Melanoma accounts for less than 5% of all skin cancers diagnosed in the United States each year, but is the leading cause of skin cancer mortality, with 76,100 new cases diagnosed and 9,710 deaths in 2014. Five-year survival for patients with early-stage disease (stage I/II) is 97%, but the prognosis for patients with stage IV melanoma is poor, with 1-year survival rates ranging from 62% to 33%, depending on the location of metastases.

While 5 new agents have received FDA approval for the treatment of melanoma since 2011 (ipilimumab, peginterferon alfa-2b, and vemurafenib in 2011; dabrafenib and trametinib in 2013; and the combination of these 2 agents in 2014), treatment of patients with metastatic or relapsed melanoma has remained challenging. Patients without a driver mutation in the MAPK pathway (BRAF\(^{V600E}\) in general) are usually first treated with interleukin-2 (IL-2) or ipilimumab, whereas patients with driver mutations (BRAF\(^{V600E}/K\), C-KIT) are considered for targeted therapies, depending on the extent of their disease and their performance status (PS). Generally, patients with good PS are initially treated with immunotherapy, as they tend to have a better prognosis and relatively slower progression of disease.

Tumor-mediated immune suppression and immune evasion is understood as one of the major obstacles to the clinical efficacy of immune-targeted therapies for cancer. Programmed death receptor 1 (PD-1) and its ligands, PD-L1 and PD-L2, are thought to be significant mediators of immunosuppression and the dysfunction of effector lymphocytes within the tumor microenvironment. PD-1 is expressed on activated T cells, and on binding to PD-L1/PD-L2 (expressed by tumor-infiltrating lymphocytes [TILs]/tumor cells and antigen-presenting cells/tumor cells, respectively), downregulates T-cell receptor (TCR) signaling. This induces T-cell anergy and apoptosis, and subsequently, immune suppression. PD-L1 expression is upregulated in multiple cancers, and levels of PD-L1 expression have been shown to predict higher tumor grade and poor prognosis in multiple different malignancies, likely because the PD-1/PD-L1 interaction suppresses TILs. Indeed, some studies have suggested that PD-L1 expression by cancer cells provides them with an “immune shield” and protects them from effector T-cell cytotoxicity.

Pembrolizumab (Keytruda; MK-3475, also previously known as lambrolizumab) is a highly selective IgG\(_4\) kappa isotype monoclonal antibody against PD-1. The antibody’s highly selective binding to PD-1 blocks the PD-1, PD-L1/PD-L2 axis, thus overcoming this major immune checkpoint inhibitor.

In September 2014, pembrolizumab (Keytruda) received FDA approval for the treatment of unresectable or metastatic melanoma in patients with disease progression following ipilimumab treatment, and, if BRAF\(^{V600E}\) mutation-positive, following treatment with a BRAF inhibitor. Two trials contributed to this drug’s positive regulatory review and approval for therapy of metastatic melanoma.
Patients alive at 1 year after starting treatment.

The drug was well tolerated overall; while 79% of patients experienced some drug-related adverse events (AEs) across all dosing groups, 66% were grade 1 to II. Common AEs included fatigue (30% all grade; 1% grade 3/4), rash (21% all grade; 2% grade 3/4), pruritus (30% all grade; 2% grade 3/4), and diarrhea (20% all grade; 1% grade 3/4). As may be expected, a higher rate of AEs was noted in patients treated with 10 mg/kg every 2 weeks (23%), compared with patients who had received 10 mg every 3 weeks (4%) or 2 mg/kg every 3 weeks (9%). Other potentially inflammatory or autoimmune AEs included hypothyroidism (8% all grade; 1% grade 3/4), hepatic transaminitis (18%; 1% grade 3/4), and pneumonitis (4% all grade; 0% grade 3/4). These AEs were generally effectively managed with corticosteroid therapy, and in 2 patients, treatment discontinuation was required.14

An expansion cohort of KEYNOTE-001 further assessed the clinical benefit of pembrolizumab in patients whose advanced melanoma had progressed after treatment with ipilimumab, and, if the patient’s tumor was BRAFmutation-positive, a BRAF or MEK inhibitor. In this trial, 173 patients were randomized to receive treatment with pembrolizumab at 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks.15 To be eligible, patients had progressive unresectable disease treated with at least 2 doses of ipilimumab 3 mg/kg or higher every 3 weeks, with progression confirmed using immune-related response criteria. This point becomes especially pertinent when considering that clinical responses to immunotherapeutic agents may differ from those observed in response to cytotoxic agents; moreover, clinical responses may only become apparent after an initial apparent increase in tumor burden or the appearance of new lesions (that would constitute progressive disease evaluated by RECIST16). In increase in tumor burden or the appearance of new lesions (that cal responses may only become apparent after an initial apparent clinity between BRAF mutational activation and immune eru, which can be further primed with the addition of BRAF inhibitors. Despite these concerns, the results of KEYNOTE-001 provide compelling evidence for the potential of pembrolizumab in combination with BRAF inhibitors, particularly in patients with BRAF V600E mutation-positive melanoma. Further studies are needed to determine the optimal sequencing and dosing strategies for these agents, as well as to explore the role of pembrolizumab in patients with BRAF wild-type melanoma.20

References
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release through tumor necrosis and apoptosis, with tumor antigen released systemically after radiation treatment. The abscondal effect refers to the eradication of distant metastases through radiation to a local site. There are two pieces to this puzzle: antigen needs to be released into the system in order to be expressed by antigen-presenting cells, and T cells need to be functional and capable of activation. PD-1 axis inhibition combined with local radiation may improve clinical outcomes of immune-mediated therapy by providing a lock-and-key effect.

In a treatment landscape that has previously proven to be challenging for patients with advanced melanoma with progression on immune therapy, pembrolizumab offers a major paradigm shift. Prospective studies are needed to assess its efficacy in combination with other treatments that are currently used for unresectable locally advanced and metastatic melanoma.

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