

Practical Management Strategies for the Metastatic Melanoma Patient

Applying the Evidence

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Preface: Program Disclosures, Accreditation, and Credit Availability

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The faculty and planning committee for this activity reported the following:

John M. Kirkwood, MD discloses that he is an Advisory Board member for scientific information for Pfizer, GlaxoSmithKline, and Schering-Plough Corporation. He is a consultant for clinical trial design for Intrexon, and Eleos. He is a member of the Schering-Plough Corporation promotional speakers' bureau.

Planning Committee

John JD Juchniewicz, MCIS, of American Academy of CME has no relevant financial disclosures to make.

Lisa Baez, North American Medical Education, has no relevant financial disclosures to make.

Jacqueline Hernandez, North American Medical Education has no relevant financial disclosures to make.

Anne Jacobson, Medical Writer, has no relevant financial disclosure to make.

OFF-LABEL DISCLOSURE STATEMENT

The faculty has disclosed that this program will discuss either non-FDA-approved or investigational uses of the following agents/devices: anti-CTLA-4 antibodies, Hsp70 agonists, interferon, and melanoma vaccines.

TARGET AUDIENCE

This CME initiative is intended for dermatologists, medical and surgical oncologists, and other healthcare professionals involved in the long-term care of patients with melanoma.

EDUCATIONAL OBJECTIVES

- Describe major top-line findings from recent research in the use of immunotherapy and chemotherapy for metastatic melanoma
- Identify early signs of immune-related adverse effects in patients undergoing immunotherapy for metastatic melanoma
- List important prognostic factors in metastatic melanoma, and their role in treatment planning
- Describe promising research that may shape the future of immunotherapy in metastatic melanoma

CREDIT AVAILABILITY

Release Date: 04/23/08 | Expiration Date: 04/23/09

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Practical Management Strategies for the Metastatic Melanoma Patient

Applying the Evidence

Introduction



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In the roundtable discussion, Practical Management Strategies for the Metastatic Melanoma Patient, three leading melanoma experts discussed the implications of new data on the clinical management of metastatic disease. In this follow-up educational activity, Practical Management Strategies for the Metastatic Melanoma Patient: Applying the Evidence, program chair, Dr. John M. Kirkwood, Professor and Vice Chairman for Clinical Research, Department of Medicine, and Director, Melanoma Skin and Cancer Program, University of Pittsburgh Cancer Institute, will guide participants through an in-depth look at the critical data shaping treatment decisions of today. This complementary activity extends the learning opportunity of the initial Practical Management Strategies for the Metastatic Melanoma Patient program, for both new and returning participants.

JOHN M. KIRKWOOD, MD: Welcome to CME Matters. In this program, we will be discussing the following educational topics:

- **Section I: Use of Immunotherapies and Chemotherapeutic Agents in Treatment of Metastatic Melanoma**
- **Section II: Strategies for Minimizing Side Effects of Immunotherapy**
- **Section III: Individualizing Patient Care in Metastatic Melanoma**
- **Section IV: Future Directions in Melanoma Research**

I. Use of Immunotherapies and Chemotherapeutic Agents in Treatment of Metastatic Melanoma

Question: What have we learned about the underlying mechanisms of metastatic melanoma progression? How might what we have learned impact the design of new therapies?

JOHN M. KIRKWOOD, MD: It has taken us the better part of a generation since we documented in careful Phase III trials the benefits of one of the earliest of the biologics we now call immunotherapies of melanoma—interferon alpha. The data we have obtained in the last year or two clearly establishes that the mechanism of action for interferon is immunotherapeutic. What we have learned is in patients treated who have metastatic disease—but more interestingly also in patients who have a resectable Stage III, potentially surgically curable disease who were treated in the adjuvant setting. Those patients who respond to this treatment have dense T-cell infiltrates into their tumors. Specifically, T-cells marked by the phenotypic cell surface antigens CD3, CD8, and CD4—killer cytotoxic T-cell markers and helper T-cell markers. In parallel, we have the observation of T-cell infiltrates that appears to be augmented by that early interferon modality. We have noted patients who are observed to survive the disease and appear to have benefited from treatment with interferon alpha, have a frequency of autoimmunity, which is significantly higher than patients who tend to have failed to benefit and therefore, manifest progression of disease, recurrence of disease, and/or mortality.

Two observations have really presaged what we now see for one of the newest candidate immunotherapies of melanoma and other solid tumors. They are: 1) T-cells rising in number within the tumor tissue; and 2) the development of manifestations of autoimmunity, either the presence of antibodies that can be documented by blood tests on the serum or the clinical manifestations of thyroiditis, hypothyroidism or hyperthyroidism, rheumatologic disorders, and other conditions like depigmentation of the skin. The newest candidate immunotherapies is the cytotoxic T-lymphocyte antigen (CTLA)-4 blocking antibodies. It is apparent this modality has the ability to take the breaks off the immune system, and elicit manifestations of autoimmunity in the colon that lead to colitis-like inflammation of the bowel in patients, at a frequency that may be 20 percent or higher in patients who derive benefit from this modality. In summary, I think what we have learned is, for interferons—one of the earliest kids on the block for anti-CTLA-4 blocking antibodies, and interleukin-2—the single approved biologic therapy of metastatic melanoma—we have added to the list in the past decade. For these biotherapies, we have observed T-cell activity and autoimmunity depression that appear to correspond to the anti-tumor benefits of each of these agents.

It is clearly apparent that whether or not a patient with melanoma has reactivity against their thyroid, colon, or other endocrine organs cannot have anything to do with the development of anti-tumor immunity. Rather, I think what we infer from this finding is these activities of the interleukins, interferons, and anti-CTLA-4 blocking antibodies appear to have something fundamental to do with the reinduction or the overcoming of tolerance to tumor markers. Ultimately, at some point in the hopefully not too distant future, we will be able to specify what new markers of tumor origin are recognized in those same patients who develop autoimmunity to endocrine organs and understand the fundamental, specific basis of reactivity that likely corresponds to the benefit of IL-2, alpha interferon, and anti-CTLA-4 blocking antibodies.

Question: What current issues relate to the use of chemotherapy in the metastatic setting?

JOHN M. KIRKWOOD, MD: The fundamental problem with chemotherapy of melanoma over the last 35 or 40 years is it has been hard to say we really believe any of the agents that are at our disposal, or any of the cytotoxic chemotherapeutic agents that are in hand at the moment, have any significant impact upon survival of the patient who has advanced inoperable Stage IV metastatic melanoma. In a paper recently published, February 2008, the first seven authors are the lead statisticians from the National Cancer Institute (NCI) and each of the cooperative groups in the North America and the last seven authors are the clinical leadership of the cooperative groups who have conducted those particular trials (Korn 2008). We summarized 70 trial arms, 2,100 patients, and in the end had to conclude that no statistically significant benefit either in terms of progression-free survival or in terms of overall survival of melanoma was apparent for a single one of these therapies.

However, we can now consider benchmarks for new therapeutic agents—the next cytotoxic or biologic agent—that can be derived from that long experience over a 35 year interval from all of the cooperative groups in North America. If we were to see activity in an agent—that at six months gave us progression-free survival in significantly more than 18 percent of patients, or was associated with survival in significantly more than 30 percent of patients at one year—that agent would have done something no agent yet in history has done—significantly alter the most important outcomes in melanoma. We believe the two most important outcomes in melanoma are: overall survival first and progression-free survival as a likely surrogate for overall survival second.

The question of why we have blundered so long may actually be brought back home when we consider what the endpoints are we have used in the past. Basically, we have focused on the drug dacarbazine—the single approved chemotherapy agent in usage for melanoma in the U.S. and the world at large—which was approved by the FDA in the mid-1970s on the basis of percentage response rates. At this time, we have to admit trials that show us even as large a difference as doubling of percentage response rates between two arms— from 18 percent to 36 percent in trials of the EROTC, or from 13 percent to 14 percent to 26 percent to 27 percent in trials of the United States cooperative groups—do not seem to correspond to any meaningful, durable impact upon overall survival. The tough question for us is whether or not any degree of activity in terms of percentage response rate would, in the end, lead to improved survival of melanoma. I have to say there is not much question in any of our minds that if you had complete responses—and with complete responses, durable responses—we all believe those should correspond to durable survival impact differences. But they would need to be seen in fractions of more than ten percent, perhaps 15 percent or even 20 percent of patients, which is sadly the ceiling of the major durable complete response rates we have seen in any trials done in the multi-center cooperative group settings in the past. That's probably the summary of the issues regarding chemotherapy in melanoma in the metastatic setting. Nothing in history has broken the sound barrier and has had an impact upon survival.

Question: As more targeted agents are being evaluated in clinical trials, how are trial endpoints changing to identify the activity of these agents?

JOHN M. KIRKWOOD, MD: This is a very pertinent question. We know much from the work that was led by Edward Korn, PhD, the biostatistician from Cancer Therapy Evaluation Program (CTEP) at the NCI, and the rest of the statisticians who worked for the last 35 years with those of us who led the cooperative group efforts in melanoma. We can say the FDA has joined us in hoping and designing approaches to new agents that will allow impact upon progression-free survival, to permit consideration of early approvals of Special Protocol Assessments (SPAs) for new agents and for the agents, which have gotten the farthest down the pike in assessment in melanoma in the cooperative groups over the past four or five years. With the agent sorafenib, we have seen progression-free survival considered as a part of the Phase III inter-group trial for—what might have been early evaluation of that large experience—actually complete by April 2008, with more than 800 patients aboard, entered, and ultimately to be evaluated in that ECOG-led inter-group trial E2603. Unfortunately, due to funding constraints, we did not carry forward the design with progression-free survival assessment in E2603.

After that trial began, a clinically-driven second-line trial of the same root chemotherapy—carboplatin and paclitaxel in combination with or without sorafenib in a placebo controlled randomized fashion—was undertaken. This trial, with more than 270 patients and termed the PRISM Trial was presented to the American Society of Clinical Oncology (ASCO) in June 2007. The data that became available about a year ago were mature for ASCO and showed that both arms of that trial demonstrated a remarkable progression-free survival median of about four months—identical with and without sorafenib. But had that trial shown an impact significantly better for progression-free survival with the experimental agent added to carboplatin and paclitaxel it would have triggered a FDA review and potentially early access to sorafenib in the country a year ago. We still have a second chance, of course, for sorafenib.

In terms of survival, the much larger trial in 800 patients, led by Keith Flaherty, MD at University of Pennsylvania and conducted through ECOG, Southwest Oncology Group (SOG), and the NCI Canada, will mature and address the question regarding the most important endpoint—overall survival for the combination of carboplatin, paclitaxel, and sorafenib (ECOG-E2603). That will be the assessment of the usual endpoint taking the longer period of time that survival assessment requires, but I think that it shows us for progression-free survival, the FDA is willing, and with sufficient resources, the participants will have been able to consider assessment of progression-free survival, even in cooperative group studies like E2603.

Trial endpoints adopting progression-free survival are clearly here to stay. They are incorporated into the industrial trials testing new Hsp70 agonists. The agent STA4783, now in multi-center Phase III trial, will look at progression-free survival as well as overall survival. The whole Phase III trial is based upon a trial that showed interesting evidence of activity for the combination of that new agent and the chemotherapeutic agent, paclitaxel. Clearly, a pattern we will see increasing in the future, and what we will hope to have before too very long, is some agent that actually does prolong overall survival where we can actually corroborate the importance of progression-free survival at six months as a predictor for overall survival—when we finally do hit the endpoint of overall survival.

Question: There has been longstanding interest in vaccines for melanoma. Is there any news to report in this area?

JOHN M. KIRKWOOD, MD: Vaccines have been the Holy Grail for many of us involved in melanoma research over the last 35 or 40 years. The sophistication of current vaccines is incredibly greater than that which we had to contend with ten, 15, or even 20 years ago. The vaccine trials now being considered with representatives of the cancer germ line are among the most interesting options we have for therapy that have ever existed, and the opportunities to use agents we know can regulate the immune system—interferons, and anti-CTLA-4 blocking antibodies, in conjunction with vaccines, is, I think, one of the most promising new avenues that lies before us.

Having said that, the last year has had two striking instances in which we can say vaccines did not do what we had hoped they would do. One of those was presented by Donald Morton, MD of the John Wayne Cancer Institute—a venerable member of the melanoma community for 40 years now and someone who has pioneered the use of a vaccine called Canvaxin. Canvaxin was taken up by a corporate entity, Sorono, and brought to large multi-center trial evaluation in a properly conducted, randomized multi-center effort. It was notable for having closed—both in Stage III and in Stage IV—patients operable for removal of all gross disease and then treated with, either BCG or BCG plus Cannabin (Morton 2004). We have noted in the presentations Dr. Morton made of these two trials, the unexpected, and I think still incompletely explained, observation that patients who received the vaccine Canvaxin in Stage III had a five-year survival that was nine percent—statistically significantly inferior to the patients who did not receive the Canvaxin but only received BCG.

This prompts us to wonder, as I think some of us have thought for many, many years—whether vaccines and all immunotherapies are potentially two-edged swords, and this phenomenon of what is known as immunological enhancement of tumors—acceleration of cancer relapse and/or progression and mortality of patients with melanoma—can be explained as a process that increased the tolerance. It did the opposite of what we hoped the vaccine would do in the patient who was treated in the setting of operable lymph node metastatic disease or Stage III melanoma. This phenomenon—immunological enhancement of cancer—is a real and ongoing problem that we must consider to evaluate each time we apply a vaccine, and like the chemotherapy agent we have known for many years, vaccines may have a downside for their potential benefit. The vaccines need to be studied prospectively, carefully. For Canvaxin, the problem is, it is a very complex vaccine. It's a cultured, tumor cell line-derived vaccine, which has such complexity we may never know exactly what it was in the three tumor cell line derived vaccines that actually promoted tolerance, inhibited effective immunity, and accelerated disease relapse and mortality in those patients who participated in that very rigorous, large, randomized study.

If it were only vaccines that had this for its legacy, we would all perhaps forget about it, but a second vaccine trial conducted by the EORTC called EORTC18991 was reported in Barcelona last September by the chair of the EORTC, Alexander M.M.Eggermont, MD, PhD of the Netherlands, as having had statistically significantly inferior survival amongst the Stage II patients. An earlier stage of melanoma was the population in which this vaccine was tested, but again, an impact on survival not completely detailed at this meeting was reported as statistically significant— $p=.02$ against the vaccine otherwise known as GMK. Basically, these are both examples of the fact that we have very active immunologically-suppressive mechanisms in our bodies. The only way that we avoid immune responses to multiple organs—the skin, the gut, the thyroid, each of the glands of the body that are potential targets to autoimmunity—is to have a very effective regulatory immune system that dampens those responses. In these cases, it may well have dampened the immune response to cancer vaccines. That really makes the story of new regulatory cytokines, interferons, and antibodies far more pertinent than we ever could have imagined. It leads, very logically, to a discussion of the anti-CTLA-4 blocking antibodies, which are really the first agents brought forward as a class on the basis of their abilities to disinhibit or remove immunoregulatory functions we believe play a part in cancer progression—in melanoma progression—as a much more regular phenomenon than we ever would have thought of before.

II. Strategies for Minimizing Side Effects of Immunotherapy

Question: In the January 30, 2008 issue of *Cancer*, new guidelines on the management of interferon-alpha-2b-related side effects in patients receiving adjuvant treatment for melanoma were published. As part of the expert panel that developed these guidelines, can you describe some of the main recommendations?

JOHN M. KIRKWOOD, MD: It was a good month for us, because we had this summary of 35 years of trials that really refocused us upon the more meaningful endpoints in metastatic disease. I think the reason for the publication of this new set of guidelines harks back to a publication Ahmad A. Tarhini and I published about ten years ago—the first careful, complete summary of the toxicities of interferons and the specific approaches to avoiding and supporting patients through those toxicities. Interferons are here to stay, and the benefit we first reported in 1993 and published, got FDA approval for interferon treatment in 1996—12 years later remains as pertinent as they were more than a decade ago. How do we get patients through this regimen of interferon treatment we proposed should last a year, and still to this day do not know we can shortcut, we can do less than a year and safely assure the patient of the optimal benefit from this modality? We all need to be very familiar with the toxicities and be prepared to support patients through this modality if we are going to treat them—is I think what this article, which was really an international consortium of investigators, really says.

The guideline authors argue that the modality of high-dose interferon is alive and well and is being applied across Europe, North America and much of the rest of the world (Hauschild 2008). So, the first important point is, no patient should enter this treatment who doesn't already fully understand the range of toxicities—it is only through complete patient education one can hope a patient will sustain this treatment, if they have been accurately given the likely range of side effects; they can then cope with those. If they are not adequately informed of the toxicities, they are much more likely to drop off treatment and potentially miss the benefit of this regimen.

The major side effect that accounts for treatment withdrawal in more patients than any other is the toxicity of flu-like symptoms and in particular fatigue. These symptoms—fevers, chill, headache, myalgia, and so forth and so on—diminish after initial treatments are delivered. The phenomenon known as tachyphylaxis allows you to project for the patient that the second day will be much better tolerated than the first, the third much better than the second, and by the end of each week, the treatment side effects will be much, much less than they were at the outset.

The treatments given intravenously that we think are a critical part of the regimen, have more acute side effects. The patient's last 11 months of treatment—the maintenance regimen given three times a week at home subcutaneously—are potentially equally important. During this time, the cumulative chronic and fatigue-related side effects are a major source of patient attrition and if one can project to the patient accurately that we will strive to keep them at more than a 60 percent level—if they consider whatever was their 100 percent level. If they can do less than two thirds of that, we will discontinue the treatment, reduce the dosage by one third, and only resume as the patient feels they are back to full tilt.

Clearly, there are toxicities that are biochemical and hematologic—hepatotoxicity, liver dysfunction, a major focus of our early trials of the interferon. When it occurs, it demands that treatment be discontinued and dosages reduced—to be resumed with normalization of the liver functions. White count and platelet count, less often, can be reduced in patients, and when this hematologic toxicity is observed, it is incumbent upon the physician to interrupt dosage, allow recovery, and then reduce dosage so that the therapy can be delivered for the balance of the time it is required.

Finally, one of the most important toxicities, happily not one that is frequent, has to do with neuropsychiatric depressive side effects—and while suicidal ideation is very infrequent and certainly well under ten percent of patients who are treated with this regimen—this is one that is critical to anticipate for the patient, their caregivers, and their families. If the patient develops profound depression or suicidal ideation, treatment should be discontinued altogether and appropriate supportive measures adopted. I think those and the summary of the much less frequent toxicities that have been encountered here are the goal for us to review. We, obviously, dwelled some time upon the autoimmunity issue, because one of the curious toxicities that we now, when we see it, are comforted to see, is the toxicity of thyroid over activity or under activity.

Hyperthyroidism and hypothyroidism—seen in 80 percent of those who developed autoimmunity which was associated with a favorable outcome of the disease—is something that every physician should follow and document. We have begun to follow patients on a three-month basis for a range of autoimmunity serologic markers. If the community physician treating the patient tomorrow with interferons wants to follow that patient in a way we think is state-of-the-art care, simply the follow-up of thyroid function is an adequate, sufficient basis for monitoring autoimmunity. If the thyroid values in thyroid function analysis show derangement, that is the basis for concluding that autoimmunity has been induced.

Obviously, that can be documented, but I think we recognize observing this and supporting the patient through it can now, in a way we didn't know before, be presented to the patient as a sign they have already likely benefited from this treatment. That helps us to keep patients on treatment. It helps us to keep patients motivated to pursue this therapy, which is the single active, single effective, single durable treatment we know for melanoma from Phase III randomized trials. It's quite significant to note that the couple of trials of alpha interferon that have shown both survival and relapse interval benefit are the only positive randomized Phase III multi-center trials ever done in melanoma in history.

Question: Were there any specific recommendations for the treatment of elderly patients?

JOHN M. KIRKWOOD, MD: I think the specific point about the treatment of elderly patients is an apt one. The question of what the differences are according to age in terms of liability to benefit have never been clearly resolved, and I think it is striking that the more we treat patients with melanoma, this is a disease that goes up with age, and the curve never flattens out. The older we are the more likely we are to have melanoma and, sadly, the more likely it is to be autonomous of a high-risk melanoma. It is pertinent that the single group of patients in the whole population where the mortality of melanoma is going up is men over 60, and those are the people, often, for whom we have hesitated to apply new agents, agents like IL-2, which requires almost Olympic athlete fitness to be able to comfortably deliver to the patient. We should probably liberalize our criteria, and as for IL-2, we now treat patients substantially older than we used to.

Also, for high-dose interferon, we do not see any evidence that the older you are the less you are likely to benefit. In fact, as we all know, the patient who comes into us at age 70 or 75 tomorrow is much more likely to make it to the age of 85 than patients ever have been before. I think we really ought to view patients in terms of their physiologic age, and many of those patients can easily tolerate high-dose interferon therapy and should be offered that therapy—patients who have cognitive brain dysfunction, who have organic brain syndrome, who are disoriented in the evening and at sundown, are not able to tolerate this therapy.

This is a therapy like a bad virus or a bad flu in a sense—provokes delirium, can provoke disorientation in patients who have any element of that to begin with. With proper discussion of the patient's coping strategies and ability to tolerate prior viral illnesses with fever, one can quickly come to the conclusion whether the patient is or is not a candidate. Certainly, no patient with an established history of active cerebrovascular disease—strokes, TIAs, and so forth—is a candidate for this modality. Likewise, somebody with unstable cardiac ischemic disease or unstable angina is not a candidate for this treatment. But with those several caveats, many other patients who previously would have been excluded from consideration can now probably be managed with adequately supportive care to receive the entire treatment.

Question: How important is managing treatment toxicities to patient compliance with treatment? What are the risks associated with poor compliance?

JOHN M. KIRKWOOD, MD: The worst risk associated with poor compliance is ongoing treatment given despite dose-limiting side effects. What I mean by that is, a patient who has renal dysfunction, proteinuria, and nephritic syndrome, is treated even though he can certainly have much more severe nephrotoxicity than someone who is appropriately monitored—the toxicity is picked up early and treatment is discontinued. This is the same for patients with hepatic insufficiency—a toxicity that we actually have not seen since the 1990s, but early in our treatment on the protocol 1684—the first cooperative group study of high-dose interferon—there were two deaths that we regarded as hepatic hepatotoxic deaths. In both of those patients, it was the failure to detect the toxicity and the failure to reduce or abort the treatment that we think was in part responsible for the toxic deaths. Happily, with notification of the entire cooperative group in which these trials were done, we have not seen a fatal hepatotoxicity since that time. The cost of not being attentive to the toxicities is greater toxicities or mortality, and the benefit of close attention to the toxicities is the ability to support patients without undue toxicity throughout the entire regimen to gain greatest anti-tumor effect.

III. Individualizing Patient Care

Question: Regarding the delivery of individualized care, there has been much discussion on the role of prognostic factors in treatment planning. What role do these prognostic factors have in treatment planning?

JOHN M. KIRKWOOD, MD: I think the “individualizing patient care” module is an interesting one. It is probably premature to hit many of those issues, and I think right now, cytogenetics, serum beta-2 microglobulin levels, and other prognostic markers are really a twinkle in our eye. They are the hope—the basis of hope for the future. A serum marker that we have tested retrospectively in our large inter-group trial serum bank is the marker known as S100. The S100 beta protein associated with melanoma—used routinely as the pathologists' tool to immunohistochemically define melanoma on the microscope slide—is also a serum marker that has been tested for the better part of a decade in multiple European trials, some Australian trials, but remarkably few United States trials to date. I think that marker is probably one that is crude but still useful first handle on baseline serum markers that could allow us to better predict who is at higher and who is at lower risk of relapse. Sadly, S100 is not present in all patients with advanced melanoma. It only is a pertinent marker for a fraction of perhaps two thirds of patients. So, we still, clearly need other markers very badly.

The marker of autoimmunity we've talked about already is one that, because it occurs after treatment has started, cannot help us to define which patients we should and which patients we should not treat with interferon at this time. We have worked with our proteomic and serum cytokine paneling laboratory members at the University of Pittsburgh. With them, we have been intrigued to find that patients who have elevated levels of serum proinflammatory cytokines appear to be the patients—when we test these markers at baseline—who are those who have the greatest benefit from interferon in our large serum bank analyses. Serum cytokines and the later appearance of autoimmunity may guide us to select those patients who are predisposed to benefit from the interferons.

We know, the benefit we see from interferon occurs in one third of patients at the most, but if we could get rid of some substantial fraction of the group that does not benefit we would substantially improve the therapeutic index of interferon. This would allow us to individualize therapy for just the patients who have the ability to benefit from this treatment. Clearly this is hope for the future, but I think it is a real prospect. We only need to carefully set our minds to this and conduct the trials in more intelligent ways in the future so we can learn how to select the people who will have the greatest benefit from each of these interventions: interleukin-2, anti-CTLA-4 blocking antibodies, and interferon alpha.

IV: Future Directions in Melanoma Research

Question: What are likely new topics for discussion at ASCO this year in the field of melanoma?

JOHN M. KIRKWOOD, MD: If those things that have been large items of major effort across the field for the past two or three years hit the ASCO presentation threshold, we will see multiple presentations that detail the precise therapeutic and toxic profiles for the anti-CTLA-4 blocking antibodies, for combinations of the CTLA-4 blocking antibodies, and other immunotherapy—One, which we have done here in Pittsburgh is the combination of high-dose interferon and ipilimumab, an anti-CTLA-4 blocking antibody, and those, I think, are very encouraging. Ultimately, we will hope we have much more effective chemotherapeutic approaches and targeted therapies. What I know of these data from those approaches, at least up to the spring of 2008, does not suggest we are going to change the history we have just talked about by June 2008 at ASCO. But, I think the understanding of ways to combine the CTLA-4 blocking antibodies, will soon be seen and hopefully the mature data presented at ASCO bear out the enthusiasm we have at this for the incomplete data upon each of those issues.

Question: What are some additional urgent priorities for future clinical trials in the metastatic setting?

JOHN M. KIRKWOOD, MD: We really need trials where there are laboratory tissue correlates—so-called translational studies. It's an overworked buzz word, but I have to say tissue-based studies have taught us more in dozens of patients than clinical trials done without those correlates have in thousands of patients in the past few years. We ought to resolve as a field, we conduct our studies with tissue biopsy correlates pre and post-intervention. It is only with those we will ever make senses of the benefit fraction and understand the issues raised earlier in this session with respect to mechanism. It's only when we understand the real in vivo mechanism of these agents we can hope to improve upon them efficiently to the benefit of our patients.

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Educational Links

What You Need to Know About Melanoma
National Cancer Institute
<http://www.cancer.gov/cancertopics/wyntk/melanoma>

Melanoma (Patient Version)
National Cancer Institute
<http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/patient/>

Patient Education Tutorial: Melanoma
National Library of Medicine
Note: Spanish translation available
<http://www.nlm.nih.gov/medlineplus/tutorials/melanoma/htm/index.htm>

Melanoma (Patient Guide)
American Academy of Family Physicians
Note: Spanish translation available
<http://familydoctor.org/online/famdocen/home/common/cancer/types/666.html>

Melanoma Treatment Guidelines for Patients
National Comprehensive Cancer Network
Note: Spanish translation available
http://www.nccn.org/patients/patient_gls/_english/_melanoma/contents.asp

Melanoma Staging Calculator
Melanoma Research Foundation
<http://www.mpip.org/frameset.shtml?tools/stager/stage.html>

Melanoma Patients' Information Page
Melanoma Research Foundation
<http://www.mpip.org/>

CME Credits

To receive CME credit for your participation, complete the self assessment post-test and program evaluation survey.

Option 1

Log on to www.MelanomaCME.com for free online assessment and instant certification.

Option 2

Complete the self assessment post-test and evaluation survey below and mail to:
American Academy of CME, 186 Tamarack Circle, Skillman, NJ 08558

Posttest Questions

- 1. T-cell activity and manifestations of autoimmunity appear to correspond to the anti-tumor benefits of all of the following therapies except:**
 - a. Interferon alpha
 - b. Interleukin-2
 - c. Anti-CTLA-4 antibodies
 - d. Dacarbazine

- 2. The recent meta-analysis of 42 phase II trials in metastatic Stage IV melanoma found that cytotoxic chemotherapy:**
 - a. Improves progression-free survival
 - b. Improves overall survival
 - c. Improves progression-free survival but not overall survival
 - d. Improves neither progression-free survival or overall survival

- 3. In the meta-analysis of phase II chemotherapy trials, the authors identified which of the following benchmarks for the treatment of phase IV melanoma:**
 - a. Progression-free survival in >6% of patients at six months and overall survival in >18% of patients at one year
 - b. Progression-free survival in >12% of patients at six months and overall survival in >24% of patients at one year
 - c. Progression-free survival in >18% of patients at six months and overall survival in >30% of patients at one year
 - d. Progression-free survival in >30% of patients at six months and overall survival in >48% of patients at one year

- 4. Combination chemotherapy of melanoma with carboplatin/paclitaxel together with sorafenib:**
 - a. Prolongs time to progression to 4 months in second-line therapy of patients with stage IV melanoma
 - b. Shows responses that are superior to carboplatin and paclitaxel alone
 - c. Has been shown to be superior to temozolomide
 - d. Has been shown to be superior to dacarbazine

- 5. All of the following are characteristic of the adverse events associated with interferon-alpha-2b in patients with melanoma, except:**
 - a. Adverse events are largely reversible
 - b. Flu-like symptoms, particularly fatigue, are the leading cause of treatment withdrawal
 - c. Symptoms tend to diminish after initial treatments are delivered
 - d. The appearance of adverse events requires treatment discontinuation until symptoms resolve

- 6. The side-effect profile of interferon-alpha-2b is marked by tachyphylaxis, a phenomenon in which patients appear to:**
 - a. Develop a tolerance to treatment over time
 - b. Accumulate symptoms over time
 - c. Develop more severe symptoms over time
 - d. Shift from one type of symptom to another over time

- 7. As patient age increases, the benefits of therapy with interferon-alpha-2b:**
- a. Disappear
 - b. Increase
 - c. Diminish
 - d. Remain comparable to those observed in younger patients
- 8. Regarding a patient's ability to tolerate therapy with interferon-alpha-2b, contraindications to therapy include all of the following except:**
- a. Active cerebrovascular disease
 - b. Unstable cardiac ischemic disease
 - c. History of stroke
 - d. Prior immunotherapy
- 9. Compared with patients who do not have elevated levels of serum proinflammatory cytokines, those with elevated serum proinflammatory cytokines levels are likely to respond to interferon therapy.**
- a. More
 - b. Less
 - c. Equally
 - d. Not at all
- 10. Which of the following prognostic factors has been widely used in the risk-stratification of patients with melanoma?**
- a. S100 beta protein
 - b. Serum beta-2 microglobulin levels
 - c. Del(13q)cytogenetic abnormality
 - d. Amp(1q21) cytogenetic abnormality

Evaluation Form

ANSWER KEY

1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6 _____ 7 _____ 8 _____ 9 _____ 10 _____

Please check your professional title:

- Physician Pharmacist/PharmD Physician's Assistant
 Researcher/Scientist Nurse/Nurse Practitioner Other _____

Please check your specialty:

- Dermatology Surgical Oncology
 Medical Oncology Other _____

CONTENT: Please evaluate the content of this educational activity.

- Is the information timely/up-to-date? Yes No
Did the activity meet your expectations?..... Yes No
Is the content relevant to your area of professional interest? Yes No
Is the content useful to you in improving care of patients?..... Yes No
Is the activity fair, balanced, and free of commercial bias?..... Yes No
If no, why not? _____
-

OBJECTIVES: Did the material presented in this activity meet the following educational objectives?

- Describe major top-line findings from recent research in the use of immunotherapy and chemotherapy for metastatic melanoma. Yes No
 Identify early signs of immune-related adverse effects in patients undergoing immunotherapy for metastatic melanoma. Yes No
 List important prognostic factors in metastatic melanoma, and their role in treatment planning. Yes No
 Describe promising research that may shape the future of immunotherapy in metastatic melanoma..... Yes No

If you selected No for any answer above, please explain why not. _____

Rate the overall clinical relevance of this activity to your practice needs.

- Poor Fair Satisfactory Good Excellent

FACULTY: Please rate each presenter using the scale below and check the appropriate box

John M. Kirkwood, MD

- Value of topic Poor Fair Satisfactory Good Excellent
Quality of Presentation..... Poor Fair Satisfactory Good Excellent

What one new thing did you learn?

What barrier(s) outside of your control have an impact on patient outcomes? (check all that apply)

- Institutional
- Insurance/financial
- Lack of practice guidelines
- Other, please list
- Lack of patient compliance/adherence
- Adverse side-effects of treatment
- Patient lack of knowledge regarding disease/treatment

What information would you like to see in future presentations that may help you address those barriers?

Do you intend to change your patient care based upon information received in this activity?

- Yes
- No
- Not Sure

How will you modify your practice performance as a result of participating in this activity?

Assess your level of commitment to making the modification to your practice stated above:

- | | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|-------------------------------------|
| Very
committed | Committed | Somewhat
committed | Not very
committed | Do not expect
to change practice |
| <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

What recommendations do you suggest to improve this activity?

As you look ahead, what CME topic is your highest learning priority?

In order to assist us in measuring the outcomes of this educational activity, would you be willing to participate in a brief post-activity questionnaire? Yes No

If yes, please include your e-mail address here: _____

Credit Information

(PLEASE PRINT)

Name _____ Degree _____

Mailing Address _____

City _____ State _____ ZIP _____

Phone _____ Fax _____ E-mail _____

Time spent in the activity: _____ (Max. 1 hour)

(Physicians, you will receive credit for only the actual amount of time you spent in the activity up to a maximum of 1 AMA PRA Category 1 Credit™.)

By signing, I certify that I have completed this educational activity.

Signature: _____ Date: _____

Please remember to fax your Evaluation Form and Registration/Credit Information back to:

(609) 921-6428 or mail to:

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186 Tamarack Circle

Skillman, NJ 08558.

For instant certification, log on to www.MelanomaCME.com

Thank you for your participation!

For further information about this and other CME programs, please email us: info@namedu.com