

# Clinical Perspectives™

## Highlights from the Perspectives in Melanoma XII Conference

Scheveningen/The Hague, the Netherlands, October 2-4, 2008

### *ABSTRACT SESSIONS*

#### **Dissemination of melanoma cells beyond the sentinel lymph node (SLN) is the rule and not the exception (O-003)**

Routine histopathology in patients with positive SLNs is frequently unable to satisfactorily identify metastatic spread to non-SLNs. **Anja Ulmer**, of Universitäts Hautklinik in Germany, described use of lymph node immunocytology with staining for the antibody HMB45 for the detection of early disseminated melanoma in SLNs and their corresponding non-SLNs. This approach was evaluated in a prospective study that included 100 completion lymph node dissections (CLNDs) from 98 melanoma patients with a histopathologically-positive (n=71) or exclusively immunocytologically-positive SLN (n=29). Microscopic evaluation was used to detect and record HMB45-positive cells per million lymphocytes for each node analyzed.

The results indicated detection of metastasis in 15 of 100 CLNDs with histopathologic examination (median, 1 positive node) and in 81 of 100 CLNDs with immunocytology (median, 3 positive nodes). Logistic regression analysis demonstrated that the number of HMB45-positive cells in the SLN was predictive of the detection of metastasis in non-SLNs by either histopathologic ( $P=.0002$ ) or immunocytologic ( $P=.007$ ) examination. The number of HMB45-positive cells in the SLN was significantly correlated with the number of HMB45-positive cells in the corresponding non-SLNs ( $r=0.51$ ;  $P=.0001$ ), although even a low number of HMB45-positive cells in the SLN was associated with substantial risk of spread to the non-SLNs. On average, 5 times more melanoma cells were observed in the SLN than non-SLNs.

Dr. Ulmer concluded the results of this study suggest that lymph node immunocytology is an accurate and practical method for early detection of disseminated melanoma in SLNs and non-SLNs, that melanoma progresses in a sequential fashion from the SLN to corresponding non-SLNs, and, more often than not, that melanoma has already spread from positive SLNs to non-SLNs, even in cases where histopathologic examination determines the latter to be negative for dissemination. Randomized studies evaluating the clinical significance of low volume metastatic disease should examine both positive SLNs and corresponding non-SLNs.

#### **Phase II clinical trial with a second-generation, GM-CSF encoding, oncolytic herpesvirus in unresectable stage IIIc and IV melanoma (O-012)**

The most promising vaccines to date have been autologous, and hence impractical for wider use, and oncolytic viruses have been insufficiently potent to provide widespread, systemic effects. **Robert Coffin**, of Biovex, Inc, in Woburn, Massachusetts, presented the results from a phase 2 trial of OncoVEX<sup>GM-CSF</sup>, a highly potent second-generation oncolytic herpes simplex encoding GM-CSF, in patients with advanced melanoma. OncoVEX<sup>GM-CSF</sup> was designed with the intent to produce a practical treatment that would combine immune stimulation with a more potent oncolytic virus backbone, thereby providing an in situ autologous vaccine that might yield synergistic systemic efficacy.

In the study reviewed by Dr. Coffin, 50 patients with unresectable stage IIIc or stage IV melanoma, ECOG PS 0-1, 0 to  $\geq 3$  prior therapies, no brain metastases, and serum LDH  $< 2 \times$  the upper limit of normal (ULN) received intralesional injection of OncoVEX<sup>GM-CSF</sup> into accessible (cutaneous, subcutaneous, and nodal) lesions, using direct injection or ultrasound guidance as necessary. OncoVEX<sup>GM-CSF</sup> was initially injected into 1 to 10 tumors followed by a 3-week interval, then every 2 weeks for up to 24 injections. One or more lesions remained uninjected to monitor distant response. Injections were performed in an outpatient setting. The primary study endpoint was overall response rate (ORR) by modified RECIST.

Of the 50 patients enrolled, 47 were clinically evaluable. OncoVEX<sup>GM-CSF</sup> treatment was very well-tolerated, primarily limited to mild flu-like symptoms generally occurring after the first injection. Seven clinical responses (all  $> 6$  month's duration) and 5 partial responses (3  $> 6$  months, and 1 ongoing at  $< 6$  months) were observed in the 47 patients (ORR=26%). Treatment responses were observed with all disease stages, but generally occurred at a lower rate as disease stage increased (ORR=43%, 30%, 25%, and 16% for patients with stages IIIc, IV M1a, IV M1b, and IV M1c, respectively). Objective response did not correlate with number or types of prior treatment, but did correlate with survival. All patients exhibiting a treatment response were still alive 11 to 35 months after initial injection, compared with only 41% of nonresponding patients. Dr. Coffin commented that these findings strongly suggested that achieving an objective response to OncoVEX<sup>GM-CSF</sup> impacted survival.

A pivotal phase 3 trial with durable response rate as the primary endpoint is scheduled for launch in early 2009. Patients enrolled in the study will include those with stage IV or unresectable stage IIIb or IIIc melanoma who have failed 1 or more prior therapies. Patients will be excluded from enrollment if they have  $> 3$  visceral metastases (not including lung), any visceral metastasis  $> 3$  cm, or serum LDH  $\geq 1.5 \times$  ULN. The plan is to have 240 patients in the OncoVEX<sup>GM-CSF</sup> arm, and 120 patients in a control arm consisting of subcutaneous GM-CSF injection. Overall survival will be a secondary endpoint.

### **A phase I/II study to determine the feasibility and efficacy of the triple combination of oblimersen (OBL), nab-paclitaxel (ABX), and temozolomide (TMZ) in patients with metastatic melanoma and normal LDH (O-014)**

As previously discussed by Dr. Garbe at the meeting, a phase 3 study involving patients with advanced melanoma demonstrated significantly greater efficacy with OBL plus dacarbazine (DTIC) versus DTIC alone.<sup>1</sup> **A. Pavlick**, of the New York University Cancer Center in New York, New York, discussed initial results from a phase 1/2 study exploring triple combination therapy with OBL, nab-paclitaxel (ABX; albumin-bound paclitaxel), and TMZ in patients with advanced melanoma. TMZ is essentially an orally bioavailable form of DTIC with similar efficacy as DTIC.

Two cohorts of patients with advanced melanoma, baseline serum LDH  $\leq 1.1 \times$  the upper limit of normal, and no prior chemotherapy received 2 different dosing regimens of OBL-ABX-DTIC triple therapy. Cohort 1 received OBL 7 mg/kg/d (continuous IV infusion, days 1-7 and 22-29), TMZ, 75 mg/m<sup>2</sup>/d (days 1-42), and ABX 175 mg/m<sup>2</sup> (days 7 and 29) for 4 56-day cycles. Cohort 2 received a similar regimen, but ABX 260 mg/m<sup>2</sup>, rather than 175 mg/m<sup>2</sup>. Peripheral blood mononuclear cells (PBMCs) and tumor biopsies obtained before and after treatment were assayed for Bcl-2 and proliferation markers, and correlated with clinical response. Serial blood samples were collected to examine possible pharmacokinetic interactions between the administered drugs.

At the time of meeting, all 14 patients planned for Cohort 1 had been enrolled, and treatment was ongoing in 10. Neutropenia and thrombocytopenia were the only grade 3/4 AEs observed in the cohort,

occurring in 1 patient each. Partial tumor responses were observed in 4 of the patients (29%), with a duration of >2 cycles. Stable disease of at least 3 cycles in duration was recorded in another 3 patients (21%). IHC analyses indicated a reduction in antiapoptotic proteins (Bcl-2) and an increase in proapoptotic proteins (Bak and BCL-XL) in responding patients. OBL and TMZ did not affect the pharmacokinetics of ABX.

Cohort 2 was closed down due to neurotoxicity in all 4 initially enrolled patients. Enrollment for a third cohort was to begin in late 2008.

## Reference

1. Bedikian AY, Millward M, Pehamberger H, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol.* 2006;24:4738-4745.

## Phase II study of fotemustine plus dacarbazine with dendritic cell vaccines as first-line in Chinese patients of advanced acral lentiginous melanoma (ALM) (O-013)

L. Si, of the Beijing Cancer Hospital and Institute in China, discussed results from a single-center, phase 2 trial in which 28 Chinese patients with previously untreated advanced acral lentiginous melanoma (ALM) received fotemustine (100 mg/m<sup>2</sup> on days 1 and 12), dacarbazine (DTIC) (400 mg/d on days 2-6), and 1 of 2 dendritic cell (DC)-based vaccines (subcutaneously on days 7, 9, and 13) every 28 days. Eighteen patients received DCs loaded with allogeneic melanoma lysates, and 10 HLA-A\*02+24+ patients received vaccines pulsed with melanoma antigen derived peptides (Mart-1, S-100, Mela-A). PFS was the primary endpoint, and overall survival (OS), overall response rate (ORR), and toxicity were secondary endpoints.

Patients received a mean of 3.82 ± 1.25 cycles. Sixteen of the 28 patients had M1c disease, involving liver metastasis in 11 of the cases. At the time of the meeting, 18 of the enrolled patients were still alive, and were followed-up for a median of 12 months (range, 7-41 months). Median PFS was 8.5 months (95% CI, 7.86-15.21), with 12 patients still progression-free at the time of the meeting. Median OS was 11+ months. Three patients achieved a clinical response, and another 7 achieved a partial response (36% ORR). Six patients had stable disease. There were 20 grade 3/4 toxicities recorded during the course of the study: 9 thrombocytopenia (1 leading to death), 5 neutropenia, 6 fatigue, and 1 hypersensitivity reaction.

Dr. Si concluded that fotemustine and DTIC plus DC vaccines was safe and tolerable in this Chinese population with advanced ALM, and the initial efficacy results indicate clinical activity that may provide a survival advantage. Further study of the regimen appears warranted.

## Phase 2 study of LY573636-sodium, a novel anti-cancer compound with a unique mechanism of action, in patients with previously-treated unresectable or metastatic melanoma (O-005)

Tasisulam (LY573636-sodium) is an investigational anticancer agent with a unique mechanism of action that is being explored in clinical trials of melanoma. **Dr. John Kirkwood** provided an overview of tasisulam before discussing the results from a recent phase 2 trial evaluating the compound in patients with previously treated unresectable or metastatic melanoma.

Tasisulam is an acyl-sulfonamide that was shown in initial screens to exhibit activity against a broad range of cancer cell lines, including melanoma. Tasisulam induces apoptosis via activation of the mitochondrial cell death pathway, which leads to cytochrome C release, caspases 2/9 activation, and ultimately apoptosis. Moreover, tasisulam-mediated mitochondrial dysfunction has been associated with decreased adenosine triphosphate (ATP) production and increased levels of ROS within cancer cells. Unlike elesclomol, which rapidly induces generation of ROS in cancer cells, the impact of tasisulam on ROS level takes much longer to develop. In terms of pharmacokinetic properties, tasisulam is highly albumin-bound (99.7%) and has a half-life of approximately 13 days. It is administered as a 2-hour IV infusion every 3 weeks using a loading and chronic dose. Dosing is based on weight and targeted a specific end-of-infusion  $C_{max}$  value. The most common tasisulam-related AEs of any grade in a prior phase 1 trial were thrombocytopenia, anemia, fatigue, and nausea, and the most common grade 3/4 AEs were thrombocytopenia, anemia, and neutropenia.

Dr. Kirkwood then went on to describe an ongoing open-label, single-arm, multicenter, phase 2 trial of tasisulam in patients with advanced melanoma, ECOG PS 0-1, no brain metastases, and no limit on the number of prior immunotherapy-based regimens. Because of the propensity of tasisulam to bind serum proteins, patients were excluded from enrollment if they were taking warfarin or warfarin-like anticoagulants or had a serum albumin level  $<3.0$  g/dL. Overall response rate (ORR) per RECIST was the primary endpoint, and secondary endpoints included PFS, overall survival, and safety/tolerability. Tasisulam was administered as a 2-hour infusion every 3 weeks until progression or unacceptable toxicity, and the  $C_{max}$  target was 420  $\mu\text{g/mL}$ . An interim efficacy analysis was to be performed when 25 patients had completed 2 cycles and undergone radiographic assessment of response.

Similar to the prior phase 1 trial, the most common AEs of any grade in the 58 patients initially enrolled and treated patients included fatigue, nausea, and thrombocytopenia. The most common grade 3/4 AEs were once again thrombocytopenia (21%), neutropenia (17%), and anemia (7%). The interim efficacy analysis revealed no clinical responses but 6 partial responses in the 25 clinically evaluable patients, for an ORR of 24%. An additionally 6 patients (36%) had stable disease as best response. Of the 25 patients, 6 had received 6 or more cycles before disease progression. Dr. Kirkwood characterized the preliminary results from this trial as encouraging and suggested they warrant further study of tasisulam alone or in combination with other agents as first- or second-line therapy for patients with advanced melanoma.

## **Nab-paclitaxel and bevacizumab as first-line therapy in patients with stage IV melanoma (O-004)**

**P. Boasberg**, of the Angeles Clinic and Research Institute in Los Angeles, California, presented the latest findings from an ongoing study evaluating *nab*-paclitaxel plus bevacizumab as first-line therapy in patients with stage IV melanoma. A prior study demonstrated combining bevacizumab with paclitaxel enhances tumor response to paclitaxel in patients with metastatic breast cancer.<sup>1</sup> *Nab*-paclitaxel is an albumin-bound form of paclitaxel that demonstrated single-agent activity in a prior phase 2 trial of patients with stage IV melanoma.<sup>2</sup> In the study reviewed by Dr. Boasberg, *nab*-paclitaxel was administered as 150 mg/m<sup>2</sup> on days 1, 8, and 15 of a 28-day cycle, and bevacizumab 10 mg/kg on days 1 and 15 of the cycle.

Dr. Boasberg presented the results from 19 patients treated between 08/15/07 and 4/30/08, after a median of 6 monthly cycles (range, 2-10). Disease control (overall response rate plus stable disease) was observed in all patients after cycle 2 (7 partial response, 12 stable disease). After cycle 4, 1 patient had achieved a clinical response, 6 exhibited partial response, and another 6 had stable disease. One patient exhibited progressive disease at this time. The PFS rate at 4 months was 87%. At the time of the meeting, 7 patients were

off-study, 5 for progressive disease, 1 for toxicity, and 1 for an unrelated event. Three patients had died, at 5, 6, and 7 months, respectively. Forty patients experienced dose-limiting toxicities, 33 due to *nab*-paclitaxel (18 with grade 3 neutropenia, 12 with grade 3 neuropathy, and 1 each with mucositis, anemia, and macular edema), and 7 due to bevacizumab (4 with hypertension, 2 with proteinuria, and 1 with hyponatremia).

Dr. Boasberg concluded that initial study results suggest the combination of *nab*-paclitaxel and bevacizumab is an effective and well-tolerated regimen when used in patients with previously untreated stage IV melanoma. Additional information will be available after the study is completed.

## References

1. Miller KD, Burstein HJ, Elias D, et al. Phase II study of SU11248, a multitargeted tyrosine kinase inhibitor (TKI) in patients (pts) with previously treated metastatic breast cancer (MBC). Presented at: San Antonio Breast Cancer Symposium 28th Annual Meeting; December 8-11, 2005; San Antonio, Texas. Available at [www.sabcs.org](http://www.sabcs.org). Accessed January 19, 2009.
2. Hersh EM, O'Day S, Gonzales R, Samlowski WE, Gordon MS, Hawkins M. Open-label, multicenter, Phase II trial of ABI-007 in previously treated and previously untreated patients with metastatic malignant melanoma. *J Clin Oncol*. 2009;23(16 suppl).

## **PV-10 chemoablation of cutaneous and subcutaneous metastatic melanoma (O-0006)**

**J. Thompson**, of the Sydney Melanoma Unit in Australia, discussed the results from a phase 1 study examining the intralesional administration of rose Bengal solution (PV-10) for chemoablation of metastatic melanoma. Prior research suggested that PV-10 may elicit local chemoablation at the injection site, as well as a bystander response on adjacent tissue. Dr. Thompson provided safety/tolerability and preliminary efficacy results for 20 patients with cutaneous and/or subcutaneous stage III/IV melanoma after PV-10 treatment. PV-10 was administered as a single treatment to 1-20 target lesions (0.5 mL per cc lesion volume), and 1 to 3 untreated lesions were examined for potential bystander effects. At 12 to 24 weeks following injection, 110 target lesions were evaluable for chemoablative effects of treatment, and an additional 40 lesions were evaluable for bystander effect.

Seventy-five percent of patients achieved clinical benefit (locoregional disease control) in injected target lesions (20% clinical response, 20% partial response, and 35% stable disease), and 15% achieved an objective response in bystander lesions. Moreover, there was a strong correlation between response in target lesions and bystander effects. For example, 25% of patients with an objective response in injected lesions also experienced an objective response in bystander lesions, and 100% exhibited disease control in bystander lesions. By comparison, only 8% of patients without an objective response in injected lesions also experienced an objective response in bystander lesions, and 75% exhibited progressive disease in bystander lesions.

Intralesional administration of PV-10 was generally well tolerated, with few systemic effects (1 case each of mild insomnia secondary to injection site pain, mild photosensitivity reaction in the injected limb, and severe photosensitivity reaction). Transient mild-to-moderate pain at the injection site was the most common AE (75% of patients), followed by local inflammation or mild infection (25% of patients).

An expanded phase 2 portion of the study began in late 2007, with an expected enrollment of an additional 80 patients with stage III/IV melanoma. All patients will receive PV-10 as in the phase 1 study, but new or incompletely responsive lesions may be treated at weeks 8, 12, or 16 after initial PV-10 administration in the phase 2 study. Follow-up for the phase 2 study will be extended from the 12-24 weeks in the phase 1 study to 52 weeks.