Original Article

# Where Are We With Adjuvant Therapy of Stage III and IV Melanoma in 2009?

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**Key Words**

Adjuvant, melanoma, interferon, pegylated

**Abstract**

Adjuvant therapy options for advanced melanoma in 2009 remain active observation, high-dose interferon, or clinical trial participation. Close observation is currently the only required adjuvant management, with the purpose of detecting the emergence of regional or metastatic disease early, when surgical management may still be possible. The National Comprehensive Cancer Network guidelines for the workup and follow-up of all stages of melanoma must be tailored to specific patients by the treating physician. This article explores the factors to consider when individualizing care within the scope of these guidelines. *(JNCCN* 2009;7:295–304)

The incidence of melanoma continues to rise. Median survival for metastatic disease is unchanged at 6 to 9 months despite persistent scientific investigation. Surgery remains standard care for melanoma confined to the primary site, regionally advanced disease, and even select cases of metastatic melanoma. With the routine use of sentinel node biopsy and radiographic imaging, detection of very small volumes of nodal and distant metastases is common, and the populations of patients with microscopic stage III and IV melanoma without evidence of disease after resection are increasing. The only standard adjuvant therapy for stage IIB/C and III melanoma is high-dose interferon alfa-2b (HDI). With a well-established relapse-free survival (RFS) benefit, this treatment has toxicities and expense, is not appropriate for some patients, and continues to inspire controversy.

For the first time since 1995, a new adjuvant agent is under review by the FDA. In a randomized phase III study conducted by the EORTC, protocol 18991, pegylated interferon alfa-2b showed a significant improvement in recurrence-free survival in resected stage III melanoma. Similar to high-dose interferon, no overall survival (OS) benefit was seen, although survival was a secondary end point and follow-up was short.

In melanoma, the adjuvant options for resected stage IIB/C and III disease are active observation, high-dose interferon, and clinical trial participation. For resected stage IV melanoma, the options are observation versus clinical trial, as high-dose interferon has not been adequately studied in this population. Further research is needed to better identify and stratify subpopulations within stages to improve prognostication and prediction of therapeutic response and identification of novel therapies. Patient referral for clinical trials is essential to expanding options and improving outcomes.

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Submitted October 9, 2008; accepted for publication January 4, 2009.

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## Background

An *adjuvant* is "additional therapy given to enhance or extend a primary therapy's effect…"[1] In melanoma, surgery remains the primary therapy and only one adjuvant option, high-dose interferon alfa-2b (HDI), has been defined. The limits of this therapy surely pertain to the heterogeneity of this tumor, host factors, and the current inability to identify the subset of patients who will derive the greatest benefit from this agent.

The incidence of melanoma continues to rise annually, with 62,480 new cases and 8420 deaths estimated in 2008. Melanoma ranks as the sixth and seventh most common cancer among men and women, respectively,

and accounts for 75% of skin cancer deaths.[2] Surgical management of melanoma involves wide excision of the primary with well-established margins.[3] Sentinel lymphoscintigraphy and biopsy (SLN), introduced into clinical practice in 1996, are recommended at wide excision for primary melanomas with a thickness 1 mm or greater, or those less than 1 mm in thickness with a level IV or higher, ulceration, or other concerning features. Currently, completion lymph node dissection (CLND) is recommended for any nodal involvement. The results of the ongoing Multicenter Selective Lymphadenectomy Trial-2 are eagerly awaited to show whether nodal observation may be an acceptable alternative in patients with a microscopic SLN, instead of CLND.

Most patients with resectable melanoma will be surgically cured. The risk for relapse or death at 5 years for stage I melanoma is less than 10%; for stage IIA melanoma, this risk is intermediate at 10% to 30%.[4] Adjuvant therapies have centered around high-risk patients, who have a risk for relapse or death at or exceeding 50%, comprised of those with stage IIB through IIIC melanoma. However, patients with stage IIIA melanoma show less than a 50% chance of recurrence or death.[5]

In 1995, the FDA approved HDI for patients after surgical resection of a primary melanoma 4 mm or greater or any primary with nodal involvement. Over the past few decades, newer and expanding categories of patients have emerged that challenge the current staging, management, and therapeutic options in melanoma. These include patients with microscopic SLN involvement, some with only isolated tumor cells, and those with surgically resected stage IV melanoma. SLNs are typically subject to greater pathologic scrutiny than the larger number of nodes removed with previously standard elective lymph node dissections (ELND). This is true for the number of sections created from each node and routine use of immunohistochemistry for melanocyte-specific antigens. Both techniques permit the discovery of previously undetected submicrometastatic disease.[6]

Microscopic SLN patients fare better than stage III patients.[7] However, whether outcomes for patients with these submicrometastases are equivalent to those for patients with negative SLN is unclear, indicating the unique biology of melanoma, in which even isolated tumor cells may be a harbinger of aggressive disease, signaling the capacity for migration. Clearly all patients with stage III disease are not the same regarding prognosis, and HDI is not appropriate for everyone. Can alternative doses, formulations, or schedules of interferon effect similar or better benefit compared with HDI with less toxicity? Are patients with microscopic nodal involvement most likely to benefit from interferon or other adjuvant therapies? Is this a function of tumor biology, tumor/host relationship, or simply a matter of tumor volume?

Improved radiographic imaging modalities–leading to detection of small-volume metastatic disease–and an increasing willingness of surgeons to resect limited metastatic disease are rendering more patients with stage IV melanoma free of radiographic evidence of melanoma. The disease-free interval from resection of the primary to emergence of metastases, and the number and sites of metastases, are key factors in predicting outcome.[8] Median survival of 40 months after resection of pulmonary oligometastases and mean 5-year survival for resected melanoma metastases of various sites as high as 23% have been reported.[8,9] These outcomes cannot be compared with those for high-risk stage III disease because patient selection for resection of distant metastases is more stringent. In the setting of isolated melanoma metastases, surgical resection should be considered based on these retrospective cohort analyses. However, the lack of established adjuvant therapy for these patients is noteworthy.

Adjuvant therapy options for advanced melanoma in 2009 remain active observation, HDI, or clinical trial participation. Close observation is currently the only required adjuvant management, with the purpose of detecting the emergence of regional or metastatic disease early, when surgical management may still be possible. NCCN guidelines for the workup and follow-up of all stages of melanoma[3] must be tailored to specific patients at the discretion of the treating physician. This article explores the factors to consider when individualizing care within the scope of these guidelines.

## Interferon

HDI was approved by the FDA after demonstrating a 1-year OS benefit over observation in resected stage IIB/C and III melanoma in a randomized phase III study, ECOG 1684.[10] The approved regimen consists of 20 mIU/m$^2$ intravenously daily, Monday through

Friday for 4 weeks, followed by 10 mIU/m$^2$ subcutaneously, 3 times a week for 48 weeks. This pivotal study randomized 287 patients with high-risk melanoma to HDI or observation after surgery. All patients with stage II disease without clinically evident nodal involvement underwent ELND in addition to wide excision. At a median follow-up of 6.9 years, statistically significant RFS (1.72 vs. 0.98 years; $P_1$ = .0023) and OS (3.82 vs. 2.78 years; $P_1$ = .0237) benefits were evident. After a median follow-up of 12.6 years, RFS benefit remained significant (hazard ratio [HR], 1.38; $P_2$ = .02) but OS benefit did not (HR, 1.22; $P_2$ = .18).[11]

Two subsequent studies further explored HDI in the adjuvant setting: ECOG protocols E1690 and E1694. E1690, initiated in 1991, randomized 642 patients with stage IIB/C or III melanoma after surgery to HDI versus low-dose interferon (LDI): 3 mIU/d subcutaneously 3 times a week for 2 years versus observation.[12] In contrast to E1684, ELND for stage II melanoma was not required and rarely performed in E1690 or E1694. HDI versus observation showed an HR of 1.28 ($P_2$ = .05) for RFS at a median follow-up of 4.3 years, favoring HDI. Comparing LDI with observation, the HR for RFS was 1.19 ($P_2$ = .17). No OS benefit was seen for HDI (HR, 1.0; $P_2$ = .995) or LDI (HR, 1.04; $P_2$ = .813) over observation. Again, the RFS benefit was maintained for HDI at 6.6 years of follow-up with no OS benefit.[11] When interpreting this study, one must consider that the median OS in the E1690 observation arm was 6 years compared with 2.8 years in E1684.[12] Despite the probable impact of differing patient populations and more aggressive surgical management between studies, another possible factor was the use of salvage HDI after relapse in the E1690 observation arm for patients with resectable recurrences. The postrelapse survival in the observation arms was 4.3 years in E1690 versus 1.8 years in E1684. An analysis adjusting for the effect of crossover from observation to HDI has not been conducted.

Begun in 1996, E1694 randomized 880 patients with stage IIB/C and III melanoma after surgery to HDI versus a GM2-ganglioside vaccine.[13] The trial was stopped early after an interim analysis showed significant RFS (HR, 1.49; $P_1$ = .00045) and OS benefits (HR, 1.38, $P_1$ = .023) for HDI over the vaccine at a median follow-up of 16 months (intent-to-treat analysis). At 2.1 years of follow-up, the RFS (HR, 1.33; $P_2$ = .006) and OS (HR, 1.32; $P_2$ = .04) benefits of HDI over the vaccine persisted.[11] However, with the recent presentation of the second interim analysis of EORTC 18961, a randomized study of adjuvant GM2-KLH21 vaccination versus observation in stage II melanoma that showed a worse outcome in vaccinated patients, the E1694 results may be due in part to the vaccine being detrimental.[14] Although the GM2 vaccines were not identical, a negative impact from the vaccine in E1694 cannot be ruled out.

A neoadjuvant approach to HDI was recently explored in a small group of 20 patients with stage IIIB/C melanoma.[15] They were treated with 1 month of induction HDI, followed by curative surgical resection, then maintenance HDI for 48 weeks; 11 patients showed an objective response, including 3 pathologic complete responses. At 18.5 months follow-up, 50% remained disease-free. This type of study permits in vivo clinical evaluation and facilitates investigation of biomarkers that associate with and may predict treatment response.

Side effects of HDI include, but are not limited to, constitutional symptoms, including fatigue, anorexia, and flu-like symptoms; bone marrow suppression; hepatotoxicity; thyroid dysfunction; and neuropsychiatric symptoms. Most patients experience some side effects and many require dose reductions or delays. Guidelines for toxicity management and dose adjustments have been published.[16]

The question remains whether alternative doses, formulations, or schedules of interferon produce a similar/better outcome than HDI with less toxicity. In Europe, the focus has been on extended courses of lower-dose interferon, a regimen that clearly reduces toxicity. LDI administered as 3 mIU/d subcutaneously 3 times weekly for 18 months was approved for the adjuvant treatment of resected primaries 1.5 mm or greater in thickness without nodal involvement based on an improved relapse-free interval over observation, but no OS benefit.[17] No benefit in disease-free survival (DFS) or OS was seen for LDI given for 36 months in resected stage III disease; extended treatment for 60 months had no advantage.[18,19]

Recently, the German Dermatologic Cooperative Oncology Group reported results from a study that randomized patients with resected stage III melanoma to observation versus LDI for 24 months versus LDI combined with dacarbazine every 4 to 8 weeks administered for 24 months.[20] Although LDI showed benefits in OS and DFS over observation,

combination LDI and dacarbazine showed no difference. Thus, improved DFS has been inconsistently observed with LDI and an OS benefit has been shown only once.

Pegylated interferon has been explored as a means of prolonging exposure, easing administration, and decreasing toxicity over standard interferon.[21] EORTC recently reported the results of their multicenter phase III study, protocol 18991, which evaluated recurrence-free survival in 1256 patients with resected stage III melanoma randomized to either 5 years of pegylated interferon alfa-2b or observation.[22] In this trial, 627 patients received induction pegylated interferon, 6 mcg/kg/wk, subcutaneously for 8 weeks followed by 3 mcg/kg/wk for 5 years. With a median treatment length of only 12 months, the 4-year RFS was superior in the treatment arm (45.6% vs. 38.9%; $P = .01$; HR, 0.82; 95% CI, 0.71–0.96) at a median follow-up of 3.8 years. A trend was seen toward improved distant metastasis-free survival in the pegylated interferon arm (48.2% vs. 45.4%; $P = .11$; HR, 0.88; 95% CI, 0.75–1.03), with no difference in OS (56.8% vs. 55.7%; $P = .78$; HR, 0.98; 95% CI, 0.82–1.16), although survival follow-up was immature.

Observed side effects were similar to those of HDI, with fatigue and depression the most common. Grade 3/4 adverse events occurred in 45% of patients in the pegylated interferon arm and 12% of patients in the observation arm. In the treatment arm, fatigue was reported in 94% (grade 3/4, 16%), liver test abnormalities in 79% (grade 3/4, approximately 10%), and depression in 59% (grade 3/4, approximately 6%); 191 (31%) patients stopped treatment because of toxicities. A similar overall incidence of toxicity has been reported for HDI, but the rate of grade 3/4 toxicities with pegylated interferon was lower, particularly for liver test abnormalities.[16] Thus, an impact on RFS was observed with a lower rate of severe toxicity. The short follow-up of this trial precludes comparison of survival data with previously conducted interferon trials.

Shorter courses of HDI have not been as effective as the full year of treatment.[23,24] Gogas et al.[24] randomized patients with resected stage IIB/C or III melanoma to 1 month vs. 1 year of HDI and evaluated for equivalency. At a median follow-up of 51 months, no difference in OS or DFS was seen. A difference in DFS at 3 years of 15% or less was designated as constituting equivalence. However, this magnitude of difference clearly has potential clinical significance. A much larger trial would be needed to more conclusively rule out an inferior result. Therefore, this regimen cannot be considered a standard adjuvant therapy option in place of 1 year of HDI. Interpretation of this study is further limited by the nonstandard interferon dosing of 15 mIU/m$^2$/d as induction with a flat maintenance dose of 10 mIU.

Another ongoing multicenter randomized phase III study, ECOG E1697, is evaluating RFS for 1 month HDI induction (20 mIU/m$^2$) versus observation in resected stage IIA/B/C and III (microscopic) melanoma. These results will be interesting not only for evaluation of induction HDI alone, but also for their use in earlier-stage disease and in smaller nodal burdens than were present in most of the E1684 and E1690 trial populations.

Whether tumor burden impacts benefit from adjuvant HDI is currently unclear. A recent retrospective analysis suggests that the RFS benefit from HDI is greatest in stage IIIA disease, specifically nonulcerated primaries with microscopic nodal involvement.[25] On subset analysis of EORTC E18991, the greatest benefit from pegylated interferon seemed to be in patients with microscopic nodal involvement (N1): 4-year RFS of 57.7% compared with 45.4% for observation.[22] However, all CIs included or crossed 1.0, or there was no treatment benefit. The recently presented results of the Sunbelt Melanoma trial contradict these studies.[26] This multicenter randomized study, halted because of slow accrual and consequently severely underpowered to detect the intended difference in outcome, showed no benefit from HDI in patients with a single SLN after CLND. Finally, subset analyses from the 3 ECOG protocols found the greatest benefit from HDI to be in different patient groups. Patients with nodal involvement, particularly palpable (macroscopic), derived the most benefit in E1684.[10] Although patients with 2 to 3 involved nodes had the maximum RFS benefit in E1690,[12] patients without nodal involvement had the best RFS in E1694.[13] These findings are likely confounded by evolving staging and surgical capabilities, but the question remains whether HDI, and other adjuvant therapies, are best used in the setting of resected microscopic tumor burden.

The oncology community continues to disagree as to the role of interferon in practice. Several re-

views and analyses of the adjuvant interferon studies have supported an RFS benefit for HDI.[11,27,28] More recently, an individual patient data meta-analysis of 13 adjuvant interferon studies comparing various doses and schedules with no interferon assessed event-free survival and OS.[29] This showed not only significant event-free survival benefit (odds ratio, 0.87; $P = .00006$) for interferon, but also an OS benefit (0.9; $P = .008$), with an absolute survival benefit of approximately 3% at 5 years. However, no differences in benefit were seen among interferon doses or duration of treatment, nor for any host or tumor features.

Despite these data, many physicians do not feel these benefits justify use of HDI. Given the dismal prognosis of metastatic melanoma and lack of proven alternatives, other clinicians advocate adjuvant HDI for appropriate patients. From a quality-of-life perspective, patients believe that an RFS benefit alone can tip the balance in favor of HDI.[30] However, many patients are not eligible for HDI because of comorbidities or age, and in addition to the unfavorable toxicity profiles, it is an expensive and time-consuming regimen to administer and receive. Currently, an assessment for and discussion of HDI in patients with resected stage IIB/C and III melanoma is reasonable and recommended. The conversation should also include possible clinical trial participation or active observation. Pegylated interferon may soon be another part of this conversation, albeit similar to HDI. For appropriate patients, some form of adjuvant systemic therapy, either HDI or a clinical trial, should be encouraged.

## Other Immunotherapies

### Granulocyte Macrophage Colony–Stimulating Factor

Granulocyte macrophage colony–stimulating factor (GM-CSF) activates macrophages and dendritic cells (DC), thus promoting antigen presentation. It has been evaluated alone and in combination with various therapies, including vaccines. Compared with historical controls, GM-CSF 125 mcg/m$^2$/d subcutaneously for 14 days per 28, administered for 1 year, improved median survival (37.5 vs. 12.2 months) in 48 patients with resected bulky stage III or IV melanoma.[31] A recent small study evaluated clinical outcome and DC maturation in patients with resected stage IIIB/C and IV melanoma treated with this same regimen for 13 cycles.[32] After 2 weeks of treatment, an increase in total and mature DCs occurred that normalized after 4 weeks. Median OS was notable at 65 months with a median RFS of 5.6 months, with no or little impact on DCs correlating with early recurrence. ECOG E4697, closed to accrual in 2006, is a double-blinded, randomized, 6-arm phase III study of combinations of GM-CSF, a peptide vaccine, and placebos of both agents in resected macroscopic stage III and IV melanoma. This study will yield results soon and provide multi-institutional controlled data to support or refute the adjuvant role of GM-CSF.

### Anti-Cytotoxic T-Lymphocyte Antigen Antibody

Another potential mechanism of enhancing or prolonging antitumor T-cell mediated immunity is through manipulation of T-cell regulatory mechanisms. CD28, the primary costimulatory receptor on T cells, promotes T-cell activation through ligation of CD80 or CD86 on antigen-presenting cells. Its negative regulatory counterpart, cytotoxic T-lymphocyte antigen (CTLA-4), downregulates T-cell activation. Expressed on activated T cells, CTLA-4 affects immune tolerance through binding CD80/86 with greater affinity than CD28. Tumors, including melanoma, elaborate several mechanisms that tip the balance toward anergy in preexisting tumor-reactive T cells. This tolerance to tumor cells permits tumor escape, progression, and resistance to treatment.

Two antagonist fully human monoclonal antibodies against CTLA-4 are in clinical investigation, ipilimumab and tremilimumab. In metastatic melanoma, both antibodies have shown response rates (RRs) of approximately 10%.[33] Some responses are delayed, can occur after initial tumor progression, and seem durable. CTLA-4 antibodies carry the risk for autoimmune toxicities, wherein the development of these immune-related adverse events correlates with antitumor response.[34,35] The role of CTLA-4 blockade in advanced melanoma remains to be determined, because tremilimumab evidenced no survival benefit over chemotherapy as first-line therapy in a large phase III study.[36] The ongoing randomized phase III study of dacarbazine +/– ipilimumab in untreated, unresectable stage III/IV melanoma has completed accrual and should report data soon.

Whether these antibodies would be more effective in the adjuvant setting against microscopic tumor burden is being explored. Small studies evaluating CTLA-

4 blockade after resection are being conducted. In 25 patients with resected stage IIIC and IV melanoma who received ipilimumab, 3 mg/kg, intravenously and a multiepitope peptide vaccine every 8 weeks for a year, only 4 relapsed at a median follow-up of 10 months.[37] After treatment of relapse, only 1 patient had evidence of disease and all were alive. Roughly half experienced immune-related adverse events, and no patient who experienced one relapsed. Despite the potential toxicities, CTLA-4 blockade in the adjuvant setting is an interesting concept that merits further investigation. An ongoing EORTC phase III trial that randomizes patients with resected stage III melanoma to ipilimumab versus placebo will provide insight into this area.

## Vaccines

Cancer vaccines have long been explored in melanoma therapy as a means of exploiting the unique relationship between this tumor and the immune system. Vaccines seek to initiate and maintain an antigen-specific antitumor immune response. However, uncertainty and debate exist regarding the best vaccine model, adjuvant, antigens, method of administration, and disease setting.

More recently, attention has focused on peptide vaccines given in combination with other immune-modulating agents, multiepitope peptide vaccines that can be presented by HLA class I or II histocompatibility complexes, and other novel strategies. The most commonly targeted antigens in melanoma include cancer-testis antigens (MAGE, NY-ESO-1) and melanocyte-differentiation antigens (gp100, tyrosinase, Melan-A). The methodology for developing vaccines continues to evolve, along with the technology for detecting the expansion of tumor-reactive T cells. A central challenge is to develop a surrogate marker of immune activation that relates to a clinical impact on disease recurrence.

Disappointingly, although vaccines have been capable of producing immunologic responses, this has not translated into clinical benefit.[38,39] Canvaxin, an allogeneic whole-cell vaccine constructed from irradiated melanoma cell lines, initially showed improved survival compared with historical controls.[40] However, it failed to show any benefit in combination with BCG over BCG alone in the 2 largest randomized phase III vaccine studies in melanoma: one in resected stage III and the other in resected stage IV disease.[39] Both trials were stopped early after interim analyses by the independent data and safety monitoring boards because of the low probability of a survival benefit. In both cases, a modest, but statistically significant decrement was seen in OS for patients who received Canvaxin.

The SWOG randomized phase III study evaluating Melacine, a cell-lysate vaccine, in resected stage II melanoma showed no benefit over observation in the overall population. [41] However, a subset analysis showed significant DFS and OS benefit for vaccinated patients with HLA-A2/C3 histocompatibility types.[42] M-VAX, an autologous, whole-cell, hapten-modified, irradiated melanoma vaccine, evidenced improved OS over historical controls in resected stage III melanoma and is now being explored in advanced disease.[43,44] Lastly, 2 separate randomized trials in resected advanced melanoma showed no difference in outcomes between controls versus vaccines constructed from viral oncolysates.[45,46]

Induction of a sustained, antitumor immune response with a vaccine and avoidance of other systemic therapies with greater side effect profiles is very attractive and would be a welcome addition to the treatment of this disease. Melanoma vaccines may ultimately prove efficacious if incremental gains can be made in immune activation and prospective patient selection, and will likely be first applicable in the setting of microscopic tumor burden. However, a potential detrimental affect of the wrong antigens or presentation of certain antigens in the wrong context should not be ignored.

## Chemotherapy and Biochemotherapy

An accepted guideline for moving a cytotoxic agent from metastatic disease into evaluation in the adjuvant setting is an RR of 20% or greater. Because most systemic chemotherapies in melanoma produce an RR of 20% or less, including temozolomide and dacarbazine, the potential for benefit in the adjuvant setting is low.[47] Adjuvant dacarbazine alone and in combination has shown no benefit in several small, statistically underpowered trials in various stages of melanoma.[48–51] With an 11% RR in the second-line treatment of advanced, unresectable melanoma, carboplatin and paclitaxel is a potentially interesting cytotoxic adjuvant regimen.[52] Depending on the observed RR in chemo-naïve metastatic melanoma in

the control arm of ECOG 2603, investigation in the adjuvant setting may be reasonable.

No data on adjuvant temozolomide are available; however, regimens combining temozolomide with radiation or other systemic agents are often administered in clinical practice because of their availability and tolerability. Of interest are the initial results of a phase II study in which chemo-naïve patients with resectable, palpable stage IIIB/C and IV(M1a) melanoma underwent neoadjuvant treatment with 2 cycles of temozolomide, 75 mg/m$^2$/d, for 6 of 8 weeks, followed by curative surgical resection.[53] Of the 13 evaluable patients, 2 complete responses, 1 partial response, and 1 stable disease were seen with a median of 1 cycle of therapy; 2 patients experienced progression and became unresectable, but 9 continued to surgery.

Another well-designed, ongoing randomized phase II study is assessing pathologic response and tolerability of temozolomide 150 mg/m$^2$/d for 7 days, alternating weekly for 8 weeks with or without pegylated interferon 0.5 mcg/kg/wk as neoadjuvant therapy in resectable stage IIIC and IV(M1a) melanoma, followed by curative surgery.[54] Patients with pathologic complete response, partial response, or stable disease are eligible for an additional 3 cycles after surgery. Thus far, 16 patients have been treated with no unexpected toxicities in either arm. Activity has been seen in both arms: 4 near pathologic complete responses, 3 pathologic partial responses, and 2 pathologic stable diseases. Tumor necrosis and fibrosis were seen in surgical specimens and additional correlative studies are underway.

Neoadjuvant regimens have inherent challenges, including need for close multidisciplinary collaboration, potential increase of surgical complications, and anxiety regarding surgical delay. However, these trial designs allow for accelerating research into host and tumor factors that may predict early response to therapy and identification of subpopulations for whom this approach may be targeted.

Biochemotherapy, combining interferon, interleukin-2, and cytotoxic agents, showed sufficiently high RRs in metastatic melanoma in early studies to satisfy conventional criteria for investigation in the adjuvant setting.[55,56] The recently accrued Intergroup trial S0008 is evaluating a modified regimen of cisplatin, vinblastine, dacarbazine, continuous infusion interleukin-2, and interferon administered on a 21-day cycle. More than 400 patients with very high-risk stage III melanoma, based on primary ulceration, bulky adenopathy, or in-transit metastases, were accrued and randomized after surgical resection to 3 cycles of biochemotherapy versus HDI. The results of the trial are eagerly awaited despite the subsequent disappointing performance of this regimen in a phase III randomized study in metastatic melanoma.[57]

## Molecular Therapy

Understanding of the molecular and genetic events that promote initiation, maintenance, and progression of cancer in general, and specifically melanoma, continues to mature. Melanoma is a heterogeneous disease. Molecular and genetic tumor profiling has permitted identification and/or clarification of relevant pathways, their aberrations, and their specific roles in melanoma biology. Patterns of aberrations are emerging and shaping development of a new system of subclassification that will likely improve prognostication.[58] Ultimately, this will translate into better outcomes through use of these factors as predictive markers for the application of current therapies, and identification of novel targets and agents.

The most well-known and studied pathway in melanoma is the mitogen-activated protein kinase (MAPK) pathway, with the activating *V600E BRAF* mutation present in most melanomas.[58,59] Other molecules and pathways for which evidence exists of a contributory role in melanoma pathophysiology include PI3K-AKT-mTOR, p16INK4a-Rb-CDK4/6-cyclin D, Wnt-β-catenin, MITF, STAT3, and c-KIT.[60]

Molecularly targeted agents are varied and have created a new class of cancer therapeutics with distinct side-effect profiles that require novel measures of antitumor activity. Several diverse agents targeting the MAPK pathway are in differing phases of evaluation in advanced, unresectable melanoma.[59] Investigation of imatinib in metastatic melanoma has renewed because of the finding of *c-KIT* alterations in a few uncommon subsets of melanoma.[61] Currently, molecular agents are not being evaluated in the adjuvant therapy of melanoma.

Segregation of therapies as molecular, cytotoxic, and immune-modulating is somewhat artificial. Overlap and interplay exists between these arenas in melanoma biology and in the effects of therapeutic agents. Recently, down-regulation of p-MEK1/2,

p-ERK 1/2, and p-STAT3 in nodal metastatic melanoma cells after treatment with induction HDI was shown and may be relevant in limiting disease progression.[62] Also notable is that the drug development path for molecular agents will likely be distinct from that for cytotoxic agents. As tumors gain and lose cellular functions from initiation to progression, probable windows of opportunity emerge to manipulate certain targets to the host's advantage that may be lost as disease advances. In other words, the best testing ground for efficacy may not be first in metastatic disease, with eventual movement into the adjuvant setting. A similar argument has been posed regarding immunotherapies. Continued collaboration between basic scientists and physician–scientists is vital to defining the targets, agents, timing, correlative studies, and correct patient populations in which to best evaluate future therapies.

## Conclusions

Melanoma is a persistent and elusive disease. Increasing incidence, improved diagnostics, and aggressive surgical intervention are identifying and rendering increasing numbers of patients free of disease. Unfortunately, the benefits of surgery are not long-lasting for many. Adjuvant therapy options remain limited and the discussions and decisions are challenging, frustrating, and time consuming. The adjuvant treatment options for resected stage IIB to III melanoma are threefold: active observation, HDI, or clinical trial participation. For appropriate patients, discussion of HDI is reasonable and recommended given its well-established RFS benefit and paucity of other options. Although pegylated interferon may soon be approved, it still offers only an RFS benefit for a year of therapy with similar side effects to HDI, although less commonly severe.

Currently, all patients with stage III melanoma share the same adjuvant options, but clearly not all patients are alike. No standard adjuvant options exist for other stages of melanoma and only limited clinical trials. Adjuvant therapy decisions must be tailored to each patient based on melanoma characteristics; host factors, including age and comorbid conditions; availability of clinical trials; patient preference; and physician experience. Continued investigation into melanoma initiation and metastatic dissemination, identification of novel therapeutic strategies and honing of current strategies, and translation into well-designed clinical trials are urgently needed. Patient referral for clinical trial participation is imperative. Understanding of the molecular and immunologic underpinnings of melanoma has advanced considerably over the past decade. Therapies with greater efficacy and tolerability will soon follow.

## Editor's Note

Despite a wealth of well-done prospective controlled randomized trials of postoperative adjuvant interferon for patients with resected high-risk stage II to III melanoma, a remarkable amount of controversy remains about the appropriate and optimal clinical application of data to individual patient care. There is a general consensus that adjuvant interferon is associated with a clinically relevant and statistically significant improvement in RFS, with little if any measurable impact on OS. Although DFS is the purest measurement of the effect of any adjuvant therapy, the exact time of relapse can be exceedingly difficult to ascertain with precision. In contrast, OS is a precise observation, but integrates the impact of both adjuvant therapy (if received) and salvage therapy.

Thus, if improving RFS is the absolute priority, acknowledging that when patients do not experience relapse they cannot die of disease, then the use of adjuvant interferon could be justified. If, however, not all patients who experience relapse will inevitably die of disease, and OS is the priority end point, then a strong argument can be made that observation with salvage therapy (if necessary) is associated with essentially the same outcome as routine interferon treatment of all patients, without subjecting most patients who cannot benefit from interferon to the substantial toxicity profile of that treatment.

The NCCN Melanoma Panel encourages clinicians engaged in discussions of postoperative adjuvant therapy to share these viewpoints with their patients to elicit priorities that will ultimately impact individual treatment decisions about whether to administer interferon. In the absence of a clear-cut answer, participation in clinical trials of adjuvant therapy is strongly encouraged. When no clinical trial is available, the committee feels that expectant observation remains an acceptable alternative to adjuvant interferon for informed patients with high-risk stage II to III melanoma.

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