

# CANCER WATCH

The Monthly News and Educational Magazine of Cancer Research

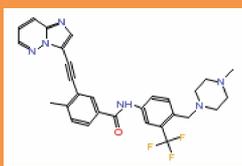
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The mission of this magazine is to transform the expanding information on cancer research into understandable language to the curious and the informed.

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## Immunotherapy Update: Ipilimumab and Intralesional Therapies

The immunotherapeutic agent ipilimumab (Yervoy), after demonstrating a 4 month lengthening of survival in metastatic melanoma, was approved in March 2011. That event ended a thirteen-year drought in approvals since that of interleukin-2 in 1998. Although interleukin-2 did extend survival, it is rarely used because of toxicity.

At this year's Second European Post-Chicago Melanoma meeting, a multi-session update on immunotherapies offered sessions on ipilimumab and on intralesional therapies. Michael Maio, MD, University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy, reported 3-year results from a study comparing ipilimumab plus dacarbazine (DTIC) with placebo plus DTIC in 502 patients. Analysis revealed overall survival (OS) of 20.8% for the ipilimumab combination as compared with 12.2% for placebo plus DTIC patients. Also, in the ipilimumab (10 mg/kg) expanded access program, 17% (138/812) of patients

were alive after 3 years. Dr. Maio noted that across a range of studies with ipilimumab at 10 mg/kg, the overall survival rate ranged from 20.4% to 25.4%.

In Dr. Maio's review of an ongoing phase II study of a frontline combination of ipilimumab and temozolomide in 64 patients with metastatic melanoma (Patel S.P., *et al.*), the overall response rate was 28% with a median PFS of 5.1 months. Median overall survival has not been reached.

"I personally think we can achieve a lot with ipilimumab, but we do have to improve its activity with different combinations of therapy," Dr. Maio concluded.

A report by Dirk Schadendorf, MD, University Hospital, Essen, Germany offered phase II results for T-VEC (Talimogene Laherparepvec) among 50 stage IIIc or stage IV melanoma (74% previously treated) patients with

injection-accessible tumors. He noted that direct replication and amplification in tumor tissue of the tumor-targeted oncolytic virus produces direct lysis, the expression of toxic proteins and an enhanced immune response. T-VEC was formerly known as Oncovex, and is an oncolytic herpes simplex virus type 1 strain engineered to replicate selectively in tumor cells and to express GM-CSF (granulocyte-macrophage colony-stimulating factor). GM-CSF recruits dendritic cells to tumor sites which in turn process and present tumor-specific antigens to mediate a tumor-specific immune response.

The response rate in the phase II trial after a median follow-up of 18 months was 26% (16% complete, 24% durable [ $>6$  months]). Patients had received T-VEC injections every two weeks for 8 cycles, with 16 additional cycles if an inflammatory reaction, partial response or stable disease occurred. One-year survival was 58% and 2-year survival was

52%. Two additional complete responses were reported after surgery, and 3 further during an extension period.

T-VEC was “quite safe,” Dr. Schadendorf said, with little grade 3 toxicity (8% fatigue, 6% asthenia).

A phase III trial (OPTiM trial) is fully enrolled (n = 430), with results expected in 2013. Included subjects have unresectable stage IIIB, stage IIIC or stage IV melanoma.

Dr. Schadendorf commented, “Agents like T-VEC that amplify and maintain immunologic responses could be a good partner, for example, with ipilimumab or anti-PD-1 agents.”

Sanjiv S. Agarwala, MD, professor of medicine, Temple University, Bethlehem, PA presented updated results with PV-10, a sterile, non-pyrogenic solution of Rose Bengal disodium (10% RB) for intralesional injection. After intralesional injection, PV-10 accumulates selectively in the lysosomes of cancer cells and elicits autolysis within 30-60 minutes. It has an established safety history in prior diagnostic and ophthalmic use. PV-10 is not metabolized and is excreted via bile. It has a short circulatory half-life of about 20 minutes.

The clinical trial, which was conducted in 7 centers in the US and Australia,

was completed in June 2012 among 80 (median age 70.0 years, 61% male) stage III/IV melanoma patients. Subjects received a median of 2 (range 1-4) treatments, with a median dose of 1.6mL and a median cumulative dose of 3.4mL. Investigators injected up to 10 target lesions and observed 1-2 untreated “bystander” lesions. Retreatment of new or partially-responsive lesions was allowed as necessary.

Dr. Agarwala reported that the objective response rate (complete response [CR] plus partial response [PR]) was 58% in target lesions and 40% in bystander lesions. Locoregional disease control (which added stable disease to CR+PR) was reported for 80% of target lesions and for 60% of bystander lesions. Bystander effects in untreated lesions correlated closely with responses in injected lesions. A systemic response was evidenced by stasis or regression of distant visceral lesions in several subjects.

The new analysis offered at this meeting stratified findings in target lesions according to disease stage. Stage III melanoma subjects, Dr. Agarwala said, exhibited consistently robust responses to PV-10. Furthermore, responses were significantly more durable in stage III patients at a mean of 9.6+ months as compared with a mean of 3.1 months for stage IV melanoma patients

(p < 0.001). Responses in stage IV patients were adversely affected by greater target tumor burden at baseline and by progression of non-study lesions that precluded repeat treatment.

The finding is guiding the planned phase III trial of PV-10, which will include only stage IIIB-IIIC disease subjects (about 180).

Locally or regionally advanced melanoma tumors without metastatic disease can be a severe problem for patients and for surgeons, said Vernon K. Sondak, MD, chair of the department of cutaneous oncology at Moffitt Cancer Center, Tampa, FL, in an interview. “The logical approach is a localized one,” he said. But whereas radiation would be the obvious solution for many cancers, melanoma is notoriously poorly responsive to radiation. Fortunately, he said a number of tools have come along to treat this group of patients, some—like PV-10 and V-TEK, create an immune effect. “If it’s shown that they are causing local destruction of tumors and are causing T-cell infiltrates, I’m interested in seeing how I can take advantage of that. If phase III trials confirm their benefits,” he said further, “adding systemic immunological therapies like ipilimumab and PD-1 with intralesional injection therapies would an extremely logical combination.” □