Agents Make "Preferred List" in Metastatic Melanoma

Presented by John A. Thompson, MD

Abstract

The 2014 version of the NCCN Guidelines for Melanoma lists 6 preferred regimens, most with a category 1 recommendation, and 8 "other active regimens." Effective new agents include ipilimumab, a monoclonal anti-CTLA4 antibody, and agents targeted against mutated *BRAF* and *MEK*. Researchers are now focused on the optimal way to combine or sequence these agents, while exploring other new classes. (*J Natl Compr Canc Netw* 2014;12:785–787)

John A. Thompson, MD, Co-Director, Melanoma Clinic, Seattle Cancer Care Alliance, Seattle, presented an update on melanoma and discussed new treatments at the 19th NCCN Annual Conference. "In the past, treatments for metastatic melanoma were largely ineffective, but now we have multiple active new drugs. With new agents we hope we can move the survival curve."

Instead of simply listing all the systemic therapy options, the NCCN Guidelines for Melanoma are now organized to show "preferred regimens," including 6 agents, most with a category 1 recommendation (based on randomized controlled trials). There is a second grouping of "other active regimens" that includes 8 agents. New opportunities for treatment include immunotherapy and molecularly targeted therapies, and their various combinations and sequences. "We are increasingly pulling from this list of preferred drugs rather than using the other category," he said.

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Anti-CTLA4 Antibodies

Reviewing the data supporting the anti-CTLA4 agent ipilimumab, an immunomodulatory drug, Dr. Thompson noted that "for the first time, we are starting to see a flat [ie, plateauing] survival curve." Approximately 20% of patients survive for 5 years, he noted.

The second-line study by Hodi et al[1] found that ipilimumab reduced mortality risk by 44% (P=.0026); in the first-line setting, Robert et al[2] documented a 28% reduction in risk (P=.0009). Median overall survival (OS) for patients receiving ipilimumab is approximately 1 year, but a significant proportion survive for years.

Recently, a multicenter retrospective review found ipilimumab to be active in metastatic uveal melanoma, which has been a challenging tumor. In 39 patients, median OS was 9.6 months, but toxicity was significant.[3]

Anti–PD-1 and Anti–PD-L1 Agents

Enthusiasm may be even greater for agents targeting the programmed death (PD) protein and its ligand, the anti–PD-1 and anti–PD-L1 agents. A report by Topalian et al[4] indicated a 31% response rate and 7% stable disease rate using nivolumab. "The response rates are encouraging, as is the relatively short time to response," Dr. Thompson noted.

In a study published last year, 52% of 135 patients responded to the optimal dose of lambrolizumab. Of these, 81% remained on treatment at a median follow-up of approximately 1 year; median progression-free survival (PFS) for all patients exceeded 7 months.[5]

There are indications that immunomodulatory drugs may work better in combination than as single agents. Wolchok et al[6] combined nivolumab with ipilimumab, both concurrently and sequentially, and observed clinical activity in 65% of patients, including responses in patients with previous ipilimumab treatment; grade 3 to 4 toxicities were also observed in 53% of patients.

The concurrent approach resulted in "a striking degree of tumor suppression, and the majority of these patients responded," he noted. "This is a far cry from the results we saw with older treatments." Concurrent nivolumab and ipilimumab is being investigated further.

Molecularly Targeted Agents

A better understanding of the genetic landscape of advanced melanoma has led to the successful targeting of key mutations, especially *BRAF* mutations, which appear to be most frequent in younger patients. The most recent major trial of the *BRAF* inhibitor vemurafenib showed an overall response rate of 53%, a median PFS of almost 7 months, and a median OS approaching 16 months.[7] The *BRAF* inhibitor dabrafenib produced a 50% response rate in a study of 733 patients and a median PFS of approximately 5 months.[8]

Responses to *BRAF* inhibitors often occur within 2 weeks of the first dose; however, resistance usually develops around 6 months and very few patients respond to this agent long term. There are probably multiple mechanisms of resistance, most of which lead to inappropriate downstream signaling of *MEK*. *MEK* inhibitors, therefore, have entered the armamentarium. Trametinib produced a median PFS of 4.8 months, resulting in a 55% reduction in progression or death ($P<.001$); at 6 months, the OS rate was 81% and there was a 46% reduction in deaths ($P=.01$), despite heavy crossover in the first-line study of 1022 patients.[9]

Combined *BRAF* and *MEK* inhibition has proved to be an even better approach both for efficacy and safety.[10] In the key study by Flaherty et al,[10] median PFS was 9.4 months with combination *BRAF* and *MEK* compared with 5.8 months for dabrafenib monotherapy (risk reduction, 61%; $P<.001$).

"The combination is clearly better than monotherapy," Dr. Thompson noted. While the combination protects against squamous cell carcinoma, dual blockade can produce fever and chills that often require temporary treatment cessation, with lower doses on resumption of treatment.

Selecting Treatment

Dr. Thompson described an approach to selecting first-line treatment for patients with metastatic melanoma. Immunotherapy with ipilimumab or IL-2 does not induce a high rate of response but does produce "a promising tail on the survival curve" with a subset of patients having durable responses. In contrast, targeted treatment can have a "dramatic" early effect, but its long-term durability is more questionable, he noted.

Patients with metastatic melanoma who have low-volume disease, who are asymptomatic and likely to remain free from symptomatic progression for 12 weeks, are good candidates for immunotherapy with IL-2, ipilimumab, or (when available), anti–PD-1. If these patients harbor a *BRAF* mutation, *BRAF*-targeted therapy (eg, dabrafenib and trametinib) can be started as second-line therapy if symptomatic disease progression occurs and the disease is deemed unresponsive to immunotherapy.

By contrast, patients who present with bulky metastatic disease, who are symptomatic or likely to experience symptomatic progression in less than 12 weeks, are probably better candidates for front-line *BRAF*-directed therapy if their tumor contains mutated *BRAF*. If a *BRAF* mutation is not detected in patients with these aggressive tumors, consideration can be given to ipilimumab or cytotoxic chemotherapy or biochemotherapy.

Future Directions

"Tremendous research progress has been made recently, and we are looking forward to having anti–PD-1 agents as a result," Dr. Thomson said. Additionally, future directions with immunotherapy include T-cell therapy (ie, cells with engineered immune-receptors), lymphokines (ie, IL-15, IL-21) alone or in combination with vaccines or checkpoint inhibitors, and receptor-directed cytokines. Research in the targeted therapy area includes compounds directed at various mutations, such as MEK, efforts to understand the mechanisms of acquired resistance to targeted agents, and combinations of targeted agents and immunomodulators.

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