Ongoing research is aimed at uncovering the underlying mechanisms of response, particularly distant response, to PV-10, Dr. Agarwala says.

In the Phase II open label, single-arm trial, 80 subjects with AJCC Stage III/IV melanoma received treatment for one to 10 target lesions and up to 10 non-target lesions; at least one target lesion had to have biopsy confirmation of the diagnosis. Target lesions were >0.2 cm diameter. Intralesional dosing was provided at 50 percent of the calculated lesion volume. Retreatment was allowed at weeks 8, 12, or 16, and all subjects were followed for 52 weeks. A Complete Response (CR) of PV-10 injected lesions was achieved in 24 percent of subjects, Partial Response (PR: at least a 30 percent reduction in tumor volume) was seen in 25 percent of subjects, and Stable Disease (SD: less than 20 percent increase in tumor volume) was seen in 22 percent of subjects. Less than one-third (29 percent) of subjects experienced disease progression (DP: 20 percent or greater increase in tumor volume).

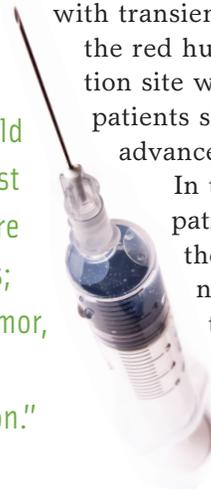
### Who is most likely to administer PV-10 therapy? What is treatment like for the patient?

"Administering PV-10 does not require any specific oncology training," Dr. Agarwala says. "The dose is calculated based on tumor volume, and local injection can be performed by a physician or even a nurse. Unlike the therapies for advanced melanoma, PV-10 could be provided by the derma-

tologist or surgeon. Providers will require training on injection techniques; depending on the size of the tumor, treatment may be injected at multiple points around the lesion."

Injection of PV-10 may be associated with transient injection-site pain. Due to the red hue of Rose Bengal, the injection site will turn bright red, which patients should be warned of in advance.

In the days following injection, patients who respond may notice the tumor turning black and necrotic and will see a reduction in size. Studies are also exploring the benefit of reinjection, likely at a period around eight weeks following the first injection.



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### Is there any possibility that PV-10 could be used within combination approaches?

There is interest in exploring whether PV-10 could be used in combination with other interventions, including surgery, Dr. Agarwala notes. "In order for PV-10 to elicit an immune response, it must be injected into an existing tumor. Therefore, it could not be used post-excision. There is some speculation that you could give PV-10 first and then excise any remaining tumor after some period of time. The ability to use this agent as a neo-adjuvant is a research question at this point," he says. There is also the possibility that PV-10 as a locally acting therapy could be used in combination with the systemic therapies recently brought to market.

All of these issues will depend on the results of Phase III trials and FDA response to those. ■

*Dr. Agarwala is an investigator for Provectus.*



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