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Melanoma Research Highlights from the 33rd ESMO Congress

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Editor's Note...

The management of patients with melanoma is made substantially easier when the primary tumor is detected early. Options are very limited when distant metastases are involved or the patient has unresectable stage III disease, although numerous agents are being investigated, either as monotherapy or in combination with cytotoxic chemotherapy.

Similarly, current adjuvant strategies for patients with surgically resected stage IIB/III disease have shown inconsistent benefit for overall survival, although high-dose interferon (IFN) therapy has consistently demonstrated benefit for relapse-free survival. We suspect there may be subsets of patients that are particularly sensitive to the benefits of adjuvant IFN treatment, but we have yet to clearly identify them.

Highlights from the 33rd European Society for Medical Oncology (ESMO) Congress held in Stockholm, Sweden, on September 12-16, 2008, as well as at a symposium linked with the Congress titled *Current Trends in Melanoma Management*, included presentations on melanoma epidemiology, the upcoming 7th Edition of the American Joint Committee on Cancer (AJCC) staging system for cutaneous melanoma, melanoma genetics, adjuvant therapy of stage IIB/III patients, and cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies as treatment for advanced melanoma.

This publication presents the latest research on these and other topics, with a particular focus on the management of patients with advanced melanoma or those at increased risk for disease recurrence following resection of the primary tumor. This material has been reviewed by Axel Hauschild, MD, Dirk Schadendorf, MD, and myself. It is my belief that the material presented here and at www.MelanomaCare.org will help further the understanding and management of melanoma.

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 European Society for Medical Oncology (ESMO) Congress, held in Stockholm, Sweden, September 12-16, 2008, was an important forum for discussion of the latest research in many areas of oncology, including melanoma, as well as current approaches to optimize patient care. This publication offers a comprehensive overview of the most important presentations on melanoma for those healthcare providers who were unable to attend this significant meeting.

Educational Objectives
Upon proper completion of this CME activity, participants should be able to:
- Identify proposed changes in the upcoming 7th Edition of the AJCC melanoma staging system compared with the 6th Edition
- Discuss the overall survival results from the phase III trial comparing extended-schedule temozolomide and dacarbazine in advanced melanoma patients
- Describe the latest findings from phase II trials of ipilimumab and tremelimumab for the treatment of advanced melanoma
- Identify the cyclin D1 (CCND1) polymorphisms that may be a biomarker for increased melanoma risk, and describe a possible mechanism of action
- Discuss possible variables that may predict response to adjuvant IFN-α2b therapy in patients with stage IIB-III melanoma

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Overview of Melanoma Epidemiology and Staging/Treatment Guidelines

Melanoma Epidemiology

Cutaneous melanoma is an increasingly common cause of morbidity and mortality in the United States and worldwide. At a satellite symposium (*Current Trends in Melanoma Management*) sponsored by Schering-Plough and linked with the 2008 ESMO Congress, **Claus Garbe** of Eberhard-Karls University in Tübingen Germany provided an overview of melanoma epidemiology.[1]

In Germany, melanoma occurs in approximately 20 per 100,000 inhabitants and is the 10th most common cancer.[2] Based on Surveillance Epidemiology and End Results (SEER) data from the National Cancer Institute, the age-adjusted incidence rate for cutaneous melanoma in the United States is approximately 25 per 100,000 for men and 16 per 100,000 for women.[3]

The highest incidence and lifetime risks are observed in Australia, and the lowest in Japan.[4] Generally lower rates are observed in northern than southern European countries.[4] Regional differences are ascribed to genetic differences in skin pigmentation and sun exposure.

The incidence of cutaneous melanoma in the United States increased in men and women during the period 1975-2000, while the mortality rate generally remained unchanged, particularly since the 1990s.[1] In the United States, the lifetime risk of developing cutaneous melanoma increased from 1 in 1,500 in 1935 to 1 in 150 in 1985 and 1 in 75 in 2000.[5,6] In 2008, approximately 62,480 individuals were expected to develop invasive cutaneous melanoma and 8,420 to die from the disease.[7] In contrast to incidence rates, a 2004 paper by Bosetti and colleagues suggested that mortality from cutaneous melanoma has leveled off or even decreased in Europe, at least since the mid-1990s,[8] and as mentioned, there are indications that melanoma mortality rates have stabilized in the United States and other countries.

Dr. Garbe then examined possible reasons for the rising incidence but declining mortality rates for melanoma.[1] He described data from a study of the German Central Melanoma Registry for 45,483 patients diagnosed between January 1976 and December 2000 in Germany, Austria, and Switzerland, which showed significant decreases in median tumor thickness and percentage of ulcerated tumors, and increases in percentage of in situ or Breslow level II tumors,[9] suggesting that mortality rates for melanoma have stabilized or decreased in many countries in recent years because earlier diagnosis has led to identification of tumors in a more favorable prognostic state. This conclusion is further supported by the finding that the survival by different tumor thicknesses did not change over this time period, suggesting earlier detection rather than improved treatment was the reason for any improvement in survival.[9]

While the improved mortality rate is heartening, it would also be helpful if researchers and clinicians were able to identify risk factors responsible for the rising incidence as well as population subsets that are refractory to early detection (such as elderly men). This would enable clinicians to identify patients at risk for melanoma and allow them and their patients to act in ways to prevent or modify these risk factors, and perhaps reverse the trend for rising incidence. Dr. Garbe discussed findings from a 1994 study by his group in Germany showing that total number of common nevi was the most important risk factor for development of melanoma in multivariate analysis,[10] supporting the results of earlier studies in other countries. The relative risk (RR) for patients with >100 melanocytic nevi was 7.6 versus those with ≤10 melanocytic nevi. Other significant risk factors included number of atypical melanocytic nevi (RR=6.1 for ≥5 melanocytic nevi vs none), number of actinic lentigines, hair color, skin type, and melanocytic nevus growth, but not any single parameter of sun exposure.[10] Dr. Garbe examined the results from a number of other studies further supporting the conclusion that increasing number of common melanocytic nevi and increasing number of atypical melanocytic nevi increase risk of melanoma.[11]

Are there identifiable predictors of number of melanocytic nevi? Pointing to the results from a 2003 study examining factors associated with development of melanocytic nevi in children,[12] Dr. Garbe stated that the answer is yes—and while some are inherited, others appear to be preventable or at least modifiable.[1] This cross-sectional study of 1,812 German children aged 2 to 7 years and their parents showed an increase in median number of nevi from 3 at age 2 years to 19 at age 7 years.[12] Multivariate regression analysis identified a number of lifestyle factors (≥3 weeks/year on holiday in sunny climates, increasing number of outdoor activities at home) and inherited factors (lighter skin complexion, high number of freckles, number of parental moles) as significant independent predictors of number of melanocytic nevi. However, previously experienced sunburns was not a significant predictor.[12]

Dr. Garbe stated that the data suggest that even intermittent mild to moderate sun exposure is capable of inducing melanocytic nevi, which have been shown to be a risk factor for development of cutaneous melanoma. Hence, reducing sun exposure during childhood would be expected to reduce development of melanocytic nevi and risk of melanoma.

Partial support for this notion was provided by a subsequent epidemiologic study by the same group of investigators using the same database of 1,812 children aged 2 to 7 years.[13] The analysis in this study was focused on the impact of sunscreen and sun-protective clothing on number of melanocytic nevi. Adjusting for potential confounding factors, multi-

variate regression analysis demonstrated an inverse dose-effect relationship between clothing at the beach or outdoor swimming pool and number of melanocytic nevi, but no significant relationship between sunscreen use and number of melanocytic nevi. Dr. Garbe stated that the group is currently performing a similar study in cooperation with Australian investigators and subjects.[1]

Staging and Treatment Guidelines

At the *Current Trends in Melanoma Management* symposium, **Merrick Ross** of the M. D. Anderson Cancer Center in Houston, Texas, provided a preview of the upcoming 7th Edition of the AJCC staging system for cutaneous melanoma, due for release in 2009.[14] The previous version (6th Edition) was the first strongly evidence-based staging system for melanoma, and incorporated a number of important changes compared with prior versions.[15] These changes included modification of tumor thickness thresholds and their use as the primary determinant of T staging, reduced emphasis on level of invasion for T staging, incorporation of ulceration, and emphasis on the number of metastatic lymph nodes (rather than their size or gross dimensions), among others. It also introduced the M1c stage associated with an elevated lactic dehydrogenase (LDH) level.

However, although the 6th Edition demonstrated the general prognostic significance of different pathologic stages for overall survival (OS), there was still some significant prognostic heterogeneity in major stage categories and prognostic overlap between particular categories (eg, 5-year survival rates of 50% and 70% for patients with stage IIC and IIIA tumors, the reverse of what would be expected).[14,15]

Another limitation of the 6th Edition was the result of trying to keep the system simple. Because of that, the stage groupings were dependent on only 2 or 3 major factors rather than all the potentially relevant factors required to more fully individualize prognosis and treatment strategies. This is particularly important as the technology now exists to make such distinctions, and we either have or may soon have targeted therapies for more individualized therapy. Lastly, the prior staging guidelines were based on data and practices that often lag behind current knowledge and clinical practice.

The upcoming 7th Edition is based on a new multicenter database of nearly 50,000 melanoma patients with a median follow-up of 5 years.[14] The general goals of this version are to:

- Maintain an anatomically-based TNM framework relevant to contemporary clinical practice;
- Identify the most powerful prognostic markers based on an expanded multicenter database and multivariate analyses;
- Establish prognostic groupings that minimize prognostic heterogeneity and prognostic overlap;
- Provide recommendations for routine reporting of conventional and new histologic factors; and
- Use mathematical modeling that incorporates several prognostic factors, in addition to the major ones in the prior guidelines.[14]

A number of stage-specific issues emerged during the development of the 7th Edition.[14] Challenges for stage I and II disease were to minimize prognostic heterogeneity and to minimize prognostic overlap with stage III. With respect to stage I disease, there was a particular focus on better understanding the prognosis of thin melanomas (T1, ≤1.0 mm thick). The plan was to identify novel prognostic factors that could be incorporated into prognostic tree analyses to better predict individual patient risk. There was also an attempt to determine whether sentinel lymph node biopsy (SLNB) could be used to minimize the prognostic overlap between patients with stage IIC and IIIA lesions.[14]

A novel prognostic factor that emerged since publication of the 6th Edition was mitotic rate.[16-19] In a study of patients with stage I/II melanoma, multivariate analysis identified a tumor mitotic rate of ≥1 mitoses/mm^2 as the second most powerful predictor of OS, behind tumor thickness.[16] Another identified mitotic rate (1-6 or >6 mitoses/mm^2) as a more powerful predictor of survival in patients with stage I/II disease than ulceration, and reported that ulceration was only an independent predictor when mitotic rate was left out of the multivariate regression model.[17]

Gimotty and colleagues used a tree-structured analysis of 10-year metastasis in patients with thin invasive melanomas (≤1.0 mm thick) to identify 4 risk groups for subsequent metastasis in which mitotic rate, growth phase, and gender played prominent roles.[18] The high-risk group was characterized by male gender, vertical growth phase lesions, and a mitotic rate >0. Interestingly, this study demonstrated prognostic heterogeneity based on just these 3 important prognostic factors.

In the AJCC melanoma database, mitotic rate was available for 40,888 patients with stage I/II melanomas, and multivariate regression analysis identified tumor thickness and mitotic rate as the first and second most powerful independent predictors of survival.[14] Similarly, an AJCC database analysis of survival rates for 4,861 T1 melanoma patients with thin melanomas (subgrouped as 0.01-0.50 or 0.51-1.00 mm thick) showed that a mitotic rate >1.0 was associated with lower 10-year survival for both thickness subgroups versus a mitotic rate ≤1.0. The 7th Edition is expected to continue employing tumor thickness and ulceration to define strata in the T category, but to use mitotic rate to replace level of invasion to define the T1b subcategory. Survival curves show a good separation based on T-classification, except for superimposed T3b and T4a curves.[14]

Previous studies have shown SLN status to be a significant independent prognostic factor for disease-free and disease-specific survival in patients with stage I/II melanoma.[20] The 7th Edition of the AJCC staging system will continue to recommend SLNB as an important component in melanoma staging and high-

Table 1. Prognostic Factors Influencing Disease-Specific Survival in Stage I/II, SLN-Positive Patients From the 2008 AJCC Database

Prognostic factor	Multiple covariate	
	Hazard ratio	*P*-value
Ulceration	2.04	.01
Largest SLN metastatic focus		
≤ 2 mm	1.0	—
>2 and <8 mm	2.51	.004
≥8 mm	2.91	.01
Total number of positive nodes		
1	1.0	—
2	1.46	.25
3+	2.10	.045

From Ross MI. New AJCC Recommendations for Melanoma Staging. Presented at: 33rd ESMO Congress Satellite Symposium: *Current Trends in Melanoma Management*; September 14, 2008; Stockholm, Sweden.[14]

light its utility for identifying occult stage III disease in patients with clinical stage IB or II disease.[14] Analyses of the 2002 AJCC database for SLN-positive stage I/II patients only showed significant prognostic heterogeneity for disease-specific survival when SLN positivity was further demarcated by total number of positive nodes, presence of ulceration, or tumor burden (unpublished data). **Table 1** illustrates findings from the 2008 AJCC database when disease-specific survival in stage I/II SLN-positive patients was evaluated based on ulceration, largest SLN metastatic focus, and total number of positive nodes.[14] Taken together, these data suggest that combining SLN status with additional risk factors can reduce prognostic heterogeneity as well as prognostic overlap in stage I/II melanoma.

With respect to stage III disease, it appears that 3 factors (number of positive nodes, ulceration, and size of the metastatic focus) can be used to better discriminate the spread of patients here.[14] As illustrated in **Table 2**, the 5-year survival rate for stage III melanoma patients with micrometastasis, no ulceration, and only 1 positive node is 81%, versus a rate of 25% for stage III patients with macrometastasis, ulceration, and ≥4 positive nodes (ie, with all 3 prognostic factors).[14]

The new guidelines will not contain any major changes for stage IV. The larger database has mostly been used to confirm the prognostic significance of metastatic site and LDH level for survival. An international database analysis of approximately 10,000 patients with stage IV melanoma is underway, and there may be some minor changes to the previous AJCC staging system for stage IV disease, although no major changes are expected.

A poster at the ESMO Congress pointed to the potential prognostic significance of 2 other markers besides LDH for patients with stage IV melanoma: 5-D-cysteinyldopa and, particularly, S-100B protein.[21] Elevated serum levels of 5-D-cysteinyldopa and S-100B protein (as well as LDH) were correlated with shortened OS in 253 patients with stage IV melanoma, and both markers exhibited appropriate sensitivity and high specificity. Moreover, the results indicated that S-100B protein was a more reliable marker of clinical outcome than LDH, reinforcing previous studies.

Overall, the 7th Edition of the AJCC staging system, with its large database, has validated the changes incorporated into the 6th Edition, while removing Clark level of invasion and substituting mitotic rate for characterization of the T1b subcategory.[14] Long-term future goals of AJCC staging are to better individual prognosis, using nomograms and novel weighted mathematical equations incorporating AJCC staging and other factors. The idea is to have an electronic web-based platform that can be easily accessed to enter various prognostic factors to generate an individualized risk profile for a given patient. Ultimately, it is hoped that genomic profiling may progress to the point that it can be used to determine risk of recurrence, type of recurrence, and response to therapy.[14]

Also at the *Current Trends in Melanoma Management* symposium, **Axel Hauschild** of the Department of Derma-

Table 2. Five-Year Survival Rate by Number of Nodes, Ulceration, and Tumor Burden for Patients With Nodal Metastases (Stage III)—AJCC Collaborative Melanoma Database

No. positive nodes	Ulceration	Micrometastasis	Macrometastasis
		5-year Survival Rate ±SE	5-year Survival Rate ±SE
1	No	0.81 ± 0.02 (n=954)	0.50 ± 0.06 (n=104)
	Yes	0.56 ± 0.03 (n=643)	0.44 ± 0.06 (n=104)
2-3	No	0.70 ± 0.04 (n=325)	0.49 ± 0.07 (n=93)
	Yes	0.48 ± 0.04 (n=272)	0.36 ± 0.06 (n=114)
>4	No	0.37 ± 0.07 (n=71)	0.39 ± 0.09 (n=61)
	Yes	0.39 ± 0.07 (n=69)	0.25 ± 0.06 (n=84)

From Ross MI. New AJCC Recommendations for Melanoma Staging. Presented at: 33rd ESMO Congress Satellite Symposium: *Current Trends in Melanoma Management*; September 14, 2008; Stockholm, Sweden.[14]

tology, the University of Kiel, Germany, provided an update on the evidence-based and interdisciplinary consensus-based German guidelines for the management of melanoma patients, which now include standardized evidence levels and recommendation grades.[22] A review of the guidelines as they apply to systemic treatment of melanoma in both the adjuvant and palliative setting was recently published in *Melanoma Research*.[23]

Treatment of Advanced Melanoma

Most patients with advanced melanoma (unresectable stage III or metastatic stage IV melanoma) present with widespread disease and are not suitable candidates for surgical treatment.[24,25] Currently, the median survival for patients with stage IV disease is 6 to 12 months. These patients require systemic therapy, and data concerning the benefits of such therapy have been very disappointing to date. In the United States, there are only 2 FDA-approved drugs in current use for advanced melanoma, dacarbazine (DTIC) and interleukin-2 (IL-2). While DTIC remains the standard of care, there has never been a phase III trial demonstrating the superiority of this agent compared with placebo (best supportive care) or other agents. Responses are relatively infrequent, short-lived when they occur, and there does not appear to be a survival benefit with DTIC or any other single-agent chemotherapy.

Equally disappointing results have been obtained with combination chemotherapy, chemohormonal therapy, and biochemotherapy.[24-26] High-dose IL-2 therapy has been associated with durable complete responses in a small proportion of patients (about 6%), but it is not possible to predict responders in advance, and the treatment is very toxic and limited to patients with access to specialized centers and personnel familiar with the therapy and to those who can tolerate the treatment. In contrast to DTIC, high-dose IL-2 therapy was never tested as monotherapy in a phase III setting and all prospective randomized clinical studies containing high-dose IL-2 have failed to demonstrate any superiority.[27]

A number of the presentations at the 2008 ESMO Congress focused on pharmacologic therapies for advanced cutaneous melanoma. **Poulam Patel** of the University of Nottingham in England presented the final results from a phase III trial (EORTC 18032) comparing temozolomide with DTIC in patients with stage IV melanoma.[28] A large proportion of the melanoma presentations examined CTLA-4 blockers as treatment for advanced melanoma, namely the monoclonal antibodies (mAbs) tremelimumab[29,30] and ipilimumab.[31-36] Other presentations evaluated various aspects of DTIC treatment[37,38] and use of molecularly-targeted agents[39-41] in patients with advanced melanoma. One study updated results on the efficacy and safety of elesclomol (STA-4783) with paclitaxel versus paclitaxel alone in patients with stage IV metastatic melanoma.[42]

Phase III Trial Comparing Temozolomide and Dacarbazine

The prodrug temozolomide converts to the same moiety with anticancer alkylating activity as DTIC. Unlike DTIC, temozolomide is orally bioavailable and crosses the blood-brain barrier. Results from phase I and II clinical trials of single-agent temozolomide therapy in patients with advanced melanoma suggested overall and complete response rates that were at least equivalent to those observed with single-agent DTIC therapy.[43,44] In addition, a phase III trial comparing temozolomide and DTIC therapy in this patient population reported similar median OS, but significantly longer median progression-free survival (PFS) with temozolomide.[45]

At the 2008 ESMO Congress, Dr. Patel presented for the first time the final efficacy and tolerability/safety results from EORTC 18032, a randomized, parallel-group, international, multicenter trial comparing extended-schedule, escalated-dose temozolomide with standard DTIC in patients with stage IV melanoma.[28] The extended dosing schedule of temozolomide was expected to enable higher total dose and improve efficacy compared with standard dosing.

In this trial, 859 patients with stage IV melanoma, World Health Organization (WHO) performance status (PS) 0/1, no evidence of brain metastases, serum LDH ≤2 x the upper limit of normal (ULN), and no prior cytokine or chemotherapy were randomized in a 1:1 ratio to receive dose-intense 7-day on/7-day off temozolomide (n=429) or standard-dose DTIC (n=430) until disease progression.[28] The primary endpoint was OS.[28] Secondary endpoints included PFS, objective response rate (ORR), duration of response, and tolerability/safety. Patients were randomized between October 2004 and May 2007. At the clinical cut-off date of December 31, 2007, 645 deaths had been reported. Median follow-up was 18 months.[28]

The 2 treatment groups were well matched for all baseline characteristics and protocol adherence.[28] Patients in the temozolomide group did not differ from those in the DTIC group for either 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 PFS (2.30 vs 2.17 months; HR, 0.92; 95% CI, 0.80-1.06; *P*=.27).[28] The ORR was significantly higher with temozolomide than with DTIC (14.5% vs 9.8%, *P*=.05), including 2.0% and 1.0% complete responses, respectively, but median duration of response was longer with DTIC (11.2 months; 95% CI, 6.2-19.5) versus temozolomide (4.6 months; 95% CI, 4.2-6.3). More patients in the temozolomide versus DTIC group experienced grade III/IV drug-related adverse events (AEs) (18% vs 9%), and more experienced grade III/IV lymphopenia (45% vs 9%) and thrombocytopenia (11% vs 6%). Slightly more patients in the DTIC group experienced grade III/IV neutropenia (16% vs 10%). There were no

notable differences between the groups for grade III/IV nonhematologic AEs.[28]

In conclusion, this study showed that extended-schedule, escalated-dose temozolomide is feasible in patients with stage IV melanoma, with an acceptable safety profile compared with DTIC, albeit with slightly more toxicity. However, the results from this phase III trial indicate that temozolomide does not improve OS or PFS in stage IV melanoma when compared with standard DTIC treatment.[28] In his discussion, Dr. Patel noted that the results from the study are not promising for temozolomide. Any difference in ORR compared with DTIC did not translate into a survival advantage for the entire population of stage IV melanoma patients or for any subgroup. Furthermore, temozolomide is much more expensive than DTIC and appears to be somewhat more toxic, which may lead to compliance problems.

Dr. Patel further noted that the results are generally in line with those from a previous phase II trial of extended-dose temozolomide in patients with advanced melanoma (ORR, 12.5%; median survival, 10.1 months)[46] and a phase III trial of standard-dose temozolomide (ORR, 13.5%; OS, 7.7 months), although temozolomide was associated with longer PFS than DTIC in the latter study.[45]

While temozolomide may be beneficial against brain metastases based on results from a phase II trial of melanoma patients with brain metastases,[47] this has yet to be proven in a phase III trial, Dr. Patel observed. Based on what is currently known, temozolomide is an oral alternative to DTIC in patients with advanced melanoma that may be considered in patients with asymptomatic brain metastases, problematic venous access, or liver failure.

An abstract reported initial results of a phase I dose-escalation trial of combination temozolomide, docetaxel, and cisplatin in patients with unresectable or recurrent metastatic melanoma.[48] The combination appeared to be well tolerated and was associated with a 32% ORR (all partial) among the 9 patients evaluable for response, and 43% ORR (all partial) among the 4 chemo-naïve patients evaluable for response.

Anti-CTLA-4 mAbs

Over the years, various strategies have been employed to induce or augment host immunity as a means to destroy melanoma cells. One of the more recent approaches involves the use of anti-CTLA-4 mAbs.[49] CTLA-4 is a CD28-family receptor that is expressed at elevated levels on the surface of activated T cells. To regulate immunity and prevent autoimmunity, components of antigen-presenting cells bind with CTLA-4 and activated T cells are "turned off," limiting the duration and intensity of the T-cell response.[49] Hence, one strategy to enhance cancer immunosurveillance involves the use of antibodies to CTLA-4, thereby blocking this negative switch for T-cell activity. Currently, 2 major anti-CTLA-4 mAbs are being evaluated in clinical trials, tremelimumab and ipilimumab.

Tremelimumab. At the 2008 ESMO Congress, **John Kirkwood** of the University of Pittsburgh School of Medicine in Pittsburgh, Pennsylvania, reported the findings from a phase II trial of single-agent tremelimumab treatment in patients with advanced refractory or relapsed melanoma (ie, as "second-line" therapy).[29] Prior therapies included DTIC, temozolomide, IL-2, or interferon-alfa (IFN-α).

All patients included in this open-label, single-arm study had unresectable stage III/IV melanoma; disease progression after treatment with DTIC, temozolomide, IL-2, or IFN-α; ECOG PS 0/1; and serum LDH level ≤2x ULN.[29] Patients were excluded from entry if they had detectable brain metastases. Patients received intravenous tremelimumab (15 mg/kg, q12w) for up to 4 cycles, and patients with clinical benefit were eligible for additional doses (2 additional cycles for patients with a complete response [CR] and 1 additional cycle for those with a partial response [PR]). The primary endpoint was best tumor response by RECIST (response evaluation criteria in solid tumors); secondary endpoints included duration of response, OS, PFS, and tolerability/safety, among others.[29]

Sixteen responses (all PRs) were observed in the 242 evaluable patients (7%), and were durable (≥170 days) in 15 of 16 cases.[29] Another 36 patients (15%) had stable disease (SD), giving a clinical benefit rate (CR + PR + SD) of 22%. Median OS was 10.1 months (95% CI, 7.9-11.7). Grade III/IV treatment-related AEs were reported in 21% of patients, and 1 patient died from a treatment-related AE. The most common AE grade III or above was diarrhea (11%). Rare AEs included endocrine disorders (approximately 4%), colitis (4%), and vitiligo (2%). An immune-related AE (IRAE) of any grade or causality was reported by 62% of patients, and 11 of 16 (69%) patients with an objective response and 27 of 36 (75%) with SD reported an IRAE.[29]

While this study did not demonstrate a second-line response rate exceeding 10%, the duration of response with this regimen leaves open the question of a role for tremelimumab in this population. Dr. Kirkwood noted that the median OS of 10.1 months observed in the trial compares favorably with the median OS of 6.2 months reported in a recent meta-analysis of phase II Cooperative Group trials in stage IV melanoma with second-line therapy,[50] but it must be noted that the exclusion of patients with an LDH >2x ULN invalidates the use of this benchmark. Once final OS data are available, correlates of clinical benefit with tremelimumab will be examined to determine whether responders can be predicted pre- or early posttherapy.

About 3 months prior to the ESMO Congress, results from a phase III trial comparing tremelimumab with chemotherapy (temozolomide or DTIC) as first-line therapy for patients with advanced melanoma were presented at the 2008 American Society of Clinical Oncology Annual Meeting.[51] In that study, tremelimumab failed to demonstrate a significant benefit for OS compared with standard chemotherapy.

Another poster at the Congress pre-

sented the results with respect to IRAEs from an open-label, randomized phase II trial of 2 different dosing regimens of tremelimumab (10 mg/kg IV q1m [n=44] or 15 mg/kg IV q3m [n=45] for up to a year) in patients with previously treated advanced melanoma.[30] Overall treatment-related AEs grade III or above were reported in 27% of patients in the 10 mg/kg monthly group and 13% in the 15 mg/kg every 3 months group. (The latter regimen corresponds with the regimen used in the prior study report of Kirkwood).[29] Serious AEs and discontinuations due to treatment-related AEs were also more common in the 10 mg/kg monthly group (23% vs 9% and 16% vs 7%, respectively). The most common treatment-related IRAEs in the study were diarrhea, rash, pruritus, and colitis. IRAEs grade III or above were more common in patients administered 10 mg/kg monthly than in those administered 15 mg/kg every 3 months, particularly with respect to diarrhea (21% vs 9%) and colitis (7% vs 2%).[30]

Ipilimumab. Nine presentations at the ESMO Congress dealt with ipilimumab studies. **Celeste Lebbé** of Saint-Louis Hospital in Paris, France, presented the results from a dose-ranging phase II study of ipilimumab treatment in pretreated patients with advanced melanoma.[52] In this study, 217 patients with unresectable stage III/IV melanoma and ECOG PS 0/1 were randomized in a 1:1:1 ratio to receive 4 weeks of induction therapy with 10 mg/kg, 3 mg/kg, or 0.3 mg/kg ipilimumab every 3 weeks (q3w) for 12 weeks, followed by the same dose as maintenance therapy every 12 weeks (q12w) starting on week 24. The 10 mg/kg induction and maintenance dosing regimen was determined to be the optimal ipilimumab regimen for this patient population. The 10 mg/kg dose yielded the highest ORR per modified WHO criteria (mWHO) (11.1% vs 4.2% and 0%, respectively; *P*=.0015) and was associated with the best median OS (11.0 vs 8.7 and 8.6 months, respectively) and 1-year survival rate (48.2% vs 39.2% and 39.9%, respectively).[52] For comparison, the median OS and 1-year survival rate for historical controls is 6.2 months and 25.5%, respectively.[53] Incidence of IRAEs appeared to be dose-dependent and was highest in the 10 mg/kg group, followed by the 3 and 0.3 mg/kg groups, but IRAEs were medically manageable and reversible in most patients. All other ipilimumab studies reported at the ESMO Congress employed this same 10 mg/kg regimen.

Other presentations examined the efficacy and tolerability/safety of ipilimumab in patients with advanced melanoma who had failed 1 or more prior therapies. A poster by **Michele Maio** and colleagues described an open-label, single-arm, phase II trial (CA184-008) showing ipilimumab activity in this patient population, as demonstrated by a median OS of 10.6 months, 1-year survival rate of 47.2%, ORR of 5.8% (all PRs), and a disease control rate or DCR (CR + PR + SD) of 27.1%.[54] As in all other trials of first- or second-line ipilimumab therapy, IRAEs were the most common AEs, and were of 4 main types: skin (49%, including rash and pruritus), gastrointestinal (31.0%, predominantly diarrhea, but also colitis), liver (9.0%, including autoimmune hepatitis), and endocrine (5.8%, including hypothyroidism and hypopituitarism).

Two posters—one by **Ian Ron** and colleagues and another by **Ruggero Ridolfi** and associates—reported on the efficacy and tolerability/safety of ipilimumab with[35] or without[34] budesonide in 115 advanced melanoma patients with or without prior treatment for metastatic disease (CA184-007). Since gastrointestinal IRAEs have been reported most frequently upon CTLA-4 mAbs therapy, budesonide (an oral corticosteroid acting in the gut with minimal systemic exposure) was included to see if it could prevent gastrointestinal IRAEs associated with ipilimumab therapy. The data from this randomized, double-blind, placebo-controlled phase II trial did not support the prophylactic use of budesonide. Any IRAE and gastrointestinal IRAEs occurred at similar rates for patients who received or did not receive budesonide, whether looking at any grade or grade III/IV events. Generally similar rates of diarrhea grade II or higher or were observed with or without budesonide in both treatment-naïve (38.1% vs 31.3%) and previously treated patients (29.7% vs 40.0%).[34,35] Likewise, generally similar ORRs, median OS, and 1-year survival rates were observed with or without budesonide in both treatment-naïve (ORR: 9.5% vs 15.6%; median OS: not reached; 1-year survival: 65.9% vs 71.4%) and previously treated patients (ORR: 13.5% vs 16.0%; median OS: 8.5 vs 14.8 months; and 1-year survival: 49.9% vs 50.8%). Although overall and 1-year survival rates appeared to be higher in treatment-naïve than in previously treated patients, the differences were not statistically significant in this relatively small study with limited follow-up (median, 16 months) at the time of the Congress.

Study CA-184-007 allowed inclusion of patients with previously-treated, stable brain metastases, and a poster by **Jeffrey Weber** and colleagues suggested ipilimumab activity in this patient subpopulation.[36] Of 12 patients with brain metastases evaluable for efficacy, 11 were still alive at 6 months, and 3 were alive at 17.3 to 24.5 months (with 1 lost to follow-up at 15.7 months). The DCR for patients with brain metastases was similar to that for the entire study population (33.3% vs 33.0%).[36] A study of ipilimumab in advanced melanoma patients with brain metastases is ongoing.

Given the immunomodulatory mechanism of action of ipilimumab and other anti-CTLA-4 mAbs, which (unlike cytotoxic chemotherapy) presumably requires some time for onset and maximal effect, traditional measures of clinical response may not be fully adequate for these agents. Consistent with this hypothesis, each of the phase II studies reported at the ESMO Congress noted 4 distinct patterns of ipilimumab response, only the first of which would be captured by standard response measures: (1) shrinkage/response in baseline lesions, (2) "stable disease" with a slow, steady decline in

tumor volume, (3) response after initial increase in total tumor volume, and (4) response in index and new lesions after the appearance of new lesions. These patterns of response were more fully described in a poster by **Harmankaya** and associates[32] and in an oral presentation by **Vanna Chiarion Sileni** of the Instituto Oncologico Veneto in Padova, Italy.[55] Harmankaya and colleagues recommended novel immune-related response criteria (irRC) for use in clinical trial designs of anti-CTLA-4 antibodies (**Table 3**).[32] Such criteria are being incorporated in upcoming trials of ipilimumab.

Another poster by **Axel Hoos** (Bristol-Myers Squibb) and associates provided a pooled analysis of data from 3 phase II studies assessing the effect of ipilimumab on peripheral T-cell populations as a means to evaluate its impact on immune function in advanced melanoma.[33] Changes in absolute lymphocyte count (ALC) with treatment were correlated with clinical response. The data showed ipilimumab treatment was associated with increases in circulating levels of activated $CD4^+$ and $CD8^+$ T cells and decreases in naïve $CD4^+$ and $CD8^+$ T cells. These changes were generally observed during the first 4 weeks of treatment and maintained to week 12. Moreover, patients with clinical benefit had, on average, a higher rate of ALC increase over time than those without clinical benefit, and the rate of ALC increase over time was significantly higher in patients with clinical benefit than in those without (P=.0006). The authors concluded that these findings are consistent with the proposed immunologic mechanism of action for ipilimumab and suggested that change in ALC over time may be useful as a predictive marker for response to ipilimumab therapy.[33]

A poster at the ESMO Congress by **Kevin Chin** and colleagues presented treatment guidelines developed and implemented in ipilimumab trials to manage treatment-related IRAEs.[31] The authors stated that prompt implementation of the guidelines may prevent development of serious complications. They also observed that, when these guidelines have been used in clinical trials of ipilimumab, high-grade IRAEs were generally reversible and medically manageable in most patients by either withholding ipilimumab therapy or administering symptomatic therapy or corticosteroids. Severe or steroid-refractory IRAEs may require additional treatment with secondary immunosuppressive regimens such as infliximab or mycophenolate mofetil.

Other Treatment Approaches

Elesclomol. This investigational drug for advanced melanoma rapidly induces the generation of reactive oxygen species in melanoma, which may activate signaling pathways leading to apoptosis. Cancer cells in general, and melanoma cells in particular, have higher levels of oxidative stress than noncancerous cells, which may make them more susceptible to the death-promoting effects of elesclomol.

Steven O'Day of The Los Angeles Clinic and Research Institute in Santa Monica, California, examined the 2-year

Table 3. Proposed New Response Criteria for Ipilimumab and Other Anti-CTLA-4 Antibodies: mWHO vs irRC

	Complete response (CR)	Partial response (PR)	Stable disease (SD)	Progressive disease (PD)
Modified WHO (mWHO) criteria	All lesions gone	•SPD of index lesions ↓ ≥50% from baseline •New lesions not allowed	•SPD of index lesions neither CR, PR, or PD •New lesions not allowed	•SPD of index lesions ↑ ≥25% from nadir AND/OR •PD is based on unequivocal progression of non-index lesions and/or new lesions
	irCR	**irPR**	**irSD**	**irPD**
Immune-related response criteria (irRC)	All lesions gone	•SPD of index + any new lesions decreases ≥50% from baseline •New lesions allowed	•SPD of index + any new lesions neither irCR, irPR, nor irPD •New lesions allowed	•SPD of index + any new lesions ↑ ≥25% from nadir •irPD is based on SPD only

WHO, World Health Organization; SPD, sum of the product of the perpendicular diameters.

From Harmakaya K et al. Ipilimumab-mediated patterns of response in patients with pretreated, advanced melanoma. Poster presented at: 33rd ESMO Congress; September 12-16, 2008; Stockholm, Sweden.[32]

OS and other efficacy and tolerability/safety results from a randomized, double-blind, controlled, multicenter, phase II trial comparing elesclomol (213 mg/m^2) plus paclitaxel (80 mg/m^2) with paclitaxel (80 mg/m^2) alone in patients with stage IV melanoma, ECOG PS 0-2, and 0-1 prior chemotherapy regimens for metastatic disease.[42] Patients were randomized in a 2:1 ratio to the elesclomol plus paclitaxel (n=53) or paclitaxel alone (n=28) groups. Treatment regimens were administered in 4-week cycles of once weekly for 3 weeks, followed by 1 week off, until progression. Crossover was allowed for the paclitaxel-alone arm after disease progression, precluding any statement on a possible survival advantage.

Prior analyses determined that the trial met its primary endpoint of improved median PFS with elesclomol plus paclitaxel versus paclitaxel alone (3.7 vs 1.8 months; HR, 0.583; *P*=.035).[42] The focus of the ESMO presentation was on the 2-year OS results. Median OS appeared to be longer with elesclomol plus paclitaxel, but this did not reach statistical significance (11.9 vs 7.8 months; HR, 0.88; 95% CI, 0.525-1.475; *P*=.63). The study was not powered for analysis of survival. Nineteen patients in the paclitaxel group crossed over to elesclomol plus paclitaxel therapy, which presumably confounded the OS results. The 2-year OS rates were 27% for elesclomol plus paclitaxel, 26% for patients in the paclitaxel-alone group who crossed over to elesclomol plus paclitaxel, and 11% for paclitaxel alone (without crossover). A nonsignificant increase in particular AEs with combination treatment was noted in particular AEs, namely hypoesthesia, constipation, fatigue, arthralgia, neutropenia, and stomatitis.[42]

As a whole, results from this study are considered encouraging and warrant further study. The phase III SYMMETRY trial has been designed to further explore the combination of elesclomol plus paclitaxel in 630 patients with advanced melanoma, using the same general design, dose, schedule, and primary and secondary endpoints as were employed in the phase II trial described by Dr. O'Day.[42] However, patients will be randomized in a 1:1 ratio in the SYMMETRY trial, and crossover will not be allowed.[42] It is anticipated that the recruitment target will be reached in February 2009.

Molecularly targeted agents. Other ongoing clinical phase II studies are also exploring the strategy of combining newer molecularly targeting agents with cytotoxic chemotherapy in an attempt to improve clinical outcomes in patients with advanced melanoma. Negative findings were reported at the ESMO Congress for the combination of high-dose bosentan plus DTIC versus DTIC alone in patients with stage IV melanoma.[41] Similarly, an ESMO poster reported that the combination of CP-4055 and sorafenib was associated with acceptable toxicity, but only modest and not encouraging activity in patients with advanced melanoma.[39]

Generally negative results were also reported in a poster describing an Italian multicenter, open-label, single-arm, phase II trial of fotemustine plus bevacizumab as first-line treatment of stage IV melanoma.[56] The primary endpoint was tumor response rate, but the study was closed after initial interim analysis for not achieving the requisite number of responses (11% ORR vs an acceptable level of >30%) and for unacceptable toxicity (>40% grade III/IV AEs). Myelotoxicity was a particular concern with this combination.

Another poster at ESMO presented results from an open-label, phase II multicenter trial of sorafenib plus DTIC in patients with advanced melanoma,[40] where 10 of the 24 (45.5%) patients achieved the DCR (0 CR + 2 PR + 8 SD), and the combination was associated with acceptable tolerability, possibly supporting further evaluation in larger clinical trials.

Other Aspects of Melanoma and its Treatment

Basic Biology: Melanoma Genetics

Dysregulation of the melanocyte cell cycle resulting in unregulated growth is understood to be a critical mechanism leading to malignant melanoma.[57] The exact steps leading to unregulated growth may differ from patient to patient, but molecular aberrations in key molecules involved in intracellular signaling are thought to be involved, either by promoting malignant transformation and proliferation or by inhibiting apoptosis or otherwise promoting survival and limitless replicative potential.[57,58]

Cyclin D1 (CCND1) is a key regulator of cell cycle progression, and aberrations in CCND1 or molecules regulating its activity have been implicated in the pathogenesis and prognosis of melanoma.[59] An ESMO presentation by **Raquel Catarino** of the Portuguese Institute of Oncology in Porto, Portugal, described a case-control study looking at the association of *CCND1* single nucleotide polymorphisms (SNPs) with susceptibility to melanoma.[60]

CCND1 is a key component involved in the regulation of checkpoint G1/S of the cell cycle, which controls the passage from G1 into the DNA synthesis (S) phase of the cycle.[57,60] Retinoblastoma protein (Rb) is a tumor suppressor protein that, in its unphosphorylated state, forms a complex with E2F transcription factor, thereby preventing the latter from inducing the expression of genes involved in transition from the G1 to S phase of the cell cycle. However, when CCND1 binds with either cyclin-dependent kinase (CDK) 4 or 6, it forms an active complex that promotes phosphorylation of Rb, causing release of EF2 and progression through the G1/S checkpoint.

Genetic variation in the form of SNPs has been identified for the *CCND1* gene. The *CCND1* A870G polymorphism is associated with the substitution of deoxyadenosine (A) for deoxyguanosine (G) at nucleotide 870, and seems to modulate alternate splicing the resulting mRNA.[60] The G allele produces 2 isoforms (a and b), the latter being associated with a longer half life. The A allele, associated with the A870G polymorphism, is more associated with isoform a. Hence, this polymorphism may be associated with elevated levels of CCND1 within the neoplastic melanocyte and predispose or help to drive melanoma development or progression. The objective of the study was to evaluate the impact of the *CCND1* A870G polymorphism on melanoma predisposition by analyzing the frequencies of this SNP in melanoma patients compared with healthy controls.[60]

For this study, DNA was extracted by salting-out protocol from 161 cases and 892 controls, and PCR-RFLP methodology was used for *CCND1* polymorphism analysis.[60] Cases (patients) and controls were grouped by genotype as either AA, AG, or GG. The GG genotype was more frequent in patients than controls (28.6% vs 18.4%), and the AG genotype was more common in controls than patients (57.4% vs 48.4%). Furthermore, individuals with a GG genotype had significantly greater risk of developing melanoma than those with a AA or a AG genotype (odds ratio [OR], 1.97; 95% CI, 1.27-3.05; *P*=.002). A multivariate logistic regression analysis confirmed the association between presence of the GG *CCND1* genotype and increased genetic susceptibility for melanoma development.

Dr. Catarino suggested the *CCND1* polymorphism may be a biomarker for melanoma risk.[60] This is important because knowledge of the mechanisms involved in melanoma development may help identify targets for the development of chemoprevention or therapeutic strategies.

Managing Resected Stage IIB/III Patients at High Risk for Recurrence

Patients with stage IIB-III melanoma are at high risk for disease recurrence following surgical resection and are often offered the option of adjuvant therapy with IFN-α or entering into a clinical trial. **Alexander M. M. Eggermont** of the Erasmus University Medical Centre in Rotterdam, the Netherlands, gave an oral presentation at the Schering-Plough–sponsored *Current Trends in Melanoma Management* symposium on the current status of systemic adjuvant therapy in melanoma, with a focus on long-term adjuvant pegylated IFN-α2b therapy.[61]

Dr. Eggermont noted that IFN-α is the only adjuvant therapy that has demonstrated consistent benefit for relapse-free survival (RFS) in stage IIB/III melanoma patients, although it has inconsistently been associated with improved OS.[61] This means, he said, that for the foreseeable future IFN-α remains the only agent available as adjuvant therapy for this patient population in the clinical setting. So it behooves the research community to better understand how to fine tune adjuvant IFN-α therapy and perhaps identify variables that will enable better selection of patients most likely to respond to this treatment.

Dr. Eggermont then turned his attention to the findings from EORTC 18991, a randomized controlled phase III trial of adjuvant therapy with pegylated IFN-α2b versus observation in patients with resected stage III melanoma (TxN1-2M0).[61,62] In this study, 1,256 patients were randomized in a 1:1 ratio to observation alone (n=629) or pegylated IFN-α2b (n=627) 6 µg/kg per week for 8 weeks (induction) then 3 µg/kg per week (maintenance) for the next 5 years. Randomization was stratified by microscopic (N1) versus macroscopic (N2) dis-

ease, number of positive nodes, Breslow thickness, ulceration, gender, and participating center, and the primary regulatory endpoint was RFS in the intent-to-treat population. Secondary endpoints included distant metastasis-free survival (DMFS) and OS.[62]

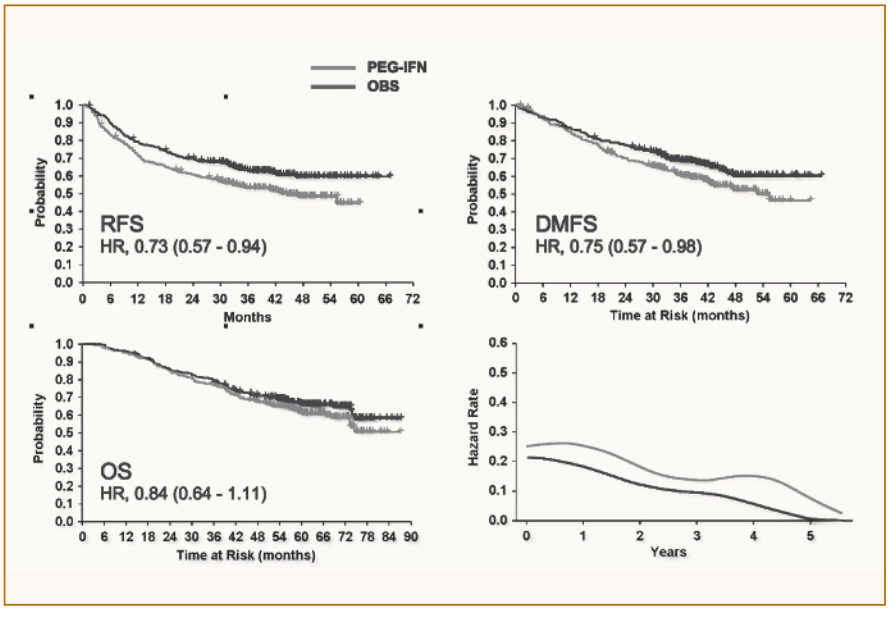
The principal objective of the trial was to determine whether adjuvant therapy with pegylated IFN-α2b could result in prolonged exposure while maintaining tolerability.[62] There was also interest in determining whether prolonged treatment with this regimen would be associated with improvement in OS.[61,62] However, while the RFS rate at 3.8-year median follow-up was significantly higher in the pegylated IFN-α2b than in the observation group (45.6% vs 38.9%; HR, 0.82; 95% CI, 0.71-0.96; *P*=.011), there were no significant differences between the groups for DMFS (48.2% vs 45.4%; HR, 0.88; 95% CI, 0.75-1.03; *P*=.107) or OS (45.6 vs 38.9; HR, 0.98; 95% CI, 0.82-1.16; *P*=.78). So, while adjuvant pegylated IFN-α2b therapy was associated with sustained improvement of RFS in fully resected stage III melanoma patients, this improvement did not translate into additional improvement in DMFS or OS in the entire trial population. Tolerability/safety with pegylated IFN-α2b was acceptable, and importantly, there was no cumulative toxicity with prolonged administration.[62]

Of note, when efficacy was examined separately for patients with microscopic (N1) and macroscopic (N2) disease after a recent 5.1-year median follow-up analysis, a treatment effect appeared to be present for RFS, DMFS, and OS in the microscopic subgroup (**Figure 1**), but not in the macroscopic subgroup (data not shown: HRs for RFS, DMFS, and OS were 0.86, 0.94, and 1.01, respectively).[61,62] These data suggest that patients with microscopic and macroscopic disease may be differentially sensitive to the effects of adjuvant IFN therapy.

Subgroup analysis of the data from the EORTC 18952 trial[63] provided additional support for the hypothesis that patients with macroscopic disease (stage III-N2) are less sensitive to the effects of adjuvant IFN than those with microscopic disease (stage III-N1) or no apparent nodal involvement (stage IIB), ie, that the impact of adjuvant IFN is stage- and tumor load-related.[61] In EORTC 18952, 1,388 patients with stage IIB or stage III melanoma were randomized to 13 months (n=553) or 25 months (n=556) of adjuvant IFN-α2b therapy or observation (n=279). IFN-α2b was administered at 10 million units (MU) 5 days a week for 4 weeks, followed by either 10 MU 3 times a week for 1 year or 5 MU 3 times a week for 2 years. DMFS was the primary endpoint.[63] Generally better results were obtained in the 25-month IFN-α2b than 13-month IFN-α2b, but of interest here, subgroup analysis by clinical stage suggested generally superior results in patients with stage IIB disease than in those with stage III-N1 disease, and in those with stage III-N1 disease versus stage III-N2 disease (**Table 4**)—consistent with stage-dependent sensitivity to adjuvant IFN therapy.[61] Also, taken together with the results from EORTC 18952, the data suggest that outcomes in patients with stage IIB or III-N1 disease get better the longer adjuvant IFN-α2b is administered.

Dr. Eggermont then turned his attention to the possible significance of autoimmunity signs and ulceration in predicting response to adjuvant IFN-α2b therapy.[61] He pointed to the 2006 article by Gogas and colleagues that suggested that autoimmunity during IFN-α2b had prognostic significance for RFS and OS in stage IIB-III melanoma patients,[64] but argued that there were problems with this analysis. Dr. Eggermont stated that they were unable to replicate these findings in their adjuvant EORTC trials.[61,65,66] Moreover, he argued that the graphic presentation of relapse and survival curves of seropositive and seronegative patients is subject to lead-time bias and thus suggests an enormous effect that is not real, since patients who relapse or die before they seroconvert end up on the poorer response curve. The proper analysis to perform is a time-dependent

Figure 1. Effect of Pegylated IFN-α2b on RFS, DMFS, and OS in Patients With Microscopic Disease After a 5.1-Year Median Follow-up (EORTC 18991)



From Eggermont A. Systemic adjuvant therapy in melanoma: where are we? Presented at: 33rd Annual ESMO Congress; September 12-16, 2008; Stockholm, Sweden.[61]

Table 4. Subgroup Analysis of DMFS and OS in the 13-Month (10 MU) and 25-Month IFN-α2b Groups in EORTC 18952

	13-Month IFN Group		25-Month IFN Group	
	DMFS	OS	DMFS	OS
Stage IIB	0.78	0.71	0.54	0.54
Stage III-N1	0.89	1.02	0.66	0.73
Stage III-N2	1.01	1.09	0.90	0.97

The numbers reflect hazard ratios for the different measures compared with the observation-only group.

DMFS, distant metastasis-free survival; OS, overall survival.

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Cox analysis. This analysis was negative for both the EORTC 18952 and the EORTC 18991 trials.[65,66] Thus, presence or emergence of autoimmune antibodies could not be demonstrated to be a strong prognostic or predictive factor in the EORTC trials. In Dr. Eggermont's opinion, it is clear that autoimmunity during adjuvant IFN-α2b therapy is not a predictive factor and cannot be used to decide whether to start or to continue therapy.

Ulceration seems to be a more promising predictive factor for response to adjuvant IFN-α2b therapy. When the results for RFS, DMFS, and OS from the EORTC 18991 (long-term pegylated IFN-α2b) were examined for stage III-N1 patients stratified for presence of ulceration, significance was obtained for all endpoints in those with ulcerated lesions but not for those without ulceration (**Table 5**).[61] Similarly, 13-month or 25-month adjuvant IFN-α2b therapy of stage IIB patients in EORTC 18952 was associated with significantly longer DMFS compared with observation (P=.015) in patients with ulcerated tumors, but not in those without ulcerated tumors (P=.81).[66]

Of course data such as these are only hypothesis-generating and need to be more fully tested in well-designed prospective trials. EORTC 18081, which will start in early 2009, is a randomized phase III trial of 2-year pegylated IFN-α2b versus observation in patients with stage II ulcerated primary melanoma >1 mm thick.[61] The results from this study should provide evidence as to whether this is a patient population likely to be sensitive to adjuvant IFN-α2b therapy translating to an OS benefit.

Detection of Distant Metastases With FDG-PET and CT in Stage III Patients

The presence of distant metastases has important treatment implications for melanoma patients, and hence determination of the best method for detecting such metastases is a key component of patient management.

An ESMO abstract by **Esther Bastiaannet** and colleagues described the results from a prospective study comparing FDG-PET with CT for the detection of distant metastases in 251 consecutive patients with clinical stage III melanoma seen at 5 hospitals between July 2003 and November 2007.[66] The analysis demonstrated that FDG-PET detected significantly more overall metastatic sites (P=.017), bone metastases (P≤.0001), and skin metastases (P=.03) than CT. These findings suggest that FDG-PET should be considered as an option for the detection of distant metastases in patients with clinical stage III melanoma.

Table 5. RFS, DMFS, and OS Results From EORTC 18991 for Patients With Stage III-N1 Melanoma Stratified by Ulceration

	RFS		DMFS		OS	
Ulceration	**Obs**	**PEG-IFN**	**Obs**	**PEG-IFN**	**Obs**	**PEG-IFN**
Absent (n=321)						
HR (99% CI)	0.74 (0.46–1.20)		0.88 (0.52–1.50)		1.18 (0.64–2.18)	
P-value	.11		.54		.49	
Present (n=186)						
No. events	62	53	59	45	44	33
4-year rates	26.8	43.8	30.1	47.4	45.4	65.0
HR (99% CI)	0.69 (0.43–1.12)		0.59 (0.35–0.98)		0.61 (0.34–1.10)	
P-value	.049		.006		.03	

RFS, relapse-free survival; DMFS, distant metastasis-free survival; OS, overall survival; Obs, observation; PEG-IFN, pegylated interferon alfa-2b.

From Eggermont A. Systemic adjuvant therapy in melanoma: where are we? Presented at: 33rd Annual ESMO Congress; September 12-16, 2008; Stockholm, Sweden.[61]

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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. **Which of the following statements is most correct concerning melanoma epidemiology in the United States and Europe?**
   A. Incidence has been rising, but mortality rates have stabilized
   B. Both incidence and mortality rates have been rising
   C. Incidence has stabilized, but mortality rates are rising
   D. Both incidence and mortality rates have stabilized

2. **Which of the following is a proposed change in the upcoming 7th Edition of the AJCC staging system for melanoma compared with the earlier version?**
   A. Modification of thickness thresholds and their use as the primary determinant of T staging
   B. Incorporation of ulceration for stage I, II, and III
   C. Emphasis on number of metastatic lymph nodes, rather than their size/gross dimension
   D. Replacement of level of invasion with mitotic rate to define subcategory T1b

3. **Based on the results from the phase III trial comparing extended-schedule temozolomide with dacarbazine (DTIC) in patients with advanced melanoma, which of the following is true?**
   A. Temozolomide is associated with significantly longer median overall survival than DTIC
   B. DTIC is associated with significantly longer median overall survival than temozolomide
   C. Temozolomide and DTIC were associated with similar median overall survival
   D. Temozolomide was associated with significantly longer median overall survival in the subgroup of patients with brain metastases

4. **Which of the following best describes the proposed mechanism of action of CTLA-4 antibodies in melanoma?**
   A. Enhancement of immune responses by blocking negative regulation of T-cell activity
   B. Interfering with cell proliferation by placing a brake on G1/S phase transition
   C. Interfering with tumor-related angiogenesis by sequestering a molecule involved in VEGFR signaling
   D. Enabling apoptosis by promoting decreases in Bcl-2 levels within melanocytes

5. **The results from a phase II study of single-agent tremelimumab treatment of advanced refractory or relapsed melanoma reported at ESMO indicate that:**
   A. Second-line tremelimumab treatment is associated with longer median overall survival than for historical controls of second-line therapy
   B. Second-line tremelimumab treatment is associated with similar median overall survival as historical controls of second-line therapy
   C. Second-line tremelimumab treatment is associated with shorter median overall survival than historical controls of second-line therapy
   D. Second-line tremelimumab treatment is associated with similar median overall survival as has been observed with first-line tremelimumab in this patient population

6. **Based on the presentations at 2008 ESMO, which of the following is NOT true concerning ipilimumab treatment of patients with advanced melanoma?**
   A. Traditional measures of tumor response may not capture the full efficacy of ipilimumab
   B. 3 mg/kg every 3 weeks during induction and every 12 weeks during maintenance appears to be the optimal dosing regimens
   C. The most common AEs with ipilimumab are immune-related and appear to correlate with efficacy
   D. Treatment-related diarrhea and colitis were not decreased by prophylactic treatment with budesonide

7. **Which of the following is true concerning the 2-year overall survival results from a phase II study comparing elesclomol with elesclomol plus paclitaxel in patients with advanced melanoma?**
   A. Median overall survival was significantly longer with elesclomol plus paclitaxel than paclitaxel alone
   B. Median overall survival was similar in the elesclomol plus paclitaxel and paclitaxel alone treatment groups
   C. Median overall survival was significantly longer with elesclomol alone than elesclomol plus paclitaxel
   D. Median overall survival appeared to be longer with elesclomol plus paclitaxel than paclitaxel alone, but the difference did not reach statistical significance

8. **Which of the following is NOT true concerning melanoma genetics based on presentations at ESMO 2008 or associated symposia?**
   A. Environmental but not genetic factors are significant predictors of number of melanocytic nevi
   B. A *CCND1* polymorphism appears to increase risk of melanoma development by increasing intracellular CCND1 levels
   C. Studies of gene polymorphisms and gene expression profiling of cell lines are both useful strategies for identifying genes involved in melanoma development or progression

9. **Based on currently available data, which of the following is/are acceptable adjuvant therapy/therapies in clinical practice for patients with resected stage IIB-III?**
   A. IL-2
   B. IFN-α2b
   C. CTLA-4 antibodies
   D. All of the above

10. **Preliminary and retrospective data suggest which of the following factors may be associated with increased sensitivity to the beneficial effects of adjuvant IFN-α2b therapy?**
    A. Mitotic rate
    B. *CCND1* polymorphisms
    C. Clark level of invasion
    D. Ulceration of the primary

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. Identify proposed changes in the upcoming 7th Edition of the AJCC melanoma staging system compared with the 6th Edition

❍ ❍ ❍ ❍ ❍

B. Discuss the overall survival results from the phase III trial comparing extended-schedule temozolomide and dacarbazine in advanced melanoma patients

❍ ❍ ❍ ❍ ❍

C. Describe the latest findings from phase II trials of ipilimumab and tremelimumab for the treatment of advanced melanoma

❍ ❍ ❍ ❍ ❍

D. Identify the cyclin D1 (CCND1) polymorphisms that may be a biomarker for increased melanoma risk, and describe a possible mechanism of action

❍ ❍ ❍ ❍ ❍

E. Discuss possible variables that may predict response to adjuvant IFN-α2b therapy in patients with stage IIB-III 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. ☐ 8. ☐ 9. ☐ 10. ☐

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