Strategies for the Development of More Effective Adjuvant Therapy of Melanoma: Current and Future Explorations of Antibodies, Cytokines, Vaccines, and Combinations

John M. Kirkwood, Stergios Moschos, and Wenjun Wang

Abstract
Adjuvant trials have evaluated the influence of multiple agents on relapse and mortality for patients with intermediate-risk (stage IIA, American Joint Committee on Cancer staging manual, 6th ed.), high-risk (stage IIB-III), or very high-risk (stage IIIB-IV) operable melanoma. A 25% to 33% reduction of relative relapse risk with high-dose IFN-α2b therapy has been documented in stage groups overall, with survival prolongation in two of these trials. In contrast, no large cooperative group trial has ever shown a significant prolongation of survival for inoperable advanced stage IV melanoma. The basis for the failure of therapies in advanced disease may lie in differences in the immune function of patients with active metastatic stage IV disease. These observations argue for the exploration of promising new therapies in adjuvant settings. Past adjuvant studies have targeted stage IIB-III patients, focusing less on the more advanced but resectable stage IIIB and IV (M1a-b) disease groups. Current chemobiotherapy (S0008) and granulocyte-macrophage colony-stimulating factor plus peptide vaccination (E4697) trials have now evaluated the higher-risk disease groups where trials may soon be expected to yield results. Predictive markers that would allow us to focus treatment on those patients who are most likely to respond would accelerate our development of adjuvant therapy for melanoma. We have recently developed a neoadjuvant approach to high-dose IFN in which the molecular and immunologic effects of IFN have been correlated with clinical antitumor effects of this therapy. In addition, the Hellenic Oncology group has shown that the benefit of high-dose IFN is closely correlated with serologic and clinical manifestations of autoimmunity. These new insights will allow us to develop more efficient approaches to adjuvant therapy of melanoma, focusing on autoimmunity and antitumor immunity with new immunomodulators, such as anti-CTLA4 antibodies and vaccination.

Adjuvant therapy of melanoma has not made significant progress since the discovery of the durable benefits of high-dose IFN on relapse-free and overall survival obtained a decade ago in trial E1684 and reevaluated in the intergroup trials E1690 and E1694. Nearly every agent that has shown any clinical evidence of antitumor efficacy in advanced melanoma has been evaluated in the adjuvant setting. Many agents that have shown no measurable antitumor effects in advanced disease have also been explored as adjuvant therapies. This article reviews the approaches that are currently being explored to improve on the adjuvant therapy of melanoma and introduces recent advances in our understanding of the efficacy of the current solitary effective therapy, high-dose IFN-α2b, which may point to more efficient strategies for the development of new, more effective interventions.

Adjuvant studies, in which treatment is given after surgery to reduce the risk of relapse and mortality from microscopic residual disease, have attempted to improve on relapse-free survival, overall survival, and distant disease-free survival. Unfortunately, few positive clinical results exist to guide selection of regimens for future adjuvant testing. In addition, in the absence of any current therapy for advanced disease for which survival improvement can be convincingly shown, we have no basis for selecting molecular or immunologic intermediate end points of use for efficiently testing adjuvant treatments. Many experts in the field would agree that improved induction of immunity against melanoma that translates to cytotoxicity against melanoma should be a relevant end point for immune therapy. However, efforts to reproducibly induce such immunity in the advanced disease setting have been hampered by poor assays, tumor-induced immune suppression and tolerance, and tumor progression and loss of both MHC and costimulatory molecules as well as the tumor antigens against which immune responses may earlier have been induced.
In contrast to the uniform failure of therapy to alter disease outcome in the advanced metastatic disease setting, adjuvant therapy administered for patients with high-risk melanoma has improved overall survival in two separate multicenter cooperative group or intergroup trials of high-dose IFN-α2b. The exploration of molecular and immunologic correlates of improved overall and relapse-free survival has its greatest potential to show meaningful correlates and intermediate end points for future application in the context of adjuvant trials and specifically high-dose IFN-α2b therapy. Immunologically, the adjuvant setting seems to differ qualitatively from the advanced disease setting. Factors that seem to impede advanced disease therapy, such as immunologic tolerance and bias of immune responses toward Th2 rather than Th1 cytokine profiles, may be more susceptible to interventions with immunotherapies, including cytokines, IFNs, antibodies, and vaccines. In addition, the host may not have become intransigently unresponsive to the therapeutic agents in advanced measurable (bulky) disease. In the adjuvant setting of bulky regional lymph node disease (stage IIIB), major antitumor responses have recently been documented using single-agent IFN-α2b at high dosage administered for 4 weeks in the neoadjuvant preoperative therapy (1). Evidence of the qualitative differences of advanced measurable disease from that of resectable disease is available in both murine and human tumor systems as reported by Tatsumi et al. (ref. 2; Fig. 1).

The prognosis of melanoma has been increasingly precisely defined based on primary and regional disease factors that have been in part articulated in the American Joint Committee on Cancer 6th Edition Melanoma Subcommittee staging proposal of 2000 (3) as adopted in the current staging system for melanoma that was published in 2002. In this context, the risk of relapse and death of melanoma can be categorized as low, intermediate, high, and very high for patients with stages IA-B, IIA, IIB-IIN, and IIIb-C or IV disease with solitary or limited but resectable distant metastatic disease (Tables 1 and 2).

The trials of IFN-α2 and other adjuvant agents may therefore be divided according to stage into four categories, although it must be stated that no evidence currently exists to support the often-stated contention that differences in relative benefit for current therapies differ among stage IIA, IIB-IIN, and IIIb-IV categories of intermediate, high, and very high relapse or mortality risk.

### Early Low-Risk Disease

In stage IA-B melanoma, such as pure radial growth phase and in situ melanoma, there is insufficient risk of disease relapse and mortality, or trials have not examined previously the benefit of IFN and other adjuvant therapies, so it is difficult to make adjuvant recommendations. Although the theoretical possibility exists that immunologic agents of low expected toxicity might be pursued in this large subset of patients, it is more likely that this group of patients will soon become the focus of prevention efforts given their relatively larger risk of new primary melanoma.

![Fig. 1. Conceptual elements of adjuvant therapy. Differences between the setting of active and inapparent disease. Patients with active stage IV melanoma display Th2-type anti-MAGE-A6, anti-EphA2 responses, whereas patients with no evidence of disease exhibit Th1-type immunity. AD, active disease; NED, no evidence of disease. X axis, production of IFN-γ; Y axis, production of interleukin-5.](image-url)
The higher-risk stage IIB and IIIA disease will be enrolled into Research and Treatment of Cancer trial staging, patients with according to the nomenclature of European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. For these groups in the European Organization for Research and Treatment of Cancer Melanoma Cooperative Group, multiple centers in Australia, and, most recently, joined by the National Cancer Institute Canada Melanoma Trials Group, the full year of therapy is not accepted as the standard long regimen, without the balance of the 11 months of s.c. treatment (Fig. 2). This study was designed before the results from the Intergroup E1694 trial confirmed the survival benefit of high-dose IFN-α2b and so was designed to include not only the large stage IIA population but also the somewhat higher-risk populations of stages IIB and IIIA. This trial has now been joined by the National Cancer Institute Canada Melanoma Trials Group, multiple centers in Australia, and, most recently, the European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. For these groups in which the full year of therapy is not accepted as the standard therapy for all patients with deep T4 disease (stage IIB) and microscopic N1a-N2a nodal disease (stage IIIA or N1 disease according to the nomenclature of European Organization for Research and Treatment of Cancer trial staging), patients with the higher-risk stage IIB and IIIA disease will be enrolled into this trial, potentially shortening the time until this important question is answered.

### Intermediate-Risk Disease

In stage IIA disease, the risk of relapse and mortality may approach 25% and by virtue of the large size of this population subset of new patients with melanoma, this group accounts for a significant fraction of the mortality toll from melanoma worldwide. Accordingly, this group has become the focus of increasing adjuvant treatment efforts both with vaccines and with cytokines. The stage II population is the predominant focus of the largest adjuvant trial undertaken in the U.S. Cooperative Groups, E1697, which tests the question of whether the induction component (i.e., 20 million units/m²/d for 20 days) of the original E1684 trial is necessary and sufficient to achieve the therapeutic benefit of this entire year-long regimen, without the balance of the 11 months of s.c. treatment (Fig. 2). This study was designed before the results from the Intergroup E1694 trial confirmed the survival benefit of high-dose IFN-α2b and so was designed to include not only the large stage IIA population but also the somewhat higher-risk populations of stages IIB and IIIA. This trial has now been joined by the National Cancer Institute Canada Melanoma Trials Group, multiple centers in Australia, and, most recently, the European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. For these groups in which the full year of therapy is not accepted as the standard therapy for all patients with deep T4 disease (stage IIB) and microscopic N1a-N2a nodal disease (stage IIIA or N1 disease according to the nomenclature of European Organization for Research and Treatment of Cancer trial staging), patients with the higher-risk stage IIB and IIIA disease will be enrolled into this trial, potentially shortening the time until this important question is answered.

### High-Risk Resectable Melanoma (Stage IIIA)

This category of disease comprised the largest single subset of the original E1684 trial as well as the subsequent intergroup trials E1690 and E1694. This disease stage with microscopic regional lymph node involvement has now become the largest issue in the adjuvant therapy of newly diagnosed melanoma, owing to the broad adoption of sentinel lymph node mapping and biopsy as specified in the American Joint Committee on Cancer 6th Edition staging recommendations. Sentinel node biopsy has identified chiefly stage IIIA N1a and N2a categories of disease, and enlarging this disease subgroup that previously had comprised a major fraction of the accrual to the intergroup trials E1690 and E1694. Unfortunately, this is a subset of disease that has not been the focus of any major U.S. cooperative group trials since 2001, when E1694 closed due to the superiority of high-dose IFN-α2b over the vaccine GMK, and no subsequent trials have been initiated targeting this group due to the lack of any new therapy that seemed to be capable of adding significantly to IFN-α2b or capable of showing superior benefit. Clearly, if the results of the E1697 study are positive and it is then possible to reduce the required therapy from 12 months to 1 month, this will facilitate the exploration of new combinations. Currently, the absence of nodal tumor tissue that might permit the assessment of potential intermediate end points for correlation with disease response, relapse-free interval, and survival has hampered the assessment of this subgroup of patients in relation to the population of patients with gross palpable nodal disease or limited distant resectable disease (tumor-node-metastasis T1N1-3bM0, stage IIIB, and T0N0M1a or M1b,c that are limited in scope and resectable). However, neoadjuvant therapy has allowed new insights into this disease and its biological and immunologic response to adjuvant interventions, such as high-dose IFN-α2b. The availability of blood markers of response to effective therapy that might serve as potential intermediate end points for the development of adjuvant therapy would clearly accelerate progress in general and specifically for this large subset of patients who now have only firm prospects of benefit with the established regimen of high-dose IFN-α2b.

### Very High-Risk Resectable Stage IIIB, Stage IICC, and Limited Stage IV Disease

Patients with bulky regional nodal disease have become the focus of two intergroup U.S. studies, both of which are ongoing and of interest to investigators, patients, and their physicians. The Southwest Oncology Group–led Intergroup Trial S0008 tests the potential survival benefit of chemobiotherapy with cisplatin, vinblastine, dacarbazine, and interleukin-2 given by continuous i.v. infusion as well as low dosages of s.c. administered IFN-α2b compared with high-dose IFN-α2b (Table 2; Fig. 3). This trial tested the regimen initially popularized by Legha et al. (4) and Eton et al. (5) and definitively tested in the Intergroup Study E3695, which focused on front-line therapy of advanced measurable metastatic stage IV melanoma. The concept that the adjuvant setting affords a qualitatively different immunologic and perhaps molecular milieu, in which disease may be categorically more responsive and potentially more curable than in the unresectable distant stage IV setting, will here have its most current test, because there has been little in the preliminary results of the

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Estimated risk (5 y), %</th>
<th>Trials conducted/planned in risk group</th>
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<tbody>
<tr>
<td>Low</td>
<td>&lt;20</td>
<td>None</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10-30</td>
<td>E1697 Intergroup Trial (phase III)</td>
</tr>
<tr>
<td>High</td>
<td>30-50</td>
<td>E1697 Intergroup Trial (European Organization for Research and Treatment of Cancer; phase III)</td>
</tr>
<tr>
<td>Very high</td>
<td>&gt;50</td>
<td>E4697 Intergroup Trial of GM-CSF, Peptide Vaccination (phase III)</td>
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<td></td>
<td></td>
<td>S0008 Intergroup Trial of Chemobiotherapy (phase III)</td>
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<tr>
<td></td>
<td></td>
<td>Neoadjuvant phase II trial of high-dose IFN-α2b</td>
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**Table 1.** Risk groupings of disease and adjuvant trials directed against these categories of disease.
patients who have regional nodal metastatic disease. The latter setting has shown improved benefit from high-dose IFN-α2b. If therapy with only 1 month (4 weeks) of i.v. high-dose IFN-α2b is effective, this will simplify the evaluation of promising new combinations of agents with high-dose IFN-α2b to build on the clinical, immunologic, and molecular effect of this therapy for patients with melanoma.

The data obtained in the context of our neoadjuvant experience amplifies the evidence of an immunological mechanism of action for HDI in melanoma recently reported by Gogas et al., (7) demonstrating that for IFN, as for IL-2 and CTLA4 antibodies, autoimmunity is a powerful correlate of therapeutic benefit. Our challenge is now to define the genetic determinants of these immunological responses, and the specific target antigens that will be key to more specific and effective therapies may be undertaken.

Open Discussion

Dr. Atkins: Were the changes in STAT-3, STAT-1, and the ratio different in responders versus nonresponders?

Dr. Kirkwood: There was a much greater impact in the responders than in the nonresponders.

Dr. Slingluff: Do you think there's a role of inflammation related to surgery that has been augmented by interferon?

Dr. Kirkwood: I would not for a minute argue that there is no possibility of impact. On the other hand, we have performed biopsies on thousands of patients with melanoma before and have never seen the disease regress in 55% after biopsy. There is no question that it would be of interest to look at the neoadjuvant intervention without any first biopsy as well.

Table 2. Approaches to improve results of adjuvant therapy for patients at very high risk of relapse/mortality

<table>
<thead>
<tr>
<th>Approach Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combine interleukin-2 and IFN with CVD: chemobiotherapy</td>
<td>Intergroup S0008: CVD-IFN-interleukin-2 × 3 mo versus high-dose interferon for 1 y.</td>
</tr>
<tr>
<td>Improve therapeutic index of high-dose IFN using induction IFN before definitive surgery as a neoadjuvant</td>
<td>UPCI 00-008 neoadjuvant trial of 1-mo i.v. high-dose IFN before surgery</td>
</tr>
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</table>

E3695 trial (6) that would support the hope of a curative effect of this therapy in advanced unresectable disease.

The Eastern Cooperative Oncology Group–led Intergroup Trial E4697 tests the potential survival benefit and impact on time to progression of granulocyte-macrophage colony-stimulating factor (GM-CSF) plus peptide vaccination versus placebo given in patients with no evidence of clinical disease after complete surgical resection of locally regionally advanced (stage IIIIB or IIIC) or metastatic melanoma (Table 2; Fig. 4). Patients are divided into HLA-A2+ and HLA-A2− groups, and only HLA-A2+ patients are eligible for peptide vaccination. The study has currently accrued 700 patients, with a goal of 800 patients, and the preliminary results of this trial will be available in the next year.

The neoadjuvant trial currently ongoing at the Pittsburgh Cancer Institute Melanoma Center (UPCI 00-008) tests the efficacy and clinical response rate of the standard 4-week induction phase of high-dose i.v. IFN-α2b given preoperatively in patients with regional palpable lymphadenopathy (stage IIIIB and C; Table 2; Fig. 5). This neoadjuvant approach assesses treatment response judged clinically and radiologically by computed tomography and positron emission tomography in the palpable regional disease of patients who at initial presentation have gross nodal metastasis or who experience disease relapse at an interval after initial surgical management. The clinical response of regional disease in these patients is then possible to correlate with overall survival and the effects of treatment on tumor tissue collected at initial biopsy done before systemic therapy and after treatment for up to 4 weeks to enable the analysis of IFN-induced changes in the peripheral blood and the tumor microenvironment for the first time. We recently reported the preliminary results (n = 20) of this neoadjuvant trial (1) and have noted a clinical objective response rate of 55% (11 of 20) in patients who are being followed up for correlation of treatment response with disease-free and overall survival at longer intervals. Currently, correlations were shown between clinical response and immunopathologic effects on the tumor (i.e., an increase in the populations of CD11c+ and CD3+ immune cells infiltrating the tumor and modulation of IFNAR2, TAP2, and the signaling pathway molecules phospho-STAT1 and phospho-STAT3).

Through the design of neoadjuvant trials and the analysis of innovative trials targeting metastatic melanoma in advanced disease in which it is possible to obtain biopsy samples, it is likely that more rapidly informative intermediate end points of immune response modulation correlated with antitumor effects may be established. It is now possible to examine the effects of candidate new therapies in both advanced metastatic disease, as has historically been done, and the neoadjuvant setting, for...
Dr. Slingluff: It’s probably worth keeping that in mind, given the experience with interleukin-12, where a little dose up-front was thought to be unimportant and it turned out to make a huge difference. Again, if this is repeated in another group in which only a fine-needle aspiration (FNA) is performed and you don’t see the same outcome, it may be worth examining.

Dr. Kirkwood: Would you worry a little less about an FNA biopsy than about a surgical biopsy?

Dr. Sosman: Yes, in terms of stirring up inflammation. How many patients of the 200 had autoantibodies?

Dr. Kirkwood: About a third had autoantibodies.

Dr. Sosman: What was the timing?

Dr. Kirkwood: Most were seen at 3 months.

Dr. Sosman: Is it feasible to look at this in another data set?

Dr. Kirkwood: We are doing it right now. We have the sera from the 1694 study, because we were looking at antibodies to ganglioside in that trial.

Dr. Ross: Did you have any patients in the neoadjuvant trial whose disease progressed prior to surgery?

Dr. Kirkwood: In two patients, we couldn’t tell if they had inflammation or progression. In the end, the surgical specimens from one of them suggested that there was tumor necrosis in the specimen. We were prepared that if there was clinically significant progression we would abort interferon administration and move directly to surgery, but we didn’t see that.

Dr. Slingluff: Recently, it has been reported that interferon-α influences many aspects of the immune system, potentially influencing multiple steps of the immune response. This has been shown to regulate or costimulate T-cell proliferation. Do you think interferon-α is having its greatest impact on the generation of new effector site via the STAT mechanisms or up-regulation of class 1 or class 2?

Dr. Flaherty: Don’t you think that the response rate to any regimen that has some activity in that patient population is going to be higher than patients with liver metastases, for example?

Dr. Kirkwood: Surely. And this is response judged at only one time point. Realize this is not RECIST criteria response; this is shrinkage of disease at day 29, before the disease is all removed by the surgeon.

Dr. Essner: It still suggests that there is real activity there, because you’re shrinking tumors.

Dr. Kirkwood: I agree with you. This is a real difference in responsiveness.

Dr. Hwu: T cells migrate very differently into lymph nodes and cutaneous sites, where we know response rates are higher with other therapies compared to other sites. This may provide an explanation regarding the high response rates observed in this study. I have a question regarding the mechanism of action of interferon, which has been shown to be reversible. We certainly contributed to the literature that says there is a 15% response rate in metastatic advanced disease. The real question is, “What is the real number for the neoadjuvant?” I never would have thought it would have been 55%, but it is likely that it is qualitatively higher than it is in the advanced disease setting.

Dr. Kirkwood: Considering the response rate is 55% and that interferon has only minimal effects in patients with metastatic disease, how do you put that together?

Dr. Kirkwood: There is something very different in advanced recurrent, sometimes multiply pretreated disease from the patient with a limited regional nodal bulk of tumor. The difference has to do with progression past a point that’s not reversible. We certainly contributed to the literature that says there is a 15% response rate in metastatic advanced disease. The real question is, “What is the real number for the neoadjuvant?” I never would have thought it would have been 55%, but it is likely that it is qualitatively higher than it is in the advanced disease setting.

Fig. 3. S0008. Phase III trial of high-dose IFN-α2b versus cisplatin, vinblastine, dacarbazine (DTIC) + interleukin-2, and IFN in patients with high-risk melanoma.

Fig. 4. E4697 Intergroup Trial. A randomized, placebo-controlled phase III trial of yeast-derived GM-CSF versus peptide vaccination versus GM-CSF + peptide vaccination versus placebo in patients with "no evidence of disease" after complete surgical resection of "locally advanced" and/or stage IV melanoma, targeting very high-risk patients with melanoma.

Arm 1
- One year high-dose IFN α2b (Intron A)
- Interleukin Therapy - Weeks 1-4
- Maintenance - Weeks 5-52

Arm 2
- Cisplatin (CDPP)
- Decarbazine (DTIC)
- Vinblastine
- Interleukin 2 (IL-2)
- Interferon α2a-2b
- O-CSF
- Repeat cycle every 21 days, maximum of 3 cycles

Fig. 5. Neoadjuvant Trial UPCI 00-008 for patients with stage IIIB and C melanoma. Treatment schema and laboratory correlates to study, targeting patients with very high-risk melanoma.

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melanoma metastases [letter]. Lancet 2002;359:978-979). The last publication in February 2004 in Clinical Cancer Research for the aggregate of all 1,912 patients on these three studies was at 4.3 years (Kirkwood JM, Manola J, Ibrahim J, Sondak V, Ernstoff MS, Rao U. A pooled analysis of Eastern Cooperative Oncology Group and intergroup trials of adjuvant high-dose interferon for melanoma. Clin Cancer Res 2004;10:1670-1677). We’ve got reasonable maturity on the data. The event rates are so low now in those populations that I can’t convince our statisticians to look again at the data. Probably within a year, we’ll be ready to look at the data sweep from 1684, 1690, and 1694 to do an update on the pooled analysis.

Dr. Sosman: In terms of the neoadjuvant study, have you looked at T1i1 versus T1i2?

Dr. Kirkwood: We haven’t done any cytokine production profiles on the tumor tissue extracted cells. Currently, we’ve only looked immunohistochemically, but that’s certainly something that could be done.

References
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