

# Clinical Perspectives™

## Highlights from the Perspectives in Melanoma XII Conference

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### *BUILDING THE FUTURE OF MELANOMA CARE* *A Satellite Symposium Sponsored by Schering-Plough*

#### **Sentinel node biopsy—Is it worthwhile or not?**

**Alessandro Testori**, of the European Institute of Oncology in Milan, Italy, discussed the goals and benefits of sentinel lymph node biopsy (SLNB) in melanoma. SLNB is primarily a minimally invasive staging procedure that is associated with minimal morbidity. SLN positivity is the strongest predictor of survival, and the predictive validity of SLNB has been validated in large, multicenter trials. Furthermore, SLNB identifies patients who are suitable candidates for additional therapy, that is, immediate completion lymph node dissection (CLND) or consideration for adjuvant therapy (interferon- $\alpha$  in clinical practice or investigational agents in the clinical trial setting). Dr. Testori stated that a very skilled pathologist is critical to maximizing the potential utility of SLNB.

Much of what we currently know about the potential benefits of SLNB, Dr. Testori offered, comes from the Multicenter Selective Lymphadenectomy Trial-I (MSLT-I). MSLT-I was a large trial of 1,269 patients with an intermediate-thickness primary melanoma who were randomized to wide excision and postoperative observation of the regional lymph node (with lymphadenectomy/CLND if nodal relapse occurred) or to wide excision and SLNB with immediate CLND if nodal metastases were detected on biopsy (ie, for positive SLNs or SLN+).<sup>1</sup> The study results showed SLN+ was the most powerful prognostic factor for overall survival (OS), pointing to its utility as a staging and diagnostic tool.

However, although disease-free survival (DFS) rates were significantly higher for patients in the SLNB than nodal observation group in MSLT-I, there were no significant between the groups for melanoma-specific survival rates.<sup>1</sup> In addition, Dr. Testori mentioned results from an Italian study of 1,300 melanoma patients which suggested SLNB does not modify the natural course of the disease. Dr. Testori suggested that a relatively limited number of SLN+ patients and a short follow-up may account for the negative findings in MSLT-I for OS. Alternatively, the 5-year survival rate was significantly higher for patients who underwent immediate CLND than for those who underwent delayed CLND, suggesting surgical management based on SLN status can significantly improve the survival for patients with nodal micrometastases.

Dr. Testori concluded his discussion by describing the general design and intent of MSLT-II. MSLT-II is a randomized, multicenter, phase 3 trial that will compare SLNB and CLND with SLNB alone in patients with cutaneous melanoma and either histopathologic or molecular evidence of metastases in the SLN. The primary objective of the trial is to determine whether removal of the SLN alone is sufficient nodal surgery in certain patients with SLN+ status, as determined by differences in DFS. A number of secondary objectives have also been defined. A total of 4,200 or more patients are planned for accrual, and as of June 27, 2008, 602 patients had been accrued. Dr. Testori stated that MSLT-II will answer some questions concerning SLNB, but it will probably raise a number of new ones as well.

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## Oncogene based treatment decisions: Fact or fiction?

**Dirk Schadendorf**, of the University Hospital of Essen in Essen, Germany, discussed the growing knowledge of the genetics and molecular biology of melanoma, and whether this can be used to guide treatment decisions in the current environment. A number of groups are known to be at heightened risk for cutaneous melanoma, including those with “fair complexion,” high nevus counts (>50), multiple dysplastic nevi (>5), a history of melanoma in themselves or family members, or intermittent-excessive sun exposure. Variants of *MC1R*, *ASIP*, and *TYR*, genes involved in regulation of pigmentation, have been linked with increased melanoma risk.<sup>1</sup>

Current data suggests there are multiple subsets of melanoma, rather than a single disease entity, and that factors such as presence of multiple nevi or solar keratoses; mutations of *BRAF*, *NRAS*, *p53*, *PTEN*; or multiple copies of *CDK4* and *CCND1* may be used to identify these subsets.<sup>2,3</sup> A number of other genetic/epigenetic changes have also been linked with increased risk of melanoma.<sup>4</sup> The consequence of these changes is typically an alteration in signaling pathways within melanocytes, and a heightened risk for melanoma development or progression. Furthermore, gene expression profiling has identified a large number of genes associated with outcomes such as distant metastasis-free survival in patients with primary melanoma, thereby beginning to elucidate the molecular mechanisms underlying poorer prognosis.<sup>5</sup> Other factors, such as ulceration or serum LDH level, have prognostic significance and appear to predict treatment response,<sup>6-9</sup> but the molecular mechanisms underlying these associations are currently unclear.

Given this database, Dr. Schadendorf questioned, is the melanoma community at a point where treatment decisions can be based on knowledge of the molecular underpinnings of the disease in individual patients? The answer to that appears to be no, at least not yet. Current knowledge has not translated into treatment decisions, although there is much ongoing research exploring the possibilities or molecularly targeted therapy for melanoma. There is little doubt that progress has been made in understanding the biology of melanoma, Dr. Schadendorf said, and we have a number of antibodies and small molecules that can target signaling pathways or other players in melanoma pathogenesis, but we still far away from basing treatment decisions on genetic or molecular alterations identified in individual patients. Current explorations of molecularly targeted therapy in melanoma suggest that targeting single signaling pathways is often not sufficient to affect meaningful change,<sup>10</sup> and that targeting multiple signaling pathways may be a more fruitful approach.<sup>11,12</sup>

## References

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### Stage IV melanoma treatment: What is new?

**Caroline Robert**, of the Institut de Cancérologie Gustave Roussy, in Villejuif, France, talked about some of the newer treatment regimens being used or investigated in patients with metastatic or stage IV melanoma, as well as general approaches to treatment in this patient population. Dr. Robert noted that the recent meta-analysis by Korn and coworkers of phase 2 Cooperative Group trials in stage IV melanoma have provided benchmarks for PFS and overall survival (OS) that should prove useful in trials of investigative therapies,<sup>1</sup> Dr. Robert also said that very rare and sometimes impressive and durable responses are observed with almost any of the treatments used. Future progress in treatment of advanced melanoma will probably come in large part from improved understanding that allows better matching of treatment regimens with individual patients and tumor subtypes. All melanoma tumors are undoubtedly not the same, and hence might be differentially responsive to different treatments.

The 2006 study by Bedikian and coworkers, demonstrating oblimersen plus dacarbazine (DTIC) improved outcomes in advanced melanoma patients without elevated baseline serum LDH (but not those with elevated levels), provided support for the notion that biomarkers can be identified and eventually used to guide treatment options.<sup>2</sup> Moreover, recent data suggests various melanoma clinical subtypes are correlated with various somatic genetic alterations and may be differentially sensitive to different molecularly targeted therapies.<sup>3-6</sup> A preclinical study by Solit and colleagues used SKMEL melanoma cell lines to show the growth inhibitory effect of MEK inhibition depended on the presence of BRAF mutations.<sup>6</sup> In addition, other work suggests that aspects of the host's immune response prior to or after initiating anticancer therapy may help predict treatment response.<sup>7-9</sup> Dr. Robert made particular mention of the promise that microarray technology holds for identifying gene-expression profiles predictive of cancer outcomes or for identifying biomarkers predictive of treatment response.<sup>10,11</sup> The outcomes of these studies may allow tailoring treatment based on disease severity or likelihood of recurrence or progression.

Dr. Robert next turned her attention to the treatment of advanced melanoma with anti-CTLA-4 antibodies (ipilimumab and tremelimumab). Of note, the spectrum of response to anti-CTLA-4 antibodies seems to be different from classical cytotoxic chemotherapy responses. In addition to classical tumor responses, a subset of patients exhibit either delayed responses (stable disease later followed by partial response or clinical response) or initial progression or evidence of new lesions before regression is observed. This spectrum of response is thought to be due to the mechanism of action of these agents, which presumably requires some passage of time before maximal effect is observed. More research is needed to

better understand the mechanism of action of these drugs and how it relates to observed clinical responses and outcomes.

Other new promising agents or approaches to treatment of advanced melanoma mentioned by Dr. Robert include antiangiogenic, proapoptotic, and pro-oxidant drugs, as well as targeted therapies focused on downstream effectors in signaling pathways and immunomodulatory drugs. Moreover, there is a need to test various combinations of chemotherapy, immunotherapy, and targeted therapy.

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