Major Changes in Systemic Therapy for Advanced Melanoma

Presented by John A. Thompson, MD

Abstract

Over the past 5 years, a host of new agents have radically changed the therapeutic landscape in advanced melanoma; gone are the days when the only active agents were interferon and dacarbazine. Nearly 25 years ago, few patients with stage IV melanoma reached 2-year survival; today, these survival curves have risen substantially. At the NCCN 21st Annual Conference, John A. Thompson, MD, discussed updates with longer duration of patient follow-up for immune checkpoint therapies. He also reviewed some of the newer approvals in advanced melanoma, including the combination of ipilimumab and nivolumab, high-dose ipilimumab, the oncolytic virus therapy talimogene laherparepvec, and the molecularly targeted combination of the BRAF and MEK inhibitors vemurafenib and cobimetinib.

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We have come a long way in the past few years in treating metastatic melanoma,” announced John A. Thompson, MD, Medical Director of the Phase I Clinical Trials Program, Co-Director of the Melanoma Clinic, Seattle Cancer Care Alliance, and Professor in the Medical Oncology Division, University of Washington School of Medicine. “We are now talking of response rates in the 60% range, which was almost unheard of a few years ago,” he continued. Dr. Thompson also serves as Vice-Chair of the NCCN Guidelines Panel for Melanoma.

Immune Checkpoint Therapies

Immunotherapies continue to have a prominent place in the first-line treatment of metastatic or unresectable melanoma. Approximately 5 years ago, based on 2 pivotal randomized trials,1,2 the monoclonal antibody directed to the immune checkpoint receptor cytotoxic T-lymphocyte antigen 4 (CTLA4) ipilimumab was approved by the FDA. Dr. Thompson briefly reviewed the long-term survival data with ipilimumab.3 He added, “We are now seeing a tail in the survival curve out to 10 years.”

The pattern of response with ipilimumab requires patient education and monitoring. “When evaluating patients in the clinic, it is important to remember that since ipilimumab is working indirectly by stimulating the immune response, we sometimes have to wait until the immune response has been sufficiently activated,” advised Dr. Thompson. In addition, patients must be alerted to the types of immune-related adverse events they may experience and instructed on when to consult with their treatment team about them.

In the 2016 NCCN Guidelines for Melanoma, anti–PD-1 (programmed death 1) monotherapy with either pembrolizumab or nivolumab is a category 1 recommendation. Supporting clinical trial data for nivolumab showed improvements in overall survival (OS) among patients previously untreated4 and those with treatment-refractory5 disease. Dr. Thompson commented on the results in the resistant population: “This has been encouraging for all of us [who treat] melanoma to look at the possibility of a flattening of the plateau of the [OS] curve. We have come a long way since the [OS] curves of 1993.”

“The big news in the past year in immunotherapy was the randomized, prospective phase III trial comparing 3 different forms of immunotherapy,” announced
Dr. Thompson. This phase III trial of approximately 1,000 untreated patients with advanced melanoma demonstrated that nivolumab alone or combined with ipilimumab resulted in better response rates and significantly longer progression-free survival (PFS) compared with ipilimumab alone, although OS data are not yet available. Based on these findings, ipilimumab was moved into the second-line and beyond therapeutic category in the 2016 NCCN Guidelines.

Dr. Thompson acknowledged that there are more adverse events with combination therapy, with grade 3/4 toxicities reported in more than half of patients. “There is a dynamic tension in melanoma clinics in terms of selecting the optimal immunotherapy for patients with melanoma between the combinations, which are more aggressive but potentially toxic, versus PD-1 monotherapy, which is more easily tolerated but may achieve a slightly lower response rate,” he explained.

Another therapeutic option was added to the updated NCCN Guidelines for Melanoma. With new FDA approval, adjuvant high-dose ipilimumab is a category 2B recommendation for use in patients with resected, high-risk disease. The supporting data on which the FDA approval was based are from the EORTC 18071 trial, which included approximately 1,000 patients with high-risk, completely resected, stage III melanoma. With follow-up almost past 4 years, ipilimumab yielded a statistically significant improvement in recurrence-free survival, although OS data are not yet available. However, this high-dose therapy requires close patient monitoring. “We know from other studies that toxicity with ipilimumab is dose-related,” Dr. Thompson said. “It is noteworthy that in this study, there were 5 treatment-related deaths. This is a sobering statistic, and we need to keep this in mind when evaluating our patients and [considering] whether to recommend adjuvant ipilimumab.”

With this toxicity profile in mind, the updated NCCN Guidelines include a caveat with this treatment. “It is approved for patients with high-risk, resected, grade III disease but is excluded for grade IIIA disease. This therapy is appropriate for patients with truly high-risk disease,” Dr. Thompson stressed.

**Oncolytic Virus Therapy**

A newly approved oncolytic virus therapy was included in the 2016 NCCN Guidelines. Intralesional injection of talimogene laherparepvec (T-VEC), which reportedly is the first oncolytic immunotherapy to demonstrate therapeutic benefit against melanoma in a phase III trial, has been added as an option in select patients with advanced melanoma. T-VEC is recommended as a category 1 option for those with stage III melanoma in transit, with a footnote in the guideline mentioning that its efficacy was noted in stage IIIB, IIIC, and IV M1a disease, and was more likely in treatment-naïve patients.

The study on which FDA approval for T-VEC was based included 436 patients with unresectable melanoma. An intralesional injection of T-VEC improved the durable response rate in patients with advanced melanoma compared with subcutaneous granulocyte macrophage colony-stimulating factor. According to Dr. Thompson, the survival differences are clear-cut in those with stage IIIB, IIIC, IV M1a disease. However, for those with stage IV M1b or M1c disease, “the differences go away,” he noted.

**Molecularly Targeted Therapy**

With half of patients with metastatic melanoma harboring an activating mutation in BRAF, therapies targeting this mutation— vemurafenib and dabrafenib—remain category 1 recommendations. However, changes from last year’s NCCN Guidelines for Melanoma center on the promotion of combination treatments with BRAF and MEK inhibitors into the first-line setting. These combination therapies include dabrafenib/trametinib and the novel vemurafenib/cobimetinib—both of which are now category 1 recommendations for BRAF-mutated disease (Figure 1).

“The field has now moved beyond BRAF monotherapy to combination BRAF and MEK inhibitor therapy,” said Dr. Thompson. He briefly reviewed some of the supporting clinical trial data for these combination therapies.

Long et al recently presented their phase III data favoring the use of dabrafenib/trametinib versus dabrafenib and placebo in 423 patients with BRAF-mutant melanoma. Improvements in both PFS and OS were seen with combination therapy. Longer follow-up from phase I and II trials revealed median OS of more than 2 years and durable responses. In fact, added Dr. Thompson, OS curves to approximately 5 years may suggest the emergence of a plateau with
Combination therapy. However, he added, a common side effect (noted in approximately 55% of patients treated) was a much higher incidence of fever. The newest BRAF/MEK inhibitor combination therapy to receive FDA approval is vemurafenib/cobimetinib. The data behind this approval come from the coBRIM clinical trial. Larkin et al reported that PFS was improved with combination therapy versus vemurafenib alone in patients with BRAF V600–mutated metastatic melanoma. In addition, response rates of 70% versus 50%, respectively, also favored the combination. Dr. Thompson noted that he is “encouraged” by the possible plateau in the OS curves.

**Selecting the Right Treatment**

“With so many agents, it is still hard to be dogmatic in our choice of initial therapy,” admitted Dr. Thompson. He concluded with a few brief thoughts on selecting the right treatment, emphasizing it may be a matter of assessing a patient’s ability to handle significant toxicity, the presence or absence of comorbidities, and the patient’s willingness to come to the clinic frequently (if necessary) to manage adverse events from treatment. Motivated patients who understand these considerations may be appropriate candidates for combination therapy. “For a patient who may be less than super compliant, it may be wise to go with a less toxic monotherapy.”

**Figure 1.** NCCN recommendations for metastatic or unresectable melanoma: first-line systemic therapy.

<table>
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<th>Preferred if need early response</th>
<th>BRAF-Mutated</th>
<th>BRAF-Wild-type</th>
</tr>
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<tbody>
<tr>
<td>• BRAF/MEK inhibitor combination (preferred):</td>
<td>• Vemurafenib/trametinib</td>
<td>• Anti–PD-1 monotherapy (nivolumab or pembrolizumab)</td>
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<tr>
<td>• Vemurafenib/cobimetinib</td>
<td>• BRAF inhibitor monotherapy (vemurafenib or dabrafenib)</td>
<td>• Ipilimumab/nivolumab combination</td>
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<tr>
<td>• BRAF inhibitor monotherapy (dabrafenib)</td>
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<table>
<thead>
<tr>
<th>All other cases</th>
<th>BRAF-Mutated</th>
<th>BRAF-Wild-type</th>
</tr>
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**References**