Pembrolizumab for Treatment of Patients with Advanced or Unresectable Melanoma

Ryan J. Sullivan and Keith T. Flaherty

Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts

Corresponding Author: Keith T. Flaherty, 55 Fruit Street, Boston, MA 02114.
Phone: 617-724-4800; Fax: 617-724-6898; E-mail: kflaherty@partners.org

Running Title: Pembrolizumab for Advanced or Unresectable Melanoma

Disclosure of Potential Conflicts of Interest

K.T. Flaherty is a consultant/advisory board member for Merck. No potential conflicts of interest were disclosed by the other author.
Abstract

From Coley’s toxin to combination immune checkpoint inhibition, strategies to activate the immune system and generate anti-cancer immunity have been ongoing for well over a century. Over the past decade, the so-called immune checkpoint inhibitors, generally monoclonal antibodies that target key regulators of T-cell activation, emerged as the most effective immune targeted agents. Pembrolizumab is the first anti-programmed death 1 (PD-1) antibody approved by the FDA for the treatment of metastatic melanoma. With responses seen in 25-40% of patients, depending on dose and setting (i.e., before or after ipilimumab), pembrolizumab specifically and anti-PD-1 antibodies generally are revolutionizing the treatment of melanoma. However, in the setting of other recent advances in the field, a number of practical issues are emerging that need to be addressed to optimize the care of melanoma patients. First, the optimal sequencing of therapy (frontline immunotherapy over molecular targeted therapy, ipilimumab versus pembrolizumab as initial immune checkpoint inhibitor) is unknown and must be evaluated through randomized trials. Second, there is strong rational to combine immune checkpoint inhibitors (i.e., anti-PD-1 with ipilimumab) and to combine immune therapies with targeted therapy agents, so determining whether combination therapy is better than direct sequencing is another critical issue that needs to be addressed in carefully carried out studies.
**Introduction**

In the late nineteenth century, William Coley began dosing cancer patients with a toxin derived from bacteria in an attempt to promote an immune response against their cancers (1). This early and crude form of immune therapy served as a proof of concept and inspired greater than a century’s worth of investigation. During this time, the pillars of adaptive immune function, namely antigen processing and presentation, antigen recognition, co-activation/anergy, and effector function were identified and subsequently targeted by various treatments tested in the clinic. One group of molecules, monoclonal antibodies targeting checkpoints of T-cell activation, recently have been developed and demonstrated activity in a number of malignancies, and, to-date, has culminated in the regulatory approval of three agents for the treatment of metastatic melanoma.

Melanoma, the fifth and seventh most common malignancy in men and women, respectively, has long been the focus of immunotherapy efforts (2). In the 1960’s and ‘70’s, non-specific (to cancer) vaccination, typically with Bacillus Calmette-Guerin (BCG), was investigated and shown to be associated with rare responses (3). With the identification and purification of type 1 cytokines, both interferon alpha 2B (IFN alfa2b) and interleukin 2 (IL-2) were proven effective (IFN in the adjuvant setting and IL-2 in metastatic setting), with durable response lasting years and even decades seen in 5-10 percent of metastatic melanoma patients treated with high-dose IL-2 (4, 5). The standard treatment for metastatic melanoma has changed dramatically over the past four years, with the regulatory approval of six therapies, compared with only two agents were approved by the FDA in the
preceding 35 years (dacarbazine in 1976, high-dose IL-2 in 1998). Specifically, in 2011, the FDA approved ipilimumab, a cytotoxic T-lymphocyte 4 (CTLA-4) inhibitor, based on the results of a randomized, Phase III trial of a gp100 vaccine, single-agent ipilimumab, or the combination of the vaccine with ipilimumab that demonstrated superiority in overall survival (OS) of ipilimumab (either alone or in combination) compared to single agent vaccine (6). Soon to follow was the approval of a BRAF inhibitor vemurafenib, also in 2011, for patients whose tumors harbored a BRAF mutation, and then the BRAF inhibitor dabrafenib and MEK inhibitor trametinib in 2013 for the same patient population (7, 8). In early 2014, the combination of dabrafenib and trametinib was approved for BRAF-mutant melanoma followed by the approval of two inhibitors of the programmed death 1 (PD-1) receptor, pembrolizumab and nivolumab, both in late 2014 (9-11).

**Immune Checkpoints**

The goal of immunotherapy is to harness the power of the human immune system to selectively attack human cancers. Since the time that immune cytokines such as IL-2 and interferon alpha were discovered and developed as therapies, the strategy has been to provide a very general stimulus that leads to a systemic inflammatory response that hopefully will trigger tumor antigen recognition, tumor-specific immune activation, and tumor destruction. In the late 1980’s and early 1990’s, so-called immune checkpoints that regulated T-cell activation were identified and included CTLA-4 and PD-1 and its ligands PD-L1 and PD-L2. These seminal discoveries have ushered in a new generation of immune therapies that specifically targeted mechanisms of immune regulation that have ultimately translated into
more effective therapies for melanoma, as well as a wide range of other malignancies.

**Preclinical Rationale for PD-1/PD-L1 Inhibitors**

Preclinical models have predicted both toxicity and efficacy of immune checkpoint blockade. For example, knockout mice for CTLA-4 develop rapidly progressing and lethal autoimmunity within a few weeks after birth (12). In contrast, PD-1 knockouts develop normally, though have splenomegaly and increased levels of certain immunoglobulins, while PD-L1 deficient mice have enhanced immunogenicity and susceptibility to develop triggered autoimmunity (such as the experimental autoimmune encephalopathy); neither PD-1 nor PD-L1 knockout mice exhibit the severe endogenous autoimmunity of the CTLA-4 knockout mice (13, 14).

Inhibition of immune checkpoints with monoclonal antibodies, however, has been associated with promising activity in murine models of cancer. The initial report of anti-tumor effects in cancer was with an anti-CTLA-4 antibody that was associated with tumor rejection (15). The therapeutic value of anti-PD-1/PD-L1 antibodies on preclinical models of cancer has also been demonstrated (16). Finally, dual monoclonal inhibition of CTLA-4 and PD-1 has been shown to be superior to single agent CTLA-4 or PD-1 inhibition, in melanoma models (17).

**Clinical Development of PD-1 Inhibitors**

**First-in-class: nivolumab**

The first anti-PD-1 antibody to be studied in the clinic was nivolumab, a fully human IgG4 monoclonal antibody that was deemed safe in a dose-exploration phase I trial that evaluated 1-5 total doses (18). Remarkably, responses were seen in 3 patients
despite so few doses being given. The second trial of nivolumab enrolled nearly 300 patients including those with melanoma (107 patients), non-small cell carcinoma (76), and renal cell carcinoma (33) (19). Responses were seen in each disease type, including in 31% of the melanoma patients. Additionally in the melanoma cohort, the median OS was 16.8 months and the 2-year survival rate was 43%. Of note, prior anti-CTLA-4 antibody therapy was not allowed. Subsequently, there have been two randomized trials of nivolumab compared to chemotherapy that have been reported, one in the frontline setting in patients without BRAF-mutations and another following ipilimumab in all patients and also BRAF targeted therapy in BRAF-mutant patients (10, 20). In the frontline setting, nivolumab was found to be superior to chemotherapy with respect to response rate, progression free survival (PFS), and OS (10). Similarly, nivolumab was found to be superior to chemotherapy following ipilimumab (20). This latter data set was responsible for the FDA approval of single-agent nivolumab in patients with metastatic melanoma following ipilimumab therapy in December 2014.

**First approved: pembrolizumab**

Pembrolizumab, the second anti-PD-1 antibody to be tested in the clinic, is a highly selective, humanized monoclonal IgG4-kappa isotype antibody against PD-1. The phase I trial was a revelation, the results of which led to the FDA approval of pembrolizumab in patients with metastatic melanoma following ipilimumab therapy in September 2014 (10, 21). The initial report of this trial documented the outcomes of 135 patients with metastatic melanoma, and includes patients who had and who had not received prior ipilimumab (21). Two doses were tested, 2 and 10
mg/kg, and doses were given every two or three weeks indefinitely. The objective response rate was 38%, median PFS was 7 months, and furthermore, over 70% of patients had some regression of disease (based on the so-called waterfall plot) (21). A later report of this trial described the outcomes of a subgroup of 173 patients with ipilimumab-refractory, metastatic melanoma who were randomized to either 2 or 10 mg/kg given every three weeks (10). Responses were seen in 26% of patients (though again over 70% had evidence of tumor regression from baseline), PFS was over 7 months, and one year survival appeared to be approximately 60% or greater, though interpretation is challenging since the median follow up at the time of publication was only 8 months.

**Tolerance of pembrolizumab**

With the introduction of the anti-CTLA-4 antibodies ipilimumab and tremelimumab into the clinic, the concept of immune-related adverse events (irAEs) became reality. With ipilimumab, common irAE’s include dermatitis, colitis, hepatitis, and hypophysitis, while less common toxicities include nephritis, uveitis, and neuritis (e.g., facial nerve palsies) among others. Severe or life-threatening side effects occur in 20-30% of patients, and in most series, the rate of fatal irAE’s is 1-2%; most commonly related to colonic perforation in the setting of immune-mediated colitis. Anti-PD-1 antibodies are also associated with irAEs, though at lower rates than anti-CTLA-4 antibodies. Table 1 details the rates of these toxicities in both melanoma patients and patients with other solid tumor malignancies.

**Clinical use of pembrolizumab**
The FDA label of pembrolizumab states that patients must have metastatic or unresectable melanoma, previously received ipilimumab, and received BRAF-targeted therapy if their tumors harbor a BRAF<sup>V600</sup> mutation. These limitations represent the first such conditions placed on an approved drug for melanoma, obviously are a sign of the progress made in the treatment of this disease, and are likely be removed when the frontline trial comparing pembrolizumab to ipilimumab (NCT01866319) is reported in the near future if pembrolizumab is determined to be superior to ipilimumab. Given this changing landscape, it is worth comparing pembrolizumab to ipilimumab and BRAF-targeted therapy with respect to response rates, rapidity of response, survival, and optimal sequencing of therapy.

The central tenets of immunotherapy, particularly when compared to molecularly targeted therapy, are:

1. Responses are uncommon, particularly after targeted therapy failure
2. Responses take time, occurring after many weeks or months of therapy
3. Benefit is long lasting.

These are certainly true with high-dose IL-2 and also ipilimumab, which is associated with tumor regression in 10-20% of patients that often take months to be realized and tend to be durable, highlighted by the over 20% 5-year survival (22-24). However, with pembrolizumab and other anti-PD-1/PD-L1 antibodies, the first two tenets are being challenged and the final tenet is, as yet, unproven.

With response rates in the 25-40% range, depending on dose level and whether given before or after ipilimumab, the data with pembrolizumab clearly
opposes the traditionally held belief that immunotherapy responses are uncommon (10, 21). Furthermore, the tumor regression rates (based on waterfall plot analysis) exceed 70% and approaches that of the BRAF inhibitor vemurafenib (21, 25). Amazingly, when patients are treated with pembrolizumab, tumor regression is expected. There is less data about response rates in the setting of BRAF-inhibitor resistant or refractory melanoma with pembrolizumab and other anti-PD-1/PD-L1 inhibitors, however one dramatic response was shown during the initial presentation of the data with MPDL3280A at ASCO in 2013 (26). In addition, Fig. 2 shows the imaging of a patient with BRAF/MEK inhibitor resistant disease treated with single-agent pembrolizumab, documenting response to therapy.

When faced with initial treatment decision, the rapidity of response is a critical factor in determining which agent to select. For example, BRAF-targeted therapy (either single-agent BRAF inhibitors or the combination of BRAF-MEK inhibitor therapy) is rightly touted as being associated with near immediate improvement in tumor-associated symptoms. While this is not always the case, most patients do feel better within a day or two after commencing therapy and FDG-PET imaging within 1-2 weeks show dramatic resolution of FDG-avidity (27). Additionally, patients with elevated LDH (typically those with rapidly growing disease and worst outcomes) were associated with similar early benefit to those who had a normal LDH in the randomized trials of these agents (25). This is quite different from the ipilimumab and IL-2 data that show patients with an elevated LDH are less likely to benefit (and in particular respond) to these therapies than those with a normal LDH (6, 28, 29). The data with anti-PD-1 antibodies is less clear,
as randomized data is just beginning to be reported, but analysis of the survival curve from the frontline nivolumab versus chemotherapy study is illustrative (30). In this trial of BRAF wildtype patients, the overall survival was significantly better in patients receiving nivolumab than chemotherapy (hazard ratio 0.42, 95%CI 0.25-0.73, p < 0.001); and the OS curves were inseparable in the first three months, suggesting that there is no benefit to a therapy that offers “quicker responses” such as chemotherapy. With pembrolizumab, responses may be seen earlier than time of first assessment (typically 12 months on clinical trials) (21). Fig. 3 shows documents the radiographic improvement of a patient treated with pembrolizumab after rapid progression following two doses of ipilimumab. Notably, the patient’s quality of life was impaired by pulmonary involvement of disease that was causing dyspnea, cough, and fatigue. Within a week after the commencement of pembrolizumab, the patient noted improvement in respiratory symptoms and by 12-weeks, marked radiographic regression of disease. While this is one dramatic case, the bottom line is that anti-PD-1 antibodies such as pembrolizumab may be associated with rapid responses and are likely as good an option as chemotherapy in patients who need a quick response.

Refinement of patient selection

Preliminary evidence supports equal efficacy for PD-1/PD-L1 antibodies in patients with or without BRAF mutations (10). With nivolumab having demonstrated a particularly striking response rate, progression free survival and overall survival impact in the first-line setting, that trial was confined to patients who are BRAF wild type (30). As more evidence emerges for PD-1/PD-L1 antibodies in the first-line
setting, we expect that they would be readily considered as a first-line treatment option for patients regardless of the underlying driver oncogene. Disease burden, the presence of symptoms and serum LDH will likely remain factors that influence decision-making regarding the use of BRAF/MEK combination therapy or a PD-1/PD-L1 antibody in the first-line setting until such time as predictive biomarkers are better elucidated and incorporated into clinical practice.

In the development of nivolumab, pembrolizumab, and MPDL3280A, the predictive value of PD-L1 expression on melanoma cells and infiltrating lymphocytes (in the case of MPDL3280A) has been investigated (30-32). In each case, it has been possible to identify low thresholds of expression of PD-L1 on tumor cells and/or tumor infiltrating lymphocytes that largely, but not completely discriminate between responders and non-responders. Specifically, response rates of 40-50% have been observed in biomarker positive patients versus 10% or less in biomarker negative patients (30-32). Whether this imperfect negative predictive value is a consequence of the dynamic nature of PD-L1 expression in tumors or the necessity to account for immunogenicity of tumors and robustness of baseline T cell recognition and homing is uncertain. But, even with the available evidence, clinicians may consider the use of PD-L1 expression in treatment decision-making when confronted with a patient whose tumor harbors a BRAF mutation, where BRAF/MEK combination therapy may be much more attractive than PD-1/PD-L1 antibody therapy for a biomarker negative patient.

Concluding Thoughts
Pembrolizumab, the first anti-PD-1 antibody approved by the FDA, is associated with unprecedented response rates in melanoma and, along with other anti-PD-1/PD-L1 agent represents a class of agents that has activity in other diseases formally not considered susceptible to immunotherapy such as non-small cell lung cancer and bladder cancer. While a number of unanswered questions regarding patient selection, sequencing, and combinatorial remain, the addition of pembrolizumab to the war chest against melanoma perhaps represents the most important therapeutic advance in this disease to date.

References


12. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA, Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue


antibody in patients with locally advanced or metastatic melanoma (mM). J Clin Oncol 31, 2013 (auppl; abstr 9010).


Table 1. Toxicity of pembrolizumab. Summary of investigator determined, related adverse events (in percent) in 411 patients with melanoma enrolled onto the Phase I trial of pembrolizumab. Grading per the common terminology criteria for adverse events (CTCAE) v.4.0.

<table>
<thead>
<tr>
<th>Adverse event, %</th>
<th>Pembrolizumab Phase I trial (411 melanoma patients) (10, 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any CTCAE grade</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36</td>
</tr>
<tr>
<td>Pruritus</td>
<td>24</td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>11</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9</td>
</tr>
<tr>
<td>Cough</td>
<td>9</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7</td>
</tr>
<tr>
<td>Chills</td>
<td>6</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6</td>
</tr>
<tr>
<td>ALT increased</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3</td>
</tr>
<tr>
<td>Colitis</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
</tr>
</tbody>
</table>
**Figure 1.** Comparison of maximal tumor regression curves (waterfall plots) in melanoma patients treated with vemurafenib (A) or pembrolizumab (B).


**Figure 2.** Pre- (A) and 12-week (B) scans of 76-year-old man with melanoma treated with pembrolizumab.

**Figure 3.** Pre- (A) and 12-week (B) scans of 67-year-old woman with BRAF-mutant melanoma treated with pembrolizumab after BRAF/MEK inhibitor therapy. Regression of pleural effusions (white arrows) and pericardiac mass (red arrows) is shown. The white dotted arrow indicates that the effusion has resolved.
Figure 1:

A

Percent change from baseline in diameters of target lesions

Disease stage
- Unresectable
- Stage IIc

Patients treated with vemurafenib

B

Percent change from baseline in longest diameter of target lesion

Prior ipilimumab treatment
- No prior ipilimumab treatment

Individual patients treated with lambrolizumab
Figure 2:
Figure 3:
Pembrolizumab for Treatment of Patients with Advanced or Unresectable Melanoma

Ryan J. Sullivan and Keith T. Flaherty

Clin Cancer Res Published OnlineFirst April 30, 2015.