# Emerging therapies for melanoma

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Metastatic melanoma is a highly challenging cancer to treat. Like other solid tumors, it is a very heterogeneous disease both clinically and biologically. Consequently, the first decision point in its management is to assess the severity of an individual patient's disease. This can be done based on the patient's symptoms and how they have evolved over the preceding 1-2 months, performance status, the extent of disease as determined by physical examination, and staging work-up, which should include either computed tomography scans of the body or a positron emission tomography/CT study as well as a brain magnetic resonance imaging scan. Patients with brain metastases as a subset (which is sizable – 20%-25% have brain metastases) require special attention because they may not respond to systemic therapies and will thus have to be managed with brain-targeted treatment options. Tumor testing for BRAF mutations is necessary in all patients with metastatic melanoma because the BRAF inhibitors (vemurafenib or dabrafenib) are a preferred choice of targeted therapy for this subset of patients, which constitutes about 50% of all melanoma patients. Immunotherapy plays an important role in nearly all patients with metastatic melanoma including those who have progressed after anti-BRAF therapy. Chemotherapy still has a significant (yet diminishing) role for patients who are no longer suitable for immunotherapy.

Targeted therapy is the preferred choice of therapy provided the tumor has presence of BRAF mutations. The first targeted therapy agent shown to have a high level of activity was the BRAF inhibitor vemurafenib, which was approved by the Food and Drug Administration in 2011. This drug has produced objective responses in more than 50% of BRAF-mutated melanoma cases and the onset of response is rapid, especially in patients who have large loads of metastatic tumor. However, the responses are not durable and typically last about 6 months before the tumor begins to progress again. The second BRAF inhibitor, dabrafenib, was approved by the FDA in May 2013 on the basis of its single-agent activity, which was similar to that of vemurafenib. MEK inhibitors are also active in advanced melanoma although the response rates are lower (22%). One such drug, trametinib, also received FDA approval in May 2013 for single-agent use in BRAF-positive melanomas. Because of their short duration of response, targeted agents are now being tested in combination with other agents. The first such attempt used a combination of dabrafenib and trametinib and the results of the phase 1-2 study[1] showed response rates of nearly 70% and a response duration that was more than 9 months longer compared with the individual single agents (5.8 months).

Immune stimulation as a form of anticancer therapy has played a more important role in managing melanoma than in any other cancer. Responses were observed in a minority of patients yet the responses were frequently quite durable and the responders often achieved long-term control (cure) of their advanced cancer. The first bona fide immunotherapy to be approved by the Food and Drug Administration for treatment of melanoma was high-dose interleukin-2, which actually did not prolong the overall survival but produced long-term remissions in 10% of the patients who were ultimately cured of their disease. Ipilimumab was the next active immunotherapy and for the first time resulted in a significant increase in the survival of patients with metastatic melanoma, although it benefited only 10%-15% of patients who were treated with it. However, the responses were durable, often lasting longer than 5-10 years.[2] It received FDA approval in 2011 and is now used for a majority of patients with metastatic melanoma.

More recently, a better understanding of the workings of the human immune system has lead to the discovery of the programmed cell death 1 (PD-1) and programmed cell death 1 ligand (PD-L1) immune checkpoint pathways, which are responsible for the often observed paralysis of the immune system in patients with metastatic cancer. Consequently several antibodies toward these immune checkpoint markers have entered into clinical trials and have shown remarkable anticancer activity in melanoma as well as in some other solid tumors. Three drugs, nivolumab, lambrolizumab, and MPDL3280A, have now

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been in clinical trials for between 3 and 5 years and have generated much interest because of their high level of anticancer activity in advanced melanoma.

Nivolumab was the first anti-PD-1 antibody to show remarkable immune enhancement. In the publication of the results of a phase 1 trial,[3] the investigators reported objective tumor regression in 26 of 94 patients (28%) with advanced refractory melanoma. The patients were recruited over a 3-year period (2008-2011). A remarkable feature of these responses is that they were rapid in onset and had long durability, lasting much longer than responses observed with target agents or chemotherapy. The more mature results of this study were updated at the 2013 annual meeting of the American Society for Clinical Oncology,[4] where the investigators reported on longer follow-up and showed a further increase in the response rate, which is now reported to be 31%, and the median duration of responses is longer than 2 years, with some lasting longer than 4 years. Nivolumab is used intravenously once every 2 to 3 weeks. There are moderately severe toxicities that are similar in spectrum – such as skin rashes, enterocolitis resulting in diarrhea, and an increase in liver enzymes – yet they are milder than those observed with ipilimumab. The immune-associated side effects were easy to control except for a few cases of pneumonitis, which is a new toxicity unique to nivolumab. The drug is currently in phase 2 clinical trials for previously treated patients as well as in untreated patients with metastatic melanoma. Recently a phase 1 trial of a combination regimen of nivolumab and ipilimumab has been completed.[5] The results of the 2-drug combination showed an objective response rate of 40% and a higher proportion of complete responses was observed (10%), indicating additive antitumor activity from the combined immune checkpoint blockade.

The second anti-PD-1 antibody to be developed is lambrolizumab, which entered clinical trials in 2011. The results of the phase 1 study were reported in 2013[6] and they showed a remarkable response rate of 38% among 135 patients with metastatic melanoma. This drug has many similarities to nivolumab in that complete regression of the tumor was observed 9% of patients and the responses are ongoing beyond 1 year on treatment. Responses were observed not only in ipilimumab-naïve patients, but also in those who had been previously treated with ipilimumab, which indicates a lack of cross-resistance between the 2 immune checkpoint inhibitors. This has formed a strong basis for the combined use of the 2 drugs, which would mean that almost 50% of all patients with metastatic melanoma would likely show good responses, and most of those responses are expected to be long lasting.

Besides the PD-1 inhibitors, there has been a parallel development of anti-PD-L1 antibodies that are targeted to block an alternative inhibitory immune pathway displayed by the tumor cells to protect themselves from the T-cell–mediated immune attack. The first such product, MPDL3280A, is a monclonal antibody. It has been in clinical trials for 2 years and the results of the phase 1 study were also reported at this year's ASCO meeting: in 140 patients with various solid tumors, the response rate (31%) was highest in patients with metastatic melanoma. The drug was given intravenously at 3-week intervals and was well tolerated by a majority of the patients. In particular, no lung toxicity has been observed so far, which may be an advantage over the anti-PD-1 inhibitors in which that toxicity has been observed in 2%-3% of the patients and has been fatal in some cases. MPDL3280A has shown a broad spectrum of antitumor activity in several other solid tumors, including in non–small-cell lung cancer where immunotherapy has been singularly ineffective in the past. The drug is now in phase 2 clinical trials in multiple solid tumors.

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