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Pembrolizumab for the treatment of advanced melanoma

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Abstract

Introduction—Since 2010 multiple targeted therapies and immunotherapies have been approved for the treatment of advanced melanoma. Pembrolizumab, a humanized monoclonal antibody directed against programmed death receptor 1 has shown significant activity in advanced melanoma resulting in its approval first as post-ipilimumab and subsequently as frontline treatment.

Areas Covered—This article reviews the approved agents for the treatment of advanced melanoma with a focus on the preclinical and clinical evidence for the use of pembrolizumab in this setting. Primary emphasis is given to the clinical development of pembrolizumab, including phase I-III trials. Finally, we explore the role of pembrolizumab in combination with other therapies and ongoing investigations into its effectiveness in expanded patient populations.

Expert Opinion—Pembrolizumab provides durable responses and represents a major advancement in the treatment options for patients with advanced melanoma. Early studies of pembrolizumab in combination with other therapeutic agents have generated significant interest and further investigations including advanced clinical trials are warranted to evaluate safety and potential improved outcomes. Pembrolizumab and other immune checkpoint inhibitors are likely to play an expanded role in the treatment of advanced melanoma and other solid tumors over the next decade.

Keywords

immunotherapy; pembrolizumab; programmed death-1; programmed death-ligand 1

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1. Introduction

Advanced melanoma is the most aggressive cutaneous malignancy with a high propensity to metastasize and a poor prognosis. In 2009, the median overall survival for patients with advanced melanoma was 6–10 months.¹ Until 2011, treatment options for advanced melanoma were limited for patients for which surgery was not an option. Dacarbazine resulted in a 5–10% non-durable response rate, and high-dose interleukin-2 (IL-2) therapy provided durable responses in 5–8% of highly selected patients, but with significant dose-related toxicities.

Since 2011, treatment options for patients with advanced melanoma have improved with the successful clinical development of v-Raf murine sarcoma viral oncogene homolog B (BRAF) and mitogen-activated protein kinase (MEK) inhibitors for mutant BRAF melanoma and immune checkpoint inhibitors targeting cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) and programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1). Treatment with BRAF and MEK inhibitors including vemurafenib, dabrafenib, trametinib and cobimetinib, either alone or in combination induced responses in >60% of patients and provided a survival advantage when compared with chemotherapy; however, their use is limited to BRAF mutant melanomas and a majority of patients relapse due to primary or acquired resistance.^{2–6} In addition to targeted agents, ipilimumab, a checkpoint inhibitor targeting the CTLA-4 receptor, has demonstrated improved overall survival in two pivotal trials and was approved in 2011 for the treatment of patients with metastatic melanoma.^{7, 8} The survival curve for patients treated with ipilimumab plateaus after 3 years at 21% (versus 10% for chemotherapy) meaning that a subset patients have durable responses resulting in long-term survival.⁹ Lastly, the discovery of PD-1 and its ligands, a key immune-checkpoint, led to the development of PD-1 and PD-L1 inhibitors, including nivolumab and pembrolizumab, for the treatment of advanced melanoma.

2. Overview of the market

Four of the eight drugs approved by the Food and Drug Administration (FDA) since 2011 for the treatment of advanced melanoma, either alone or in combination, target BRAF (vemurafenib, dabrafenib) or MEK1/2 (trametinib, cobimetinib) in melanomas that specifically harbor mutations in BRAF. Both vemurafenib and dabrafenib improved clinical outcomes when compared to chemotherapy and induced objective responses in 48% and 50% of patients, respectively.^{2, 3} These agents showed a median progression-free survival ranging from 5.1 – 6.7 months compared to 1.6 – 2.9 months for patients receiving traditional dacarbazine therapy. Overall survival (OS) improved to 84% for vemurafenib-treated versus 63% for dacarbazine-treated patients at 6 months.² Combination therapy using dabrafenib plus trametinib or vemurafenib plus cobimetinib improved response rates, progression-free survival (PFS), and overall survival compared to monotherapy in multiple randomized phase III trials.^{5, 6, 10, 11} Dabrafenib plus trametinib showed an objective response rate in 67% of patients, PFS of 9.3 months, and OS of 93% at 6 months.⁶ Vemurafenib plus cobimetinib had a similar response rate of 68%, PFS of 9.9 months, OS of 81% at 9 months (median duration not reached) in patients with untreated, unresectable, locally advanced or metastatic BRAF V600 mutation-positive melanoma.⁵ While offering

patients new treatment options, these agents are limited by primary and secondary resistance mechanisms resulting in disease progression within 12 months in a majority of patients. Nonetheless, there does exist a smaller subgroup of patients with lower volume of disease, normal lactate dehydrogenase (LDH) who had ongoing responses for over 3 years.^{12, 13}

By modulating the immune response, checkpoint inhibitors have offered a novel approach to the treatment of advanced melanoma. Multiple immunotherapeutic agents have gained FDA approval since 2011 including ipilimumab, nivolumab, and pembrolizumab monotherapies as well as combination ipilimumab plus nivolumab. Ipilimumab, a fully human IgG1 antibody against CTLA-4, was the first immune checkpoint inhibitor approved based on positive results from two randomized phase III clinical trials showing improved overall survival.^{7, 8} Pembrolizumab, an anti-PD-1 IgG4 antibody, received breakthrough status and was first approved by the FDA for treatment of patients with ipilimumab-refractory advanced melanoma in 2014 and later as a frontline treatment option for treatment-naïve patients. Similarly, nivolumab, an anti-PD-1 IgG4 monoclonal antibody, also showed promise in patients previously treated with ipilimumab and in untreated patients.^{14, 15} It received accelerated FDA approval in 2014. Based on the complementary activity that nivolumab and ipilimumab showed in metastatic melanoma, a phase III trial was conducted to compare combined nivolumab and ipilimumab versus monotherapy.¹⁶ PFS was 11.5 months (95% confidence interval [CI], 8.9 to 16.7) with the combination therapy, as compared to 2.9 months (95% CI, 2.8 to 3.4) with ipilimumab, and 6.9 months (95% CI, 4.3 to 9.5) with nivolumab. Nivolumab in combination with ipilimumab was subsequently approved by the FDA in 2015 for the treatment of patients with BRAF V600 wild-type, unresectable or metastatic melanoma. Talimogene laherparepvec (T-VEC), a first-in-class virus therapy, was approved in 2015 for the treatment of patients with inoperable melanoma tumors. This article will focus on the clinical development and future prospects of pembrolizumab for the treatment of advanced melanoma.

3. Introduction to pembrolizumab

Evasion of the immune system by tumors is one of the critical steps required for the development of metastatic cancer. The PD-1/PD-L1 receptor-ligand interaction plays a critical role in tumor-induced immune suppression in melanoma.¹⁷ PD-1 was first discovered in 1992 as a receptor involved in classical programmed cell death.¹⁸ It is expressed on T-cells, B-cells, monocytes, and antigen presenting cells and functions in response to its ligands, PD-L1 and PD-L2, to negatively regulate B- and T-cell function. Overexpression of PD-L1 and PD-L2 by tumor cells or antigen presenting cells within the tumor microenvironment enables cancer to evade active T-cell immune surveillance (Figure 1). Inhibitors of the PD-1/PD-L1 interaction, including pembrolizumab (previously known as MK-3475 and lambrolizumab), were therefore developed in order to reactivate the immune system by restoring the cytotoxic function of tumor-infiltrating lymphocytes.

Pembrolizumab is an IgG4 humanized monoclonal antibody directed against PD-1 to prevent negative immune regulatory signaling by blocking the PD-1/PD-L1 interaction (Figure 1). It contains the variable region sequence of a high affinity mouse anti-human PD-1 antibody ($K_D=28\text{pM}$) grafted into a human IgG4 immunoglobulin containing a S228P

mutation in the Fc region for stabilization.¹⁹ Unlike other immunoglobulin G subclasses (IgG1, IgG2 and IgG3), the IgG4 isotype has a low affinity for C1q and Fc receptors which allows pembrolizumab to bind to PD-1 on T cells without activating the complement system.²⁰ Thus, pembrolizumab is capable of blocking the PD-1/PD-L1 interaction while simultaneously preserving the host T-cell antitumor functions.

4. Pharmacodynamics and pharmacokinetics

The pharmacokinetics and pharmacodynamics of pembrolizumab were studied in the dose escalation Part A of the phase 1 study KEYNOTE-001 in patients receiving doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks.²¹ According to the prescribing information, in patients with solid tumors the geometric mean [% coefficient of variation (CV%)] for clearance, steady state volume of distribution, and terminal half-life are 202 mL/day (37%), 7.38 L (19%) and 27 days (38%), respectively.²² With a regimen of dosing every 3 weeks, steady state concentrations are reached by 19 weeks. There is a proportional increase in the peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab within the dose range of 2 to 10 mg/kg every 3 weeks.

5. Clinical efficacy

5.1 Phase I studies

The international phase I expansion study KEYNOTE-001 (ClinicalTrials.gov Identifier: NCT01295827) in which patients with melanoma were treated with 10mg/kg every 2 or 3 weeks or 2mg/kg every 3 weeks was designed in part to assess antitumor activity in addition to safety, maximum tolerated dose, pharmacodynamics, and pharmacokinetics. Results from 135 non-randomized patients with advanced melanoma, including both patients who had received prior treatment with ipilimumab and patients who had not, showed a 38% confirmed response rate (95% confidence interval [CI]: 25 to 44%) across all dose cohorts by Response Evaluation Criteria in Solid Tumors (RECIST) criteria.¹⁹ Similar results were obtained by means of investigator assessment using immune-related response criteria (irRC), which permits for the transient appearance of new lesions and takes into consideration immune-related stable disease.²³ The ipilimumab-naïve cohort was restricted to patients that had not received prior treatment with ipilimumab and had received no more than two prior regimens of systemic therapy. The ipilimumab-treated patients included only patients who had full resolution of ipilimumab-related adverse events and no history of severe immune-related adverse events. No difference in response was observed between ipilimumab-naïve and ipilimumab-treated patients (37% [95% CI, 26 to 49] and 38% [95% CI, 23 to 55], respectively). The non-randomized dose schedules revealed differences in overall response rate and toxicity. Patients receiving 10mg/kg every 2 weeks had a confirmed response rate of 52% compared with a confirmed response rate of 25% in patients receiving 2mg/kg every 3 weeks.

The KEYNOTE-001 study also included 520 patients with advanced melanoma randomized to 1 of 3 cohorts: ipilimumab-refractory patients were assigned to receive pembrolizumab either 2mg/kg or 10mg/kg every 3 weeks, ipilimumab-naïve patients were randomized to

receive pembrolizumab either 2mg/kg or 10mg/kg every 3 weeks, and a final cohort included both ipilimumab-naïve and ipilimumab-treated patients were randomized to receive 10mg/kg every 2 weeks or 3 weeks. Results reported from the ipilimumab-refractory cohort (n=173) demonstrated an overall response rate of 26% in the 2mg/kg group (n=81) and 26% in the 10mg/kg group (n=76) (difference 0%; p=0.96).²⁴ In the ipilimumab-naïve cohort (n=103), overall response rates were 33% in the 2mg/kg group (n=51) and 40% in the 10mg/kg group (n=52) (difference 7%; p=0.48).²⁵ The final cohort with ipilimumab-naïve and ipilimumab-treated patients again showed no significant differences efficacy and safety between patients treated with 10mg/kg every 2 versus 3 weeks.²⁶ Given the lack of both statistically and clinically significant differences in ORR, the FDA approved pembrolizumab dosing schedule of 2mg/kg every 3 weeks for the treatment of patients with unresectable or metastatic melanoma after treatment with ipilimumab or after treatment with ipilimumab and a BRAF inhibitor in patients with BRAF mutant melanoma.

5.2 Phase II

KEYNOTE-002 (ClinicalTrials.gov Identifier: NCT01704287), a randomized phase II study established pembrolizumab as the standard of care for the treatment of ipilimumab-refractory melanoma, defined as confirmed progressive disease within 24 weeks after two or more ipilimumab doses.²⁷ Two pembrolizumab doses, 2mg/kg and 10mg/kg every 3 weeks, were compared with investigator-choice chemotherapy in patients with ipilimumab-refractory melanoma (n=540). The primary endpoint, progression free survival, was improved in patients who received either pembrolizumab 2mg/kg (HR 0.57, 95% CI 0.45-0.73; p<0.0001) or pembrolizumab 10mg/kg (HR 0.50, 95% CI 0.39-0.64; p<0.0001) compared to patients treated with chemotherapy. Both doses resulted in similar 6-month progression-free survival 34% (95% CI 27–41) in the 2mg/kg group versus 38% (95% CI 31–45) in the 10mg/kg group compared to 16% (95% CI 10–22) in the chemotherapy group. Consistent with results from KEYNOTE-001, no significant differences were observed between the two pembrolizumab doses.

5.3 Phase III

A randomized, controlled, phase III study, KEYNOTE-006 (ClinicalTrials.gov number, NCT01866319), compared 2 years of pembrolizumab 10mg/kg every 2 weeks (n=279) or every 3 weeks (n=277) to four doses of ipilimumab 3mg/kg every 3 weeks (n=278) in patients with ipilimumab-naïve advanced melanoma.²⁸ Both pembrolizumab regimens improved progression-free and overall survival in patients with advanced melanoma. The interim analysis crossed a prespecified boundary for overall survival, the trial was stopped early for efficacy and the results were unblinded. Interim analysis demonstrated a 6-month progression-free survival rate of 47.3 % for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab (HR 0.58; P<0.001 for both pembrolizumab regimens vs. ipilimumab; 95% CIs 0.46 - 0.72 and 0.47 – 0.72, respectively). Estimated 12-month survival rates were 74.1%, 68.4%, and 58.2% for pembrolizumab every 2 weeks, pembrolizumab every 3 weeks, and ipilimumab, respectively (HR for pembrolizumab every 2 weeks, 0.63; 95% CI, 0.47 - 0.83; P=0.0005; HR for pembrolizumab every 3 weeks, 0.69; 95% CI, 0.52 - 0.90; P=0.0036). Response rates by RECIST criteria were 33.7%, 32.9%, and 11.9% for patients treated with pembrolizumab

every 2 weeks, pembrolizumab every 3 weeks, or ipilimumab, respectively. After a median follow-up of 7.9 months, responses were ongoing in 89.4%, 96.7%, and 87.9% of patients, respectively. Benefit was observed in all prespecified subgroups, including patients whose tumors were either PD-1 positive or PD-1 negative by immunohistochemical analysis. Again, no differences were observed between the two pembrolizumab regimens consistent with KEYNOTE-001 and KEYNOTE-002 studies. Based on this study, the FDA approved an expanded indication for the use of pembrolizumab 2mg/kg every 3 weeks as a frontline treatment for patients with advanced melanoma.

6. Combinations

Combining therapies that work through complementary, non-redundant mechanisms provides an opportunity to enhance antitumor immunity and improve outcomes for patients with advanced melanoma. In advanced melanoma, the combination of ipilimumab and nivolumab has already been shown to improve progression-free survival and objective response rates compared with either agent alone, albeit with higher toxicities.¹⁶ The combination of pembrolizumab with ipilimumab is currently under investigation to evaluate safety, tolerability, and preliminary efficacy (ClinicalTrials.gov Identifier: NCT02089685).²⁹ In addition, trials are currently underway to investigate the safety and efficacy of pembrolizumab in combination with other immunomodulatory agents, oncolytic viruses (talimogene laherparepvec), targeted therapies, and traditional chemotherapies. Preliminary results reported for pembrolizumab plus epacadostat (incb024360), an indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor, showed that the combination was well tolerated and produced an overall response rate of 57% in a small cohort of melanoma patients (n=7) (ClinicalTrials.gov Identifier: NCT02178722).³⁰ T-VEC, a herpes simplex virus-1-based oncolytic immunotherapy designed to replicate in tumor cells and stimulate an anti-tumor immune response, is currently being studied in a phase III clinical trial in combination with pembrolizumab and preliminary results revealed a complete response rate of 22%, a partial response rate over 50% and a tolerable side effect profile (ClinicalTrials.gov Identifier: NCT02263508).³¹ Triplet therapy with pembrolizumab, dabrafenib, and trametinib is being investigated as part of a 3-part dose-finding and preliminary efficacy study to determine if the combination is well tolerated and improves progression-free survival in patients with advanced melanoma (ClinicalTrials.gov Identifier: NCT02130466). Planned trials combining pembrolizumab with chemotherapy, radiotherapy, and tumor infiltrating lymphocytes will also help to elucidate the most effective treatment options for patients with advanced melanoma.

7. Toxicity

In the phase I study of pembrolizumab, the highest rate of drug-related adverse events (AEs) was observed in patients receiving 10mg/kg every 2 weeks compared to patients receiving either 10mg/kg every 3 weeks and 2mg/kg every 2 weeks (23%, vs. 4% and 9%, respectively).¹⁹ Overall, 79% of patients who received at least one dose reported a drug-related adverse event and 13% of patients experienced a grade 3 or 4 adverse event. Fatigue, rash, pruritus, and diarrhea were most commonly experienced with rare autoimmune and inflammatory events being less common. Pneumonitis was reported in 4% of patients (no

grade 3 or 4). One 96-year-old man who was diagnosed with pneumonitis on CT scan, and subsequently stopped treatment, died during the course of the study. After developing shortness of breath and receiving glucocorticoids, his clinical course was complicated by bronchoscopy and biopsy related acute bronchopneumonia and pneumothorax. Although glucocorticoid treatment reduced his pulmonary infiltrates, the patient died from a myocardial infarction and bronchopneumonia. Adverse events during the phase II study, KEYNOTE-002 (ClinicalTrials.gov number, NCT01704287), were generally low grade and included no drug-related patient deaths.²⁷ Treatment-related AEs led to permanent discontinuation of a study drug in 4 patients receiving pembrolizumab 2 mg/kg every 3 weeks (3%), 12 patients receiving pembrolizumab 10 mg/kg every 3 weeks (7%), and 10 patients treated with chemotherapy. The most common adverse events which occurred in both the 2 mg/kg and the 10 mg/kg groups were fatigue at 21% and 28%, pruritis at 21% and 23%, and rash at 12% and 10%, respectively. Among those patients undergoing chemotherapy, the most common adverse events were fatigue (32%), nausea (30%), decreased appetite (15%) and anemia (15%). Rash and pruritis was more frequently experienced in patients undergoing pembrolizumab therapy than chemotherapy. Adverse events of grades 3–4 were higher in the group receiving chemotherapy (45 [26%] of 171 patients) than those in the pembrolizumab groups (20 [11%] of 178 patients in the 2 mg/kg group and 25 [14%] of 179 patients in the 10mg/kg group).

Adverse events during the course of the phase III study, KEYNOTE-006 (ClinicalTrials.gov number, NCT01866319), were generally low grade and included no patient deaths in response to the application of pembrolizumab.²⁸ Mean exposure duration of the patients being dosed with pembrolizumab every 2 weeks (P1) was 164 days, while the patients being dosed with pembrolizumab every 3 weeks (P2) experienced a mean exposure of 151 days. Patients receiving ipilimumab experienced a mean exposure duration of 50 days. AEs of grade 3 or higher attributed to a study drug occurred in 13.3%, 10.1%, and 19.9% of patients, respectively. The rate of permanent discontinuation for these study drugs due to AEs related to treatment was lower in both P1 and P2 (4.0% and 6.9%, respectively) than in patients receiving ipilimumab (9.4%). The most common adverse events that occurred in the P1 and P2 pembrolizumab groups were fatigue (20.9% and 19.1%, respectively), diarrhea (16.9% and 14.4%, respectively), rash (14.7% and 13.4%, respectively), and pruritus (14.4% and 14.1%, respectively). Diarrhea was the only specific grade 3–4 toxicity that occurred in >1% of pembrolizumab-treated patients, and diarrhea and fatigue were the only grade 3–4 toxicities that occurred on >1% of patients in the ipilimumab-treated group.

8. Conclusion

Impressive response rates paired with durable clinical responses observed following anti-PD-1 treatment has renewed interest in immunotherapy for the treatment of advanced melanoma regardless of BRAF mutational status. Pembrolizumab has a tolerable safety profile and improves overall survival in patients with advanced melanoma. Phase I-III trials investigating pembrolizumab have established it as a first line treatment for advanced melanoma. Future investigations will focus on identifying biomarkers to predict response and toxicity, combining pembrolizumab with additional therapies, and expanding treatment

to additional patients with melanoma and other advanced malignancies that can potentially derive benefit.

9. Expert opinion

The development and FDA approval in 2014 of pembrolizumab represents a major advancement for the treatment of advanced melanoma. Multiple trials have demonstrated improvement in progression-free and overall survival establishing pembrolizumab as an important option for patients with advanced disease. By blocking the PD-1/PD-L1 interaction and preventing negative immune regulatory signaling, pembrolizumab appears to generate durable responses. When considered alongside its overall response rates and tolerable safety profile, the potential for long-lasting response makes pembrolizumab an attractive first-line option for patients and practitioners; however, a majority of patients will not be cured and will require additional therapy.

In addition to combinations, determining the most effective sequence of therapies is critical especially in the case of BRAF-mutant melanoma. For patients with mutant BRAF melanoma, determining whether it is best to start treatment with immunotherapy or BRAF/MEK inhibitors remains a critical unanswered question. This question is currently under investigation in the Phase III randomized clinical trial by ECOG (ClinicalTrials.gov Identifier: NCT02224781). Patients with V600 BRAF mutated melanoma will start with either dabrafenib/trametinib or ipilimumab/nivolumab and switch to the other treatment upon progression. Given the potential for durable responses with pembrolizumab, nivolumab and ipilimumab, we recommend starting treatment with immunotherapy in all patients with non-mutant BRAF melanoma as well as in patients with mutant BRAF melanoma, good performance status, and low LDH. If available and tolerated, we suggest starting with a combination of anti-PD-1 and anti-CTLA-4 antibodies for improved outcomes; however, anti-PD-1 therapy alone is an acceptable alternative in patients where toxicity is a concern. For patients whose tumor has a BRAF mutation and whose disease is no longer controlled with anti-PD-1 agents, targeted therapy using a BRAF/MEK inhibitor combination is recommended over chemotherapy. For patients with mutant BRAF melanoma, high tumor burden, elevated LDH, and a poor performance status, targeted therapy with BRAF/MEK inhibitor combination represents a preferred upfront option to reduced disease burden. In this setting, immunotherapy represents an alternative frontline agent or may prove useful after tumor stabilization or progression on targeted therapy. Optimal sequence of therapeutic options for patients with mutant BRAF melanoma is currently under investigation, the results of which are eagerly awaited.

Development of biomarkers for anti-PD1 targeted immunotherapies is an area of active investigation. Among these, PD-L1 expression has been studied with mixed results and cannot be recommended at this time for prospective patient selection for anti-PD-1 therapy.³²

The effectiveness of pembrolizumab and other immunotherapeutic agents in the neoadjuvant and adjuvant setting is an active area of investigation. KEYNOTE-054, a randomized phase III trial, is currently testing whether adjuvant pembrolizumab can improve recurrence free

survival in patients with stage IIIA, IIIB, and IIIC melanoma (ClinicalTrials.gov Identifier: NCT02362594). Combining surgery with immunotherapy is also being studied in a phase IIB non-randomized trial using pembrolizumab in the neoadjuvant setting to determine if pembrolizumab can shrink tumors enough to permit resection and improve patient outcomes (ClinicalTrials.gov Identifier: NCT02306850). These investigations along with clinical trials such as the phase IB basket trial evaluating pembrolizumab in 20 different types of cancer (ClinicalTrials.gov Identifier: NCT02054806) are expanding the population of patients that stand to receive benefit from pembrolizumab in the future.

While advanced melanoma had limited treatment options before 2010, the recent rapid approval of multiple therapeutic agents holds promise for improved patient outcomes. Immunotherapy for the treatment of melanoma cannot be ignored and its role is likely to become evermore important over the coming decade. The use of pembrolizumab, and emerging PD-1/PD-L1 inhibitors, in combination therapies and in expanded patient populations will be an area of great focus in the future. The rapid development and approval of pembrolizumab has been a critical turning point for the treatment of advanced melanoma and evidence suggests that it will play an expanding role in future treatment of multiple cancer types.

Drug summary box

Box 1

Drug Summary

Drug Name	Pembrolizumab
Phase:	FDA Approved
Indication:	Cancer
Pharmacology description	IgG4 humanized monoclonal antibody against PD-1
Route of administration	Intravenous
Pivotal Trials:	
KEYNOTE-001	First-in-human dose-finding cohort with nonrandomized and randomized expansion cohorts. Designed to evaluate safety, maximum tolerated dose, antitumor activity, pharmacodynamics, and pharmacokinetics. Helped establish FDA approved dosing schedule of 2mg/kg every 3 weeks. ^{19, 24}
KEYNOTE-002	Randomized phase II study established pembrolizumab as standard of care for ipilimumab-refractory melanoma. Two doses of pembrolizumab were compared with investigator-choice chemotherapy in patients with ipilimumab-refractory melanoma. Results showed similar 6-month progression-free survival, 34% in the 2mg/kg group versus 38% in the 10mg/kg group. ²⁷
KEYNOTE-006	Randomized, controlled phase III study comparing pembrolizumab to ipilimumab in patients with ipilimumab-naïve advanced melanoma. Established pembrolizumab as frontline treatment for advanced melanoma. ²⁸

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Figure 1.

Mechanism of action of pembrolizumab for the treatment of melanoma. T-cell receptor (TCR) signaling is activated when antigenic peptides from cancer cells are presented on major histocompatibility complexes (MHC). TCR signaling results in the expression of the programmed death-1 (PD-1) receptor, which inhibits immune responses when engaged with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2) expressed on cancer cells and antigen presenting cells (APC). Pembrolizumab inhibits the interaction of PD-1 with its ligands resulting in reactivation of the immune system and restoration of the cytotoxic function of tumor-infiltrating lymphocytes.