Pembrolizumab: Pharmacology and Therapeutics Review

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Abstract

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.

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 9710 deaths in 2014.[1] Five-year survival for patients with early-stage disease (stage I/II) is 97%,[2] 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.[2]

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),[3] treatment of patients with metastatic or relapsed melanoma has remained challenging. Patients without a driver mutation in the MAPK pathway (*BRAF*$^{V600E/K}$ 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.[4]

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.[5-7] 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,[8] 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,[9-12] 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.[13]

Pembrolizumab (Keytruda; MK-3475, also previously known as lambrolizumab) is a highly selective IgG4 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.

On September 4, 2014, pembrolizumab 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.

In the KEYNOTE-001 trial,[14] a phase 1 study, 135 patients with advanced melanoma were treated with pembrolizumab at a dosage of 10 mg/kg every 2 weeks, 10 mg/kg every 3 weeks, or 2 mg/kg every 3 weeks. Notably, all patients had measurable metastatic or locally advanced unresectable melanoma. Major exclusion criteria included melanoma of ocular origin, prior treatment with PD-1/PD-L1 blocking agents, current immunosuppressive therapy, infection, or autoimmune disease. A total of 69% of patients in the study population had progressed following treatment with ipilimumab, other immunotherapy, BRAF inhibitor, or chemotherapy, and 31% had not received prior systemic therapy. Using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, the response rate observed across all dosing cohorts was 38% (95% confidence interval [CI], 25-44). Importantly, this rate did not differ in patients who had been treated with ipilimumab (38%; 95% CI, 23-55) compared with those who had not (37%; 95% CI, 26-49). The highest response rate (52%) was noted in patients who had been treated with 10 mg/kg every 2 weeks (95% CI, 38-66). Overall, median progression-free survival (PFS) was >7 months, with 81% of pa-

tients 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 I 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 *BRAF*^{V600E} mutation-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 RECIST[16]). In addition to the exclusion criteria from KEYNOTE-001, patients were excluded from the expansion cohort if they had a history of grade 4 immune-related AEs or grade 3 immune-related events requiring high-dose/prolonged steroid treatment. Patients with brain metastases could be included if they had not had central nervous system progression for 8 weeks prior.

The study's primary end point was overall response rate (ORR) according to RECIST, although ORR was also assessed using immune-related response criteria. At both treatment dosages, ORR was 26%. Median response duration was not reached at the time of analysis for publication (range, >6 to >37 weeks), and 88% of patients with response were alive without further treatment or progression. Interestingly, ORR in the *BRAF* wild-type subgroup was 28% (95% CI, 20-36), compared with 19% in the *BRAF*-mutant subgroup (95% CI, 7-39), and while these differences are thought-provoking with regard to current considerations for interaction between *BRAF* mutational activation and immune resistance to other agents such as interferon (IFN), these confidence intervals overlapped. Median PFS in the 2-mg/kg group was 22 weeks (95% CI, 12-36) and 14 weeks (95% CI, 12-24) in the 10-mg/kg group (hazard ratio [HR] = 0.84; 95% CI, 0.57-1.23). Using immune-related response criteria, estimated PFS in each group at 24 weeks was 57%. The updated survival analysis revealed that the HR difference in overall survival (OS) between the two groups was 1.09 (95% CI, 0.68-1.75).[15]

As in KEYNOTE-001, the drug was well tolerated overall, with similar safety profiles in both groups. Drug-related AEs occurred in 82% of patients in each cohort, although only 12% of patients experienced a grade 3/4 AE. Because of its target, inflammatory and autoimmune adverse reactions are of particular significance; grade 3/4 immune-related AEs occurred in only 3 out of 142 patients. One patient each had autoimmune hepatitis, maculopapular rash, and pancreatitis. Other potentially immune-mediated AEs included pneumonitis, rash, diarrhea, and hypophysitis, all of which were grade 3/4 and occurred with 1% frequency. These events were managed with treatment interruption and treatment with corticosteroids, with only 4 patients requiring treatment discontinuation.[15]

Although pembrolizumab has been studied at 3 different dosing schedules detailed above, it has been approved for intravenous injection at 2 mg/kg every 3 weeks, since there did not appear to be significant differences between the dosages and schedules evaluated. Elimination half-life of this agent is 26 days, and thus far, no clinically important differences have been noted in its clearance in patients with renal impairment or mild hepatic impairment. The drug is generally well tolerated, with the vast majority of patients experiencing grade 1 or 2 AEs. However, as with other immunotherapies, it is essential to maintain a high index of suspicion for immune-mediated toxicities, including pneumonitis, colitis, hepatitis, endocrinopathy ranging from hypophysitis to hyper- and hypothyroidism, and nephritis, though these are relatively infrequent.

The promising clinical efficacy of pembrolizumab noted thus far leads to several compelling questions in terms of its potential in combination with agents that are already approved. In the expanded cohort of KEYNOTE-001, patients who were *BRAF* mutation-positive had a lower ORR (19%) compared with patients who were *BRAF* wild type (28%), raising the question of whether combined PD-1 axis and BRAF inhibition would lead to improved outcomes in *BRAF* mutation-positive melanoma. Similarly, ECOG 1684 showed that high-dose IFN alfa-2b prolongs relapse-free survival and OS in patients with high-risk resected melanoma.[17] OS was 3.8 years, and it is conceivable that PD-1 axis blockade may potentiate this treatment's effects. Indeed, since adjuvant high-dose IFN alfa-2b is thought to work by eradicating early micrometastases, further priming the immune system by inhibiting the PD-1 axis may potentiate these effects. This rationale can also be applied to pegylated IFN alfa-2b, which has been shown in the adjuvant setting to have a significant effect on recurrence-free survival in stage III melanoma.[18]

It has been hypothesized that radiotherapy stimulates antigen

release through tumor necrosis and apoptosis, with tumor antigen released systemically after radiation treatment.[19] The abscopal 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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