Clinical Perspectives™

Highlights from the Perspectives in Melanoma XII Conference

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

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Editor's Note...

Cutaneous melanoma continues to be a troublesome cancer associated with poor prognosis when diagnosed during later stages. In 2008, an estimated 62,480 individuals in the United States were expected to be diagnosed with invasive cutaneous melanoma and 8,420 to die from the disease. Much research is ongoing to better understand the pathogenesis of melanoma and how to better manage patients diagnosed with the disease.

This publication presents highlights from the Perspectives in Melanoma XII conference, held in Scheveningen/The Hague, the Netherlands, on October 2-4, 2008. A wide range of areas related to melanoma biology, staging, and treatment were presented at this conference and a related satellite symposium, and should be of significant interest to practicing clinicians and researchers.

Only what we considered to be the most relevant material is presented here due to space limitations. The content is divided into sections that parallel those at the conference, including the satellite symposium. The entire publication has been reviewed by Keith T. Flaherty, MD, Dirk Schadendorf, MD, and myself, as well as many of the individual presenters. Substantial additional highlights from the conference are available at www.MelanomaCare.org.

It is my sincere hope that the information presented in this publication and at www.MelanomaCare.org will help to advance the understanding and treatment of melanoma. We welcome any comments you might have.

Sincerely,

John M. Kirkwood, MD,
Managing Editor

Continuing Medical Education Information

Target Audience
Dermatologists, surgical oncologists, general surgeons, medical oncologists, and oncology nurses involved in the management of patients with melanoma.

Statement of Need
The Perspectives in Melanoma XII meeting, held in Scheveningen/The Hague, the Netherlands, October 2-4, 2008, was an important forum for discussion of the latest research in many areas of melanoma research. This publication offers a comprehensive overview of the most relevant presentations for those healthcare providers who were unable to attend this noteworthy meeting.

Educational Objectives
Upon proper completion of this CME activity, participants should be able to:
- Better comprehend how insights into melanoma biology/pathogenesis speak to drug resistance and are helping to drive biomarker and treatment development
- Review the importance of the sentinel lymph node both for staging and as a potential focus of attack for regional immunotherapies
- Summarize the current state of adjuvant therapy in melanoma and areas of ongoing research
- Identify alterations in immune function associated with melanoma development or progression, and strategies to improve immune function in melanoma patients
- Evaluate the current state of development of molecularly targeted and other emerging therapies for melanoma

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NEW INSIGHTS INTO MELANOMA BIOLOGY, PATHOGENESIS, AND EPIDEMIOLOGY

Sun tanning in Iceland: models for understanding melanoma epidemiology. **Phillippe Autier**, of the International Agency for Research on Cancer (IARC) in Lyon, France, presented the results from research of factors potentially associated with the dramatic increase in melanoma incidence observed in Iceland between 1990 and 2000. Until the early to mid 1990s, the incidence of cutaneous melanoma was notably lower in Iceland than in other Nordic countries.[1] However, by 2000, the incidence in Iceland was greater than in other Nordic countries. Dr. Autier and colleagues used data from the Icelandic Cancer Registry (ICR) to analyze temporal trends in melanoma incidence in Iceland, and compared these rates with temporal trends on travels abroad and sunbed use.

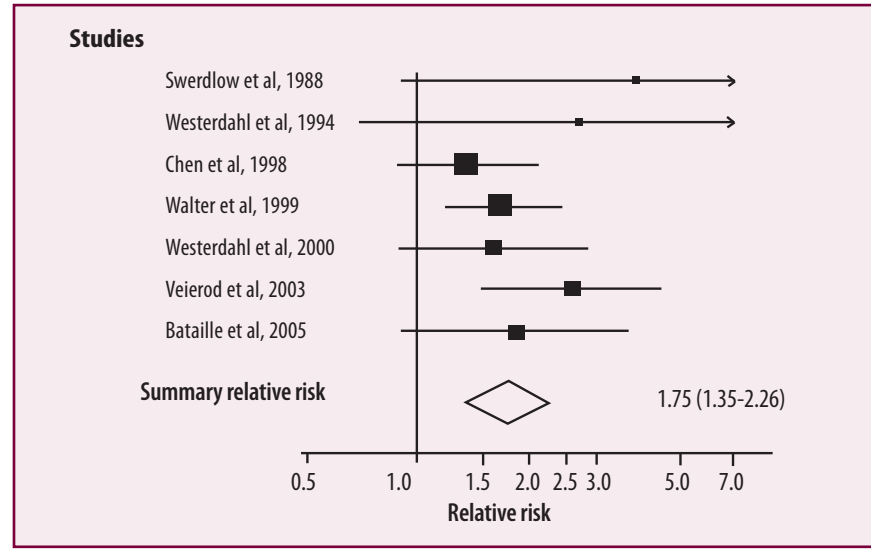
Analyses showed a generally continuous increase in melanoma of the head and neck, trunk, and upper and lower limbs in males from 1955 to 2006. Conversely, the analyses of melanoma in women showed a significant breakpoint in 1992, after which incidence increased 11% per year until 2001 ($P<.0001$). The post-1992 increase was mainly due to melanoma of the trunk, particularly in women under age 50. Greater detection due to improved screening appeared to be a possible reason for the melanoma increase in women, Dr. Autier said, but is not consistent with the increase of trunkal melanoma compared with melanoma of the lower limbs. Other possible explanations included increases in travel to sunny areas and sunbed use.

Dr. Autier pointed to a 2004 study by Rafnsson and colleagues identifying risk factors for melanoma in a sample of Icelanders that demonstrated a link between history of sunny site vacations or sunbed use or increased frequency of severe sunburn after age 19 for both men and women.[2] Furthermore, more men than women reported never using a sunbed (34% vs 12%), and history of sunbed use was greater for younger than for older women (3.3% of women age 20-39 never used a sunbed, compared with 15.7% and 32% of women age 40-59 and >60, respectively).[2] Other data indicated an increase in the number of sunbeds in Reykjavik, Iceland, from 7 in 1979 to 56 in 1984 and 207 in 1988.[3] Moreover, the average number of sunbed sessions per year in subjects age 20 or older during the period 1996-2006 was greater in Iceland (2.9) than in Sweden (1.2) or the United Kingdom (0.5).[3] Dr. Autier also noted that the increase in melanoma of younger women is not confined to Iceland[4] and recent literature includes a review showing an association between sunbed use and incidence of cutaneous melanoma (**Figure 1**).[5]

Dr. Autier reported that Icelandic dermatologists started to discourage sunbed tanning, and that since 2001, the incidence of trunkal melanoma has decreased in Icelandic women. In addition, the mortality rate from melanoma in Iceland has remained essentially constant in men and women since the 1970s to the present. Taken together, these data suggest that ultraviolet A exposure from sunbeds has near-term effects on melanoma risk and does not require prolonged lag time for impact assessment. The data also suggest that sunbeds may increase the risk of thin melanomas having a relatively indolent course, although this requires further study.

Targeting a novel embryonic pathway in melanoma. **Mary J. C. Hendrix**, of Northwestern University in Chicago, Illinois, discussed research from her laboratory suggesting the possibility of using proteins derived from the embryonic microenvironment to reprogram metastatic melanoma cells and promote their reversion to nonmalignant melanocytes.[6] Embryonic stem cell progenitors and aggressive tumor cells share many attributes and show a convergence of signaling pathways. Alternatively, studies demonstrate that compound(s) present in the embryonic, but not the melanoma cell microenvironment have the capacity to suppress the tumorigenic phenotype and promote reversion of at least a

Figure 1. Relative Risk for Cutaneous Melanoma Associated With First Use of Indoor Tanning Equipment at Age <35 Years



From IARC Working Group on Artificial Ultraviolet (UV) Light and Skin Cancer. *Int J Cancer*. 2007;120(5):1116-1122.[5]

subset of melanoma cells toward a melanocytic phenotype.[6-9]

Dr. Hendrix and her colleagues have developed a 3-dimensional model to study the impact of the microenvironment of human embryonic stem cells (hESCs) on melanoma cells.[10] In a series of experiments involved in this and other models, they have demonstrated that a protein called Nodal is expressed in hESCs and overexpressed in aggressive melanoma cells.[6,10]

Nodal is an embryonic morphogen belonging to the transforming growth factor-β (TGFβ) superfamily that maintains hESC pluripotency. Nodal expression is negatively regulated by 2 extracellular proteins—Lefty A and Lefty B—that are critical in cell-fate differentiation. Lefty is expressed by hESCs but not by aggressive melanoma cells, which accounts for Nodal overexpression in the latter cells. Exposure of metastatic melanoma cells to the microenvironment of hESCs, which contains Lefty, causes downregulation of Nodal expression, reduced clonogenicity, and a decrease in tumor formation. In addition, Nodal inhibition has been associated with reversion of metastatic melanoma cells towards a less aggressive melanocyte-like phenotype, induction of apoptosis, and reduced tumorigenicity.

Dr. Hendrix concluded that these experiments suggest that Nodal may be a new biomarker for disease progression and highlight Nodal and possibly other interrelated compounds as potential new targets for therapy in melanoma.

IMPACT OF EMERGING TECHNOLOGIES FOR BIOMARKER DEVELOPMENT

Gene profiling. Understanding the mechanisms of cutaneous melanoma progression, and subsequent development or use of targeted therapies to disrupt these mechanisms, may be advanced by studies correlating genome-wide gene expression from primary melanomas with clinical outcome. **Alan Spatz**, who has recently relocated from Europe to McGill University in Montreal, Quebec, presented results of an European Organization for Research and Treatment of Cancer (EORTC) Melanoma Cooperative Group initiative evaluating gene expression profiling of primary cutaneous melanomas.

A recent study by Spatz and associates used gene expression profiles from primary melanomas to identify 254 genes associated with distant metastasis-free survival (DMFS), many of which are involved in activating DNA replication origins, or so-called replication origins firing (ROF)-related genes.[11] In particular, expression of several mini-chromosome maintenance (MCM) genes (*MCM2, 3, 4,* and *6*) and geminin were significantly associated with poorer overall survival (OS) as well as DMFS, and a multivariable Cox model showed expression of MCM4 and MCM6 were significant independent predictors of OS. Dr. Spatz discussed findings from other researchers suggesting that overexpression of certain DNA-replication "licensing" factors (eg, CDT1 and CDC6), which interact with MCMs on the ROF site of chromatin to facilitate replication, may also be involved in melanoma progression.[12] Furthermore, geminin has been demonstrated to interact with these licensing factors to prevent re-replication of DNA—suggesting a complex interaction of factors and genomic profile associated with susceptibility to melanoma metastasis or progression.

Spatz and associates have also identified *human pituitary tumor-transforming gene 1* (*hPTTG1*) as a gene involved in early acquisition of metastatic potential in melanoma.[13] *hPTTG1* codes for securin, a protein involved in sister chromatid separation, and is frequently overexpressed in nodular melanoma associated with cells in the vertical growth phase. It may promote melanoma progression through aneuploidy and genetic instability, or apoptosis inhibition through p53. Other genes or proteins whose expression Dr. Spatz mentioned as having been implicated or suggested to play a role in melanoma progression include *BRCA1* and BRCA1-IRIS, p53, and *telomeric repeat-binding factor 2* gene (*TRF2*). BRCA1-IRIS has also been linked with MCM2 and geminin.[14]

In addition to altered expression of genes involved in DNA replication/cell proliferation, overexpression of a large number of genes involved in DNA repair has also been linked with melanoma metastasis through examination of gene expression profiles.[15] Besides facilitating distant metastases, overexpression of these genes may explain the resistance of melanomas to traditional cytotoxic chemotherapies.

Dr. Spatz concluded his presentation by pointing to data suggesting that the classification of melanoma based on histologic analysis focused on the lateral epidermal component[16] may be improved through the integration of genetic or molecular factors such as *p53, KIT, BRAF, NRAS, CDK4,* and *CCND1*—particularly when evaluating sun-exposed melanomas.[17-20] He suggested that melanoma is a heterogeneous group of diseases, and that solar elastosis is an important phenotypic variable that discriminates between categories, and appears to affect expression of certain identifiable genes.

Biomarker development and the role of proteomics. Currently, clinicians can generally predict outcomes for melanoma patients based on tumor characteristics such as tumor thickness and ulceration (among others),[21] but these predictions are derived from analyses of large numbers of patients, and there is a

need for markers to provide a more accurate prognosis for individual patients with melanoma. **Dirk Schadendorf**, of the University Hospital Essen in Essen, Germany, discussed the possibility that, at some time in the future, proteomics may be able to improve clinicians' ability to predict outcomes in *individual* melanoma patients, either by identifying novel protein biomarkers or by identifying proteomic profiles that are predictive of outcomes.

Dr. Schadendorf noted that during the last 20 years there has been a general evolution from a focus on single biomarkers present in serologic samples to tumor-associated gene expression and tumor-specific defects in individual genes. More recently, there has been a further shift from examination of single markers to "pattern recognition," as determined through analysis of alterations in the genome (genomics) or protein expression (proteomics) in patients versus normal controls, or among patients with different stages of disease. The goal is to identify markers or patterns of gene and/or protein expression that provide a reliable estimate of individual risk of tumor progression and/or response to (targeted) therapy. Ultimately, Dr. Schadendorf said, we would like to not only predict progression, but also define patient subgroups that are most likely to benefit from one or another course of therapy.

To date, S100B protein has been the most widely used serologic marker in melanoma. Serum level of S100B protein has been shown to correlate with tumor load and stage of disease, and appears to be a useful marker for relapse or metastasis and response to therapy,[22] without predictive value for tumor-free patients (ie, postresection stage I/II patients). Dr. Schadendorf and colleagues have been using serum proteomics to identify individual proteins or patterns of expression that may discriminate early- and late-stage melanoma and predict disease progression.[23]

At the *Perspectives in Melanoma* meeting, Dr. Schadendorf described a recent study that used matrix-assisted laser desorption/ionization time of flight (MALDI-ToF) mass spectrometry and protein chip technology to analyze the serum from patients with stage I, III, or IV melanoma.[23] Serum S-100B levels were only evaluated for comparison. Proteomic analysis identified a peak corresponding with an average mass value of 11,700 Da that was more highly expressed in stage IV than in stage I patients. Furthermore, patients with stage III disease could be correctly assigned as progressors or nonprogressors in 82% of cases based on proteomic profiles, whereas elevated serum S100B level detected relapses in only 21% of cases.[23]

More recent studies from the laboratory identified the protein with elevated expression in stage IV patients as serum amyloid A (SAA), and demonstrated that it is a highly significant serum marker of poor prognosis in patients with stage I-IV melanoma ($P<.0000005$).[24] More specific analyses of patients with stage III disease demonstrated that elevated versus normal SAA level was associated with significantly poorer survival ($P=.043$), as was elevated S100B ($P=.034$) or C-reactive protein (CRP) level ($P=.0055$), but not elevated lactic dehydrogenase (LDH) ($P=.93$). Similarly, for patients with stage IV disease, elevated SAA ($P=.000083$), CRP ($P<.0000005$), and S100B levels ($P=.0010$) were also associated with poorer survival, although SAA and CRP appeared to be more powerful predictors. As expected, elevated LDH was also a highly significant predictor of survival in this patient population ($P<.0000005$). Stage I-IV patients with both normal SAA and normal CRP levels had the highest probability of survival, while those with elevations in both markers had the lowest. Intermediate probability was associated with elevation of either one or the other, but not both, serum markers.[24]

Dr. Schadendorf emphasized that it is crucial that the data of proteomic profiling and prognosis are validated. The data should be validated using independent sample sets, ideally from different centers and collected in a prospective fashion. It is also important that multiple platforms be used to validate the data. Furthermore, before one can talk about identification of a new marker for clinical usage, the marker needs to be prospectively validated in relation to other known biomarkers in large clinical trials. Ultimately, it is hoped that new markers can be identified that increase insights into the various physiologic processes of melanoma and lead to innovative concepts for diagnosis and treatment.

ADVANCES IN STAGING AND SURGERY

Biologic and immunologic factors within the sentinel node. Clinically, sentinel lymph node biopsy (SLNB) plays a critical role in melanoma staging and treatment decisions based on the presence or absence of SLN metastases. Also, for patients shown to have tumor-positive nodes, immediate complete lymph node dissection (CLND) may provide some therapeutic benefit, compared with delayed CLND. From a basic science view, the SLN allows investigation of the interactions between the microenvironment of the primary tumor and adjacent regional lymph nodes. **Richard Essner**, of the California Oncology Research Institute and UCLA School of Medicine in Los Angeles, California, described research suggesting that the earliest significant immune interactions of melanoma may occur at the level of the regional lymph node basin and alterations to this immune response may have therapeutic implications. By reducing the presence of immunosuppressive and growth-enhancing factors in the SLN, the growth and spread of SLN metastases could be prevented.

Dr. Essner described results from a study he conducted with Masayuki Kojima showing downregulation of dendritic cell (DC) activation markers (CD80, CD86, CD40), and corresponding T-cell receptors (CTLA-4 and CD28) in the SLN of patients with early-stage melanoma compared with matched nonsentinel nodes.[25] Downregulation of DC activation was not related to altered T- or B-cell expression, nor was it affected by the timing or nature of the skin biopsy of the melanoma. Interleukin (IL)-10 overexpression in the SLN was a factor driving diminished immune function in these patients. These results point to suppression of regional host immune function in SLN from melanoma patients that is present during early-stage disease.

A more recent study by Dr. Essner and associates of early stage I/II patients who underwent wide excision and SLNB showed that IL-10 and interferon (IFN)-α levels were dramatically higher in the SLN than in nonsentinel nodes or SLN metastases, but not in patients without residual disease or with tumor-negative SLNs.[26] These results point to the presence of melanoma as the source of the regional immunosuppression.

Essner and associates developed the hypothesis that reversal of regional immunosuppression could be possible with intratumoral injection of immune-enhancing agents such as granulocyte-macrophage colony stimulating factor (GM-CSF; Leukine, Bayer). Moreover, a study with peritumoral injection of Leukine 2 to 5 days prior to wide excision and SLNB was associated with significantly higher SLN T-cell area, DC area, and DC density than in patients who did not receive peritumoral Leukine. GM-CSF is a cytokine known to promote DC proliferation and recruitment and upregulation of costimulatory molecules (ie, to boost immune function).

Hence, the findings from this study lent support to the notion that locoregional immunotherapy may be able to reverse cytokine-mediated immunosuppression in the SLNs from patients with early-stage melanoma. Dr. Essner stated that a number of studies point to the concept that immunotherapy is more likely to be beneficial in melanoma when used early rather than in more advanced disease, when host immune function is very severely disrupted.

Further support for the concept of locoregional immunotherapy was provided by a randomized, single-blinded, phase II trial in which patients with stage I melanoma were assigned to receive peritumoral administration of either GM-CSF or saline around the wide excision site prior to surgery.[27] Local administration of GM-CSF was associated with increased frequency of mature DCs in the SLN, and enhanced binding to T cells. A subsequent study by the same group using a similar experimental design showed that preoperative intradermal GM-CSF administration was associated with an increase in melanoma-specific $CD8^+$ T-cell reactivity in the SLNs from patients with stage I disease.[28]

Dr. Essner has completed a gene array profiling study of primary melanoma that has identified increased expression of vascular endothelial growth factor (VEGF) and other tumor growth inhibitors in the microenvironment of the primary tumor (CAV1, LIMK1, and MMP15) as potential markers of melanoma progression from stage I/II to III (unpublished data). Recent studies in a mouse melanoma model have suggested overexpression of VEGF is associated with immunosuppression, and that blockade of VEGF receptor (VEGFR) activation would enhance the efficacy of GM-CSF vaccination, promoting immunity and prolonging animal survival.[29] Another recent study reported that combining antibodies to cytotoxic T-lymphocyte antigen-4 (CTLA-4) with GM-CSF vaccination enhanced elimination of tumors in a mouse melanoma model by improving the balance of effector to regulatory T cells (ie, by improving immune cancer surveillance).[30] The immune and antitumor effects of combination therapy were greater than those observed with GM-CSF vaccination or anti-CTLA-4 alone.

Dr. Essner stated that he and his coinvestigators continue to look for other immune-related markers associated with tumor in the SLN and suggested a variety of approaches for blocking the development of regional metastases. A recent publication by Essner and his colleagues identified 5 novel inflammatory genes in SLNs associated with altered expression in tumor-positive versus negative SLNs.[31]

Dr. Essner also described a randomized study he and his colleagues are conducting that further evaluates the therapeutic value of GM-CSF administration at the primary tumor site prior to SLNB. A key question he and other investigators eventually hope to answer is whether converting patients with tumor-positive regional lymph nodes to negative might occur with locoregional immunotherapies. While this theoretical possibility cannot be excluded, there is no data to support this hypothesis.

Regional immunologic assessment of toll receptor agonists and cytokines. Interactions between the primary cutaneous tumor or its microenvironment and the SLN are critical for subsequent risk of melanoma spread, and intradermal injection of immunomodulatory agents at the primary tumor site may be used to decrease this risk. **Tanja de Guijl**, of Vrije Universiteit Medical Center in Amsterdam, the Netherlands, discussed the evaluation of localized immune-modulating compounds designed to facilitate DC migration and augment cytotoxic T-cell activity in the SLN via mechanisms involving toll-like receptors (TLRs).

In melanoma patients, impaired activation of DCs in the primary tumor site or their suboptimal subsequent migration to the SLN may result in impaired immune surveillance of tumor cells in the latter site and increased risk of further melanoma spread, Dr. De Gruijl stated. A recent study using an ex vivo human skin explant model demonstrated that the skin microenvironment affects the

activation state of migrating DCs, and that IL-10 interferes with DC activation and is associated with a phenotypic shift from mature $CD83^+$ DCs (ie, active DCs) to immature $CD14^+$ macrophage-like cells prior to migration.[32] Conversely, prior conditioning of the tissue microenvironment with GM-CSF or IL-4 prevented the phenotypic shift.

In a single-blinded, saline-controlled, phase II study in 12 patients with stage I melanoma, intradermal injection of GM-CSF around the excision site increased the number and activation state of DCs in the SLN and enhanced their binding with T cells, suggesting local treatment of the primary tumor site facilitates the recruitment of mature DCs to the SLN and boosts T-cell–mediated antitumor immunity.[27]

This hypothesis was supported by 2 subsequent studies, the first demonstrating that intradermal GM-CSF treatment increased the number of mature DCs in injected skin and that these frequencies correlated with the number of mature DCs in the SLN,[33] and the second showing increased tumor antigen-specific $CD8^+$ T-cell activity in the SLN from stage I melanoma patients receiving an intradermal GM-CSF injection.[28] In the latter study, melanoma-specific cytotoxic T-cell activity correlated with the number of mature DCs in the SLN.

Dr. De Gruijl noted that the previous studies focused on the activation of myeloid DCs (MDCs) in the SLN, but that plasmacytoid DCs (PDCs) comprise another important DC subset of the regional lymph nodes. Activated PDCs release IFN-α, which boosts the activity of T and natural killer cells, as well as causing activation of conventional MDCs. A subsequent single-blinded, saline-controlled, phase II trial of 23 patients with stage I/II melanoma used local administration of a bacterially derived unmethylated cytosine-phosphate-guanine (CpG) DNA sequence (CpG-B or PF-3512676; formerly CPG 7909) that binds TLR-9 and activates PDCs.[34] Pretreatment with CpG-B was associated with activation of SLN-resident PDCs, increased release of inflammatory cytokines, and reduced frequencies of potentially immunosuppressive regulatory T cells ($CD4^+CD25^{hi}CTLA\text{-}4^+FoxP3^+$). CpG-B injection was also associated with increased numbers of $CD8^+$ T cells reactive with melanoma-associated antigens and natural killer cells.[35] Further, combined administration of low-dose GM-CSF and CpG-B resulted in higher activation of MDCs as well as PDCs compared with CpG-B administration alone (unpublished data).

Dr. De Gruijl concluded that these studies highlight the different subsets of DCs present in the SLN of melanoma patients, and how local administration of cytokines and/or TLR ligands may be used to target these DC subsets to enhance cytotoxic T-cell–mediated antitumor immunity within the SLN. Strategies such as these might be useful as adjuvant therapy.

IMMUNOTHERAPY

Enhancing the immune response to melanoma through CTLA-4 blockade. **Jedd Wolchok**, of Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, New York, discussed CTLA-4 blockade as treatment for advanced melanoma, focusing on initial studies to identify characteristics predictive of response to anti-CTLA-4 agents. CTLA-4 is a co-inhibitory molecule expressed on the surface of activated cytotoxic T cells and regulatory T cells that serves as an immunologic checkpoint or negative regulator of continued T-cell response.[36] Hence, blockage of CTLA-4 is one strategy for prolonging the duration and intensity of host antitumor responses. Two anti-CTLA-4 monoclonal antibodies (tremelimumab and ipilimumab) are in advanced phases of development, and have shown durable clinical benefit in a subset of refractory metastatic melanoma patients, with manageable mechanism-based toxicities.[37]

Dr. Wolchok described data he and his colleagues have collected from patients treated with ipilimumab at MSKCC. Patients there were treated with a regimen of 4 induction doses of 10 mg/kg every 3 weeks, followed by maintenance therapy of 10 mg/kg every 12 weeks for patients exhibiting benefit and lack of major toxicity. Dr. Wolchok reported that tumor responses (RECIST or WHO criteria) have been observed in ipilimumab-treated patients, as well as atypical or unique patterns of clinical response. The latter included a slow steady decline in tumor burden with eventual fulfillment of criteria for response as late as week 24, response in baseline target lesion in the context of appearance of a new lesion, and overt progression preceding response. Like others, he has observed immune-related adverse events (AEs) that are medically reversible.

Dr. Wolchok stated that his group has been prospectively collecting serum and peripheral blood mononuclear cells from their patients at various time points pre- and post-ipilimumab therapy to analyze immunologic changes occurring during treatment. The intent is to better understand the mechanism of action of ipilimumab and other anti-CTLA-4 antibodies, and to identify the subset of melanoma patients who experience durable benefit from these agents. Dr. Wolchok noted that these analyses are still very preliminary, but that some potentially important observations have already been made.

For example, some patients have been observed to develop de novo antibody responses to a panel of cancer-testis antigens, and particularly NY-ESO-1/LAGE-1. NY-ESO-1 antigen is expressed in a broad range of cancer subsets and elicits both antibody and T-cell responses. In the MSKCC study, more than 50% of ipilimumab responders exhibited NY-ESO-1 seropositivity, compared with far fewer

of the nonresponders. Furthermore, patients with NY-ESO-1 seropositivity had detectable posttreatment $CD8^+$ (cytotoxic T cell) and $CD4^+$ (regulatory/helper T cell) T-cell responses to NY-ESO-1. Overall, ipilimumab treatment was associated with increased NY-ESO-1-specific T-cell responses, demonstrating a polyfunctional response pattern that included IFN-γ, MIP-1β, and TNF-α. Ipilimumab treatment was also generally associated with an increase in the ratio of $ICOS^{high}$ to $FoxP3^+$ T cells.

Taken together, these data suggest response to ipilimumab in patients with advanced melanoma may occur more frequently in those who have pre-existing or induced NY-ESO-1 antigen-specific T- and B-cell responses. Portions of this study were published subsequent to the meeting.[38]

Dr. Wolchok said they are currently using protein arrays to identify antigenic targets and immunologic signatures of response based on serologic reactivity after CTLA-4 blockade.

Targeting novel immune regulating costimulatory molecules. **Jeffrey Weber**, of H. Lee Moffitt Comprehensive Cancer Center and Research Institute in Tampa, Florida, highlighted 4 agents targeting or regulating costimulatory molecules that are being explored as potential therapies for melanoma. The first, anti-CTLA-4 antibodies, were discussed in greater detail in other presentations. In addition to anti-CTLA-4 antibodies, Dr. Weber also discussed a human IgG 4 antibody (MDX-1106) directed against the molecule programmed death-1 (PD-1), a human anti-CD137 agonist monoclonal antibody (anti-41BB or BMS-663513), and another monoclonal antibody directed against CD40 that has agonistic properties (CP-870,893).

PD-1 is a receptor expressed on activated $CD8^+$ and $CD4^+$ T cells that binds B7-H1 (PD-L1), a ligand expressed by many human tumors that has been correlated with poor clinical outcome in patients with renal cell carcinoma or ovarian cancer. PD-1 is a negative regulator of T-cell activity. Activation of PD-1 pathways blocks T-cell receptor signal transduction and may be associated with suppression of antitumor immunity. PD-1 blockade appears to augment tumor-specific immunity and overcome regulatory T-cell suppression of $CD8^+$ T cell antigen-specific reactivity. MDX-1106 (ONO-4538) is a recently developed anti-PD-1 human monoclonal antibody that binds with high affinity to PD-1 to abrogate PD-1 activity.

Initial results from a dose-escalation phase I trial of MDX-1106 in 39 patients with various refractory or relapsed tumors, including 9 with melanoma, were reported at the 2008 ASCO meeting.[39] The targeted maximum single dose, 10 mg/kg, was achieved without dose-limiting toxicities (DLTs), and repeated dosing was associated with only 1 ≥ grade III toxicity (colitis). Grade I/II AEs included pruritis, rash, fatigue, polyarticular arthropathy, and thyroid-stimulating hormone elevation. Only 1 of the 36 patients evaluable for tumor response at 12 weeks achieved a partial response (PR) (for >6 months) after administration of a single dose of MDX-1106, and 4 others demonstrated lesional regressions not meeting PR criteria, including 2 with melanoma. MDX-1106 enhanced $CD8^+$ but not $CD4^+$ T-cell infiltrates 4 weeks following a third dose in a melanoma patient exhibiting regression of lymph node metastasis.

BMS-663513 is a fully human monoclonal antibody directed against CD137, a member of the tumor necrosis factor (TNF) receptor family that functions as a costimulatory molecule for $CD8^+/CD4^+$ T cells. BMS-663513 binding of CD137 stimulates CD137 function. In syngeneic tumor models, anti-CD137 agonists demonstrated single-agent activity that was linked with infiltration of tumors by cytotoxic $CD8^+$ and $CD4^+$ T cells. Other preclinical studies showed additive or synergistic activity when anti-CD137 agonists were combined with various other antitumor modalities. Dr. Weber discussed the results from a recent phase I/II study of BMS-663513 in patients with melanoma or other cancers.[40] Doses up to 15 mg/kg were tolerable, with only infrequent DLTs, and no apparent dose-relationship with toxicity. Three of 47 melanoma patients (6.4%) achieved PRs for >8 months with BMS-663513. A phase II trial is currently evaluating the safety/tolerability and efficacy of different regimens of BMS-663513 in patients with advanced melanoma.

The third investigational agent discussed by Dr. Weber was CP-870,893, a CD40 agonist monoclonal antibody. CD40 is another member of the TNF receptor family that is primarily expressed on the surface of activated T cells. In animal models, activating antibodies against CD40 overcome immune tolerance and have been associated with antitumor activity.[41,42] Moreover, combining an anti-CD40 antibody agonist with a peptide-based antitumor vaccine enhanced activity further.[41]

The safety/tolerability and immunomodulatory and antitumor effects of CP-870,893 were examined in a recent phase I dose-escalation study of 29 patients with advanced solid tumors, including 15 with melanoma.[43] The maximum tolerated dose (MTD) was estimated to be 0.2 mg/kg. The most common AE was mild cytokine release syndrome (chills, rigors, fever). Four patients evaluated by RECIST after a single infusion of CP-870,893 achieved PRs at the MTD or higher (14% of all patients and 27% of melanoma patients); another 7 exhibited stable disease. Dr. Weber noted that these results are promising and that the antibody is currently being investigated in combination with carboplatin and paclitaxel in a randomized phase II study.

Postchemotherapy effects and the initiation of immunity. Mounting evidence indicates that radiotherapy and some chemotherapy (eg, anthracyclines and platinum agents) may mediate antitumor effects via interactions with the host immune system. Moreover, TLR4 appears to play a pivotal role in the immunogenic-

ity of tumor cell death triggered by these chemotherapies and radiotherapy,[44] as discussed by **Lionel Apetoh**, of Brigham and Women's Hospital and Harvard Medical School in Boston, Massachusetts.

High mobility group box 1 protein (HMGB1), one of the ligands for TLR4, is released from dying tumor cells and is necessary for the host DCs to efficiently process and present tumor antigens.[44,45] More specifically, HMGB1 binds TLR4 expressed on the surface of DCs and is required for the promotion of tumor-specific cytotoxic T-cell responses. Consistent with this, blocking HMGB1 release from chemotherapy- or radiotherapy-treated tumor cells or neutralizing it with an anti-HMGB1 antibody prevents antigen presentation to T cells and impairs the host antitumor immune response.[44]

Furthermore, additional studies using mice lacking functional *TLR4* confirmed that the TLR4-HMGB1 interaction is mandatory to obtain optimal antitumor immune responses against tumor cells after chemotherapy or radiotherapy.[45] These findings appear relevant to humans given that breast cancer patients carrying a loss-of-function *TLR4* polymorphism (Asp299Gly) relapse more quickly after anthracycline-based chemotherapy and radiotherapy than those with the normal allele.[45,46] Dr. Apetoh noted that chloroquine corrects cross-presentation defects in human *TLR4* Asp299Gly monocyte-derived DCs, and that this may have clinical relevance for cancer patients harboring this polymorphism.

TARGETED THERAPIES

Targeting signaling in melanoma. **Keith T. Flaherty**, of the University of Pennsylvania in Philadelphia, Pennsylvania, discussed some of the complexities of trying to target signaling pathways as treatment for cutaneous melanoma. Early success with molecularly targeted therapies of signal transduction pathways has been less with melanoma than with a number of other cancers, probably due to the increased complexity of melanoma versus other tumor types. Various mutations in components of signaling pathways, particularly those involved in the MAP and PI3 pathways, have been identified in melanoma. Nearly all melanomas have activated MAP kinase (MAPK) and PI3 kinase pathways that have been linked with melanoma development or progression. However, as early research has suggested, it does not necessarily follow that targeting one particular melanoma-associated mutation or molecule will be effective or optimal treatment for the disease.

Signaling molecules frequently mutated or amplified in sporadic melanoma include c-KIT, NRAS, BRAF, PTEN, AKT, and MITF, among others.[47] BRAF is the most commonly reported mutation in melanoma (~60%), and the most common BRAF mutation (~80%) occurs in the kinase region (BRAF V600E).[47,48] Sorafenib is a multitargeted kinase inhibitor with activity against BRAF as well as a number of receptor tyrosine kinases. Studies evaluating sorafenib as melanoma monotherapy revealed limited activity, but ongoing trials are further investigating sorafenib in combination with other anticancer agents for melanoma. Furthermore, agents with greater selectivity than sorafenib for the BRAF V600E mutation versus wild-type BRAF (eg, SB590885 and PLX-4032) have been developed and await greater investigation in melanoma,[49] as have multitargeted kinase inhibitors with greater potency than sorafenib against BRAF (eg, RAF-265).

However, Dr. Flaherty noted, there is a growing realization that single-agent BRAF inhibitor therapy is not the optimal strategy for treating melanoma. Preclinical human mouse xenograft studies demonstrate that sorafenib monotherapy significantly reduces cell proliferation, but does not completely inhibit it, suggesting melanomas have other, non-BRAF/MAPK-mediated growth pathways.

Individual targeted agents will continue to be developed and tested through phase I trials, but over time, these agents will be tested in combination with traditional chemotherapies or with other targeted therapies to attack multiple aberrations in particular melanoma tumors. Dr. Flaherty pointed to a recent study by Smalley and colleagues showing growth and invasion of metastatic melanoma 3-dimensional spheroids was blocked by combined administration of MAPK/extracellular signal-regulated kinase (MEK) inhibitors and PI3 kinase inhibitors, but not by either MEK or PI3 kinase inhibitors alone.[50]

Dr. Flaherty indicated it is unclear at this time whether targeted agents might best be used to inhibit kinases and pathways associated with melanoma oncogenesis or the downstream consequences of these genetic events (eg, angiogenesis or evasion of immune recognition)—or some combination of the two. Current investigations are looking at more personalized targeted therapy (ie, analyzing patient tumors for mutations in known signaling pathways and then tailoring therapy based on this evidence). In the future, we might expect to see US Food and Drug Administration (FDA) approval of regimens tailored to groups defined by mutations.

Targeting apoptosis in melanoma. During this session, **Peter Hersey** of Newcastle University Calvary Mater at Newcastle, Australia, discussed apoptosis as a potential therapeutic target in melanoma. Dr. Hersey said melanoma development is characterized by both unregulated cell division and resistance to cell death or apoptosis, but that secondary events are probably even more important for inducing resistance to apoptosis. Chief among these is the endoplasmic reticulum (ER) stress that develops in rapidly proliferating melanoma cells, and the subsequent adaptations made by the cells to deal with ER stress. Dr. Hersey identified a number of key components in the antiapoptotic mechanisms found in melanoma, and potential treatments that target these components to improve outcomes in melanoma.

The 2 major pathways that can initiate apoptosis are the stress-related 'intrinsic' or mitochondrial death pathway and the transmembrane 'extrinsic' death pathway.[51] Regardless of how initiated, cancer cell-related apoptosis is dependent on mitochondrial changes. Mitochondrial pathways to apoptosis are regulated by Bcl-2 family proteins, which include both prosurvival/antiapoptotic proteins (eg, Bcl-2, Bcl-XL, Mcl-1) and proapoptotic proteins. Proapoptotic proteins can be further separated into those that share multiple domains with antiapoptotic proteins (eg, Bax and Bak) and others that share only the BH3 homology domain (eg, Bid, Bik, Bim, Bmf, Noxa, Puma, Bad, and Hrk). Key players in the extrinsic pathway for apoptosis initiation are TRAIL and its receptors. In melanoma, the extrinsic pathway commonly leads to the activation of BH3-only proteins such as Bid and apoptosis via the intrinsic pathway.

A number of agents targeting antiapoptotic proteins are currently under investigation, including oblimersen (Bcl-2 antisense), gossypol (an oral inhibitor of Bcl-2, Bcl-XL, and Mcl-1), and obatoclax (a pan-inhibitor of Bcl-2, Bcl-XL, and Mcl-1), and BH3 mimics such as ABT-747 bind Bcl-2 proteins and release the proapoptotic effects of BH3-only proteins.[52] However, Dr. Hersey said, manipulation of the Bcl-2 family is unlikely to be enough to effect change in melanoma, given that MEK/ERK and PI3K/Akt/mTOR

signal pathways are typically activated in melanoma and shut down apoptosis. The MEK/ERK pathway protects melanoma cells from ER stress-induced apoptosis, and MEK/ERK inhibition sensitizes melanoma cells to ER stress-induced apoptosis.[53] Inhibitors of the PI3K/Akt/mTOR pathway might also prove to be useful in melanoma (although this remains to be demonstrated), including the PI3K inhibitor SF1126, Akt inhibitors perifosine and CMEP, and mTOR inhibitors such as temsirolimus, everolimus, and deforolimus.

As discussed in his earlier presentation, Dr. Hersey noted that ER stress is also associated with upregulation of GRP78 chaperone protein, p53 downregulation, and a switch to glycolysis/acidification of the microenvironment, all of which may contribute to the resistance of melanoma cells to apoptosis. A number of GRP78 inhibitors are currently under investigation (eg, veripelostatin, prunustatin A, and efrapeptin J, among others), and at least 1 study suggested melanoma resistance to cytotoxic chemotherapy may be overcome by pretreatment with proton-pump blockers that inhibit acidification of the tumor microenvironment.[54]

What about TRAIL-related apoptosis? Studies indicate that TRAIL-induced killing is rapid and specific, but it requires TRAIL death receptors, which are often downregulated in melanoma cells. TRAIL induces apoptosis through interactions with the death receptors TRAIL-R1 (DR4) or TRAIL-R2 (DR5).

A recent study by Zhuang and associates showed a correlation between decreased TRAIL-R2 expression and melanoma progression (ie, lower expression in thick versus thin melanomas and in metastatic melanoma in lymph node and subcutaneous metastases).[55]

Tunicamycin is an agent that induces ER stress, but which also causes a selective upregulation of TRAIL-R2. A recent study by Jiang and colleagues demonstrated that tunicamycin can sensitize cultured melanoma cells and fresh melanoma isolates to TRAIL-induced apoptosis.[56] So agents that upregulate TRAIL receptors are also under study as potential antimelanoma therapy, either by themselves or in conjunction with cytotoxic chemotherapy.

Dr. Hersey concluded his presentation by noting that knowledge of apoptosis in general and antiapoptotic processes in melanoma continues to expand and has highlighted a number of potentially interesting targets for antimelanoma therapy. The conclusion that may ultimately be drawn is that all primary treatments, including immunotherapy, should be given in combination with treatments targeting the apoptotic resistance mechanisms that are commonly observed in melanoma cells.

REPORTS ON IMPORTANT ONGOING CLINICAL TRIALS

Temozolomide. **Poulam Patel,** of The University of Nottingham in Nottingham, United Kingdom, presented the final results of the international, multicenter, randomized phase III trial (EORTC 18032) comparing extended schedule, escalated-dose temozolomide (TMZ) with dacarbazine (DTIC) in patients with stage IV melanoma.

Patients enrolled in the study had no prior cytokine or chemotherapy for stage IV disease, no evidence of brain metastases, WHO performance status (PS) 0 or 1, and an LDH ≤2× the upper limit of normal (ULN). They were randomized in a 1:1 ratio to receive dose-intense 7-day-on, 7-day-off TMZ (150 mg/m^2/day; n=420) or standard dose DTIC (1,000 mg/m^2 qid; n=419) until progression.

The extended-dose schedule for TMZ was expected to allow for higher total dose and possibly greater efficacy compared with standard dosing. TMZ converts to the same active moiety as DTIC, but unlike DTIC, TMZ is orally bioavailable and crosses the blood-brain barrier. DTIC is the generally accepted standard of care for patients with advanced melanoma.

The results after a median follow-up of 18 months showed no significant difference between TMZ- and DTIC-treated patients either in terms of median OS (9.13 vs 9.36 months; hazard ratio [HR], 1.00; 95% confidence interval [CI],0.86-1.17; *P*=1.0) or median progression-free survival (PFS) (2.30 vs 2.17 months; HR, 0.92; 95% CI, 0.80-1.06; *P*=.27). The overall response rate (ORR) was higher in the TMZ group than in the DTIC group (14.5% vs 9.8%; *P*=.05), but median duration of response appeared to be longer with DTIC (11.2 vs 4.6 months with TMZ). Extended-schedule TMZ was somewhat more toxic than DTIC (18% vs 9% grade III/IV drug-related AEs), primarily due to increased rates of grade III/IV lymphopenia (45% vs 9%) and thrombocytopenia (11% vs 6%), but was considered to have acceptable safety.

In conclusion, Dr. Patel said, this large phase III trial failed to demonstrate improved OS or PFS with extended-dose TMZ compared with the current standard of care, DTIC, in patients with advanced melanoma. The results of this trial are negative for TMZ, although it may be an acceptable treatment alternative in patients desiring an orally administered agent, and possibly in those with brain metastases, provided that higher drug acquisition costs and greater toxicity are not an issue.

ABSTRACT SESSIONS

Prognostic or predictive factors

Clinical response to the MAGE-A3 immunotherapeutic in metastatic melanoma patients is associated with a specific gene expression profile present at the tumor site. **Jamila Louahed**, of GlaxoSmithKline Biologicals in Rixensart, Belgium, described results of a gene expression profiling by microarray analysis of 75 patients with in-transit or unresectable stage III or IV M1a melanoma who had been immunized with recombinant MAGE-A3 protein combined with adjuvant systems AS15 or AS02B. Patients were randomized with respect to the adjuvant system as part of a larger phase II trial. All patients entered in the analyses had tumors positive for MAGE-A3 protein.

Prior results from the phase II trial indicated MAGE-A3 Antigen-Specific Cancer Immunotherapeutic clinical activity, and the aim of the present gene expression analysis was to try and identify markers predictive of that clinical activity. Gene expression profiling was performed on tumor biopsies collected prior to immunization.

Initial and follow-up analyses identified 2 gene clusters that were differentially expressed in patients exhibiting clinical benefit in response to MAGE-A3 treatment (objective response, stable disease, or mixed response) versus those who did not benefit from treatment. Most of the genes associated with this gene expression signature (GS) were immune-related, suggesting a different pretreatment immune status or microenvironment in tumors subsequently shown to be sensitive or insensitive to the vaccine.

Furthermore, higher MAGE-A3 immune response and more frequent clinical activity were observed with the AS15 than AS02B adjuvant system. The predictive value of the identified GS was suggested by the finding that median time to treatment failure was shorter in the GS- versus GS+ population (2.3 vs 10.3 months; HR, 0.31; 95% CI, 0.13-0.76).

Dr. Louahed commented that this predictive GS will be prospectively validated in future phase III trials. In a larger context, it is hoped that gene expression profiling analyses, such as performed here, will be able to identify tumors that are likely to respond to vaccines prior to administration, thereby improving on the disappointing results of vaccine trials reported to date.

Immunotherapy

Analysis of the onset and resolution of immune-related adverse events during treatment with ipilimumab in patients with metastatic melanoma. **Celeste Lebbé**, of Saint-Louis Hospital in Paris, France, presented the results from a pooled analysis of safety/tolerability data from 4 phase II trials (CA184-004, 007, 008, and 022) of the anti-CTLA-4 antibody ipilimumab in patients with advanced melanoma.

All 325 patients had unresectable stage III or IV melanoma that was either previously untreated (14%) or treated (86%), ECOG PS 0-1, no brain metastases, and received at least 1 dose of ipilimumab induction at 10 mg/kg as monotherapy every 3 weeks × 4. Nonprogressing patients received maintenance dosing once every 12 weeks beginning at week 24. Patients were evaluated for time to onset and resolution of the most frequently reported immune-related AEs.

Of the 325 patients, 275 (84.6%) had a drug-related AE, including 235 (72.3%) with an immune-related AE. For 82 patients (25.2%), the immune-related AE was rated as grade III/IV (20.9% grade III and 4.3% grade IV); 3 patients (0.9%) experienced a grade IV immune-related AE. Grade III/IV immune-related AEs most commonly involved the gastrointestinal system (12.3%), liver (6.8%), skin (2.8%), and endocrine system (2.5%).

For most patients the first appearance of these AEs was during the first 12 weeks or induction phase of ipilimumab therapy. The median time to onset of grade III/IV immune-related AEs of the skin, liver, gastrointestinal tract, and endocrine system was 4.4, 6.7, 6.9, and 10.1 weeks, respectively. The median duration of grade III/IV immune-related AEs was 3.3 weeks for the skin, 3.6 weeks for the liver, 2.1 weeks for the gastrointestinal tract, and 20.6 weeks for the endocrine system. Grade III/IV immune-related AEs of the skin resolved in a median of 3.6 weeks, while those of the liver, gastrointestinal tract, and endocrine system resolved in a median of 4.0, 3.0, and 20.6 weeks, respectively.

Dr. Lebbé concluded that most patients with advanced melanoma who received ipilimumab as part of a phase II trial experienced mild to moderate or grade I/II AEs (50%), while about 25% experienced severe (grade III/IV) immune-related AEs. Most AEs were manageable and reversible, and most immune-related AEs involved the gastrointestinal tract, skin, liver, or endocrine system. Immune-related AEs of the gastrointestinal tract, skin, and liver generally resolved within 2 to 6 weeks of onset, although those involving the endocrine system typically took longer to resolve. Dr. Lebbé noted that an algorithm for the management of the most commonly occurring immune-related AEs has been developed and was used in the 4 phase II trials evaluated here.[57]

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BUILDING THE FUTURE OF MELANOMA CARE

A Satellite Symposium sponsored by Schering-Plough

Adjuvant interferon: Which interferon for which patient? During the *Building the Future* symposium, **Alexander M. M. Eggermont**, of Erasmus University in Rotterdam, the Netherlands, elaborated on his prior presentation regarding the EORTC trials of adjuvant IFN-α therapy in melanoma patients at high risk for disease recurrence. The particular focus of Dr. Eggermont's talk during the symposium was on trying to identify predictive factors for patient response to adjuvant IFN-α.

He highlighted the generally abysmal results obtained over the years from most melanoma trials of adjuvant therapy since those of high-dose IFN. Very few trials have reported positive benefit for OS with adjuvant therapy, and a number of recent vaccine trials have reported detrimental effects for OS. IFN-α is the only compound that has demonstrated consistent benefit for relapse-free survival (RFS) when used as adjuvant therapy, and this appears to be a durable benefit based on the latest results from the EORTC 18991 and 18952 trials presented earlier at the *Perspectives in Melanoma* conference and, prior to that, at the 2008 ESMO Congress.

Given current understanding, Dr. Eggermont projected that IFN-α is likely to remain the only agent available for clinical use as adjuvant therapy in high-risk melanoma patients, for many years to come. However, despite the consistent and durable benefits of adjuvant IFN-α for RFS, the agent has not been associated with consistent or even common OS benefit. This may be because only a fraction of patients are sufficiently sensitive to adjuvant IFN-α for the RFS benefit to be translated into significantly prolonged OS, and we currently do not have the tools to identify this subfraction of highly responsive patients.

With that in mind, Dr. Eggermont examined post-hoc analyses from updated evaluations of EORTC 18991 and 18952, large randomized phase III trials of adjuvant IFN-α therapy in patients with stage IIB and/or stage III melanoma. These post-hoc analyses were focused on trying to provide hypothesis-generating clues as to predictors of patient responsiveness or sensitivity to adjuvant IFN-α therapy.

EORTC 18991 compared long-term pegylated IFN-α2b treatment with observation in patients with resected stage III melanoma,[58] while EORTC 18952 compared observation with 13 or 25 months adjuvant treatment with standard IFN-α2b.[59]

The final results from EORTC 18991 (median follow-up, 3.8 years) suggested the benefits of adjuvant pegylated IFN treatment versus observation for median RFS were greater in stage III patients with microscopic nodal involvement (N1) than in those with clinically palpable lymph node involvement (N2), and in those with only 1 positive lymph node compared with ≥2 positive lymph nodes.[58] Furthermore, multivariate analysis indicated significantly longer DMFS with adjuvant pegylated IFN versus observation for patients with N1 (HR, 0.70; 99% CI, 0.49-1.00; *P*=.011) but not N2 disease (*P*=.72), and for patients with only 1 positive node (HR, 0.70; 99% CI, 0.51-0.97; *P*=.005) but not those with 2 to 4 or with ≥5 positive nodes (*P*=.91 and .47, respectively).

The results from EORTC 18952 (median follow-up, 4.7 years) supported the stage-dependency of the adjuvant IFN effect (with 25-month treatment) for DMFS, as well as distant metastasis-free interval and OS, and are generally consistent with the findings from EORTC 18991 showing stage-dependency of adjuvant IFN therapy. Furthermore, a post-hoc analysis of outcome by tumor ulceration status suggested adjuvant pegylated IFN therapy versus observation was associated with significantly longer RFS, DMFS, and OS for patients with ulcerated stage III-N1 disease, but not in those without ulceration. These results suggest that patients with microscopic stage III disease and ulceration might be the most responsive to adjuvant IFN therapy, and that OS benefit with adjuvant IFN may be observed in this subpopulation of high-risk melanoma patients.

Post-hoc analyses of EORTC 18952 also pointed to ulceration as being critical for benefit from adjuvant IFN in patients with earlier/stage IIB disease. Dr. Eggermont further suggested that the biology of ulcerated primary tumors is different from nonulcerated tumors, which may contribute to a heightened receptiveness to adjuvant immunotherapy.

Dr. Eggermont did note that post-hoc analyses are hypothesis-generating, and that prospective, appropriately designed trials will be required to more fully test the hypothesis that patients with resected IIB–stage III-N1 melanoma and ulcerated primary tumors are most responsive to adjuvant IFN therapy. Nonetheless, the results from these post-hoc analyses do provide clues as to factors that may predict response to adjuvant IFN.

EORTC 18081 is a randomized phase III trial that has been designed to investigate the impact of 2 years pegylated IFN therapy versus observation in patients with stage II ulcerated primary melanomas >1 mm thick. This trial has been approved by the executive committee and is expected to be activated around May 2009.

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Posttest

For each question or incomplete statement, please indicate your answer or completion in the space provided on page 16.

1. **Based on Dr. Hendrix's studies of the microenvironment of human embryonic cells and aggressive melanoma cells, which of the following may be a potential target for therapeutic interventions in melanoma?**
   A. Lefty A
   B. Lefty B
   C. Nodal
   D. STAT3

2. **Recent gene profiling studies by Dr. Spatz and associates indicated that _____ was a significant independent predictor of overall survival.**
   A. NY-ESO-1
   B. MCM4
   C. SAA
   D. GRP78

3. **Based on the work of Dr. Essner, intradermal injection of GM-CSF around the excision site in stage I melanoma patients is associated with _____ in the corresponding sentinel lymph node.**
   A. Upregulation of proapoptotic Bax
   B. A higher pSTAT1/pSTAT3 ratio
   C. Upregulation of mature dendritic cells
   D. Upregulation of total STAT3

4. **Work by Dr. Hersey and colleagues suggest that one of the reasons for the resistance of melanoma cells to apoptosis is _____.**
   A. Decreased TRAIL-R2 expression
   B. Decreased Mcl-1 expression
   C. Decreased GRP78 expression
   D. Increased p53 expression

5. **Which of the following is true concerning the final results from the large randomized phase III trial (EORTC 18032) comparing extended schedule temozolomide (TMZ) with dacarbazine (DTIC) in stage IV melanoma patients?**
   A. TMZ was associated with significantly longer median overall survival.
   B. TMZ was associated with significantly longer median progression-free survival.
   C. Overall response rate was similar for the 2 treatment groups, but median duration of response appeared to be longer with TMZ.
   D. TMZ was somewhat more toxic than DTIC, primarily due to increased grade III/IV lymphopenia and thrombocytopenia.

6. **Studies of signaling pathways in melanoma, and treatments targeting these pathways, indicate (which of the following is true):**
   A. c-KIT is the most commonly reported mutation in sporadic melanoma.
   B. Optimal treatment may involve single-agent therapy with an agent like sorafenib.
   C. Better results are achieved when kinases and pathways involved in oncogenesis are targeted rather than downstream consequences of these events.
   D. Optimal treatment may involve targeting multiple aberrations in particular tumors.

7. **Based on post-hoc analyses of EORTC 18991 and 18952 presented by Dr. Eggermont, which of the following has been hypothesized to be a predictor of IFN-α response in patients with stage IIB/III melanoma?**
   A. Serum LDH level
   B. Ulceration
   C. Autoimmunity signs
   D. Clark level of invasion

Evaluation Form

Please use the scale below in answering these questions. Fill in the circle completely. You may use pen or pencil to fill in the circles.

Very Low	Low	Moderate	High	Very High

1. *To what extent were the objectives of the educational activity achieved?*

A. Better comprehend how insights into melanoma biology/pathogenesis speak to drug resistance and are helping to drive biomarker and treatment development ❍ ❍ ❍ ❍ ❍

B. Review the importance of the sentinel lymph node both for staging and as a potential focus of attack for regional immunotherapies ❍ ❍ ❍ ❍ ❍

C. Summarize the current state of adjuvant therapy in melanoma and areas of ongoing research ❍ ❍ ❍ ❍ ❍

D. Identify alterations in immune function associated with melanoma development or progression, and strategies to improve immune function in melanoma patients ❍ ❍ ❍ ❍ ❍

E. Evaluate the current state of development of molecularly targeted and other emerging therapies for melanoma ❍ ❍ ❍ ❍ ❍

Very Low	Low	Moderate	High	Very High

2. *To what extent were you satisfied with the overall quality of the educational activity?* ❍ ❍ ❍ ❍ ❍

3. *To what extent was the content of the activity relevant to your practice or professional responsibilities?* ❍ ❍ ❍ ❍ ❍

4. *To what extent did the educational activity enhance your knowledge of the subject area?* ❍ ❍ ❍ ❍ ❍

5. *To what extent did the activity change the way you think about clinical care and/or professional responsibilities?* ❍ ❍ ❍ ❍ ❍

6. *To what extent will you make a change in your practice and/or professional responsibilities as a result of your participation in this educational activity?* ❍ ❍ ❍ ❍ ❍

7. *To what extent did the activity present scientifically rigorous, unbiased, and balanced information?* ❍ ❍ ❍ ❍ ❍

8. *To what extent was the educational activity free of commercial bias?* ❍ ❍ ❍ ❍ ❍

Answer Posttest Questions Here

1. ☐ 2. ☐ 3. ☐ 4. ☐ 5. ☐ 6. ☐ 7. ☐

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