

Review

# Managing Advanced Melanoma: Targeting the PD-1 Pathway with Pembrolizumab

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## ABSTRACT

Melanoma is a malignancy that arises from melanocytes found mostly in the skin and represents the most dangerous form of skin cancer owing to its metastatic potential and historically poor responsiveness to therapeutic intervention. Recently, key pathways and mechanisms involved in subverting anti-tumor immune based activity have been discovered. Integral to these advances are “immune checkpoints,” discovered to control immune reactivity to cancer cells and the tumor microenvironment. The mechanisms to which cancer hijacks the immune regulatory response signals serve as vital targets for therapeutic interventions. Pembrolizumab – Keytruda® was granted accelerated approval on October 28, 2014 under the FDA’s priority review program and represents the first approved humanized, monoclonal antibody directed against PD-1. Targeting PD-1, pembrolizumab re-activates suppressed T-cell mediated immune reactivity benefiting patients with unresectable or metastatic melanoma and disease progression following ipilimumab or *BRAF* inhibitor therapy. This paper will review the PD-1 signaling pathway and the role of pembrolizumab in advanced melanoma management.

## Introduction

Melanoma is a malignancy arising from the pigment-producing melanocytes found mostly in the skin. Of the 3.5 million skin cancers diagnosed each year in the United States (US), melanoma represents the most dangerous form of skin cancer owing to its metastatic potential and historically poor responsiveness to therapeutic intervention (1-3). Although melanoma represents less than 5% of skin cancers, it is unfortunately the result of 75% of the skin-cancer-related deaths. In 2014 alone, it is estimated that in the US 76,100 new cases of melanoma will be diagnosed and of those diagnosed an estimated 9,710 will die of this malignancy (4). Although rates are similar for both genders under the age of 65 years, men greater than 65 years are more than twice as likely as women of comparable age to be diagnosed (4,5). In addition to age-related

incidence, genetic and environmental factors are also involved. Certain phenotypic characteristics correlate with increased risk and include blue or green eye color, red or blonde hair color and presence of skin freckles (6). Additionally, Caucasians have a 20-fold increased risk as compared to dark-skinned populations (6). The major environmental factor involved in melanoma development is UV radiation exposure where the risk is associated with severe sunburns before the age of 20 (1-2). Recently investigators have revealed that this risk is increased by 80% among individuals who suffered at least 5 blistering sunburns between the ages of 15 to 20 years (6). Along with other known risks, these findings continue to highlight the importance of protecting the skin against sun exposure early in life. While most patients present with localized melanoma which is

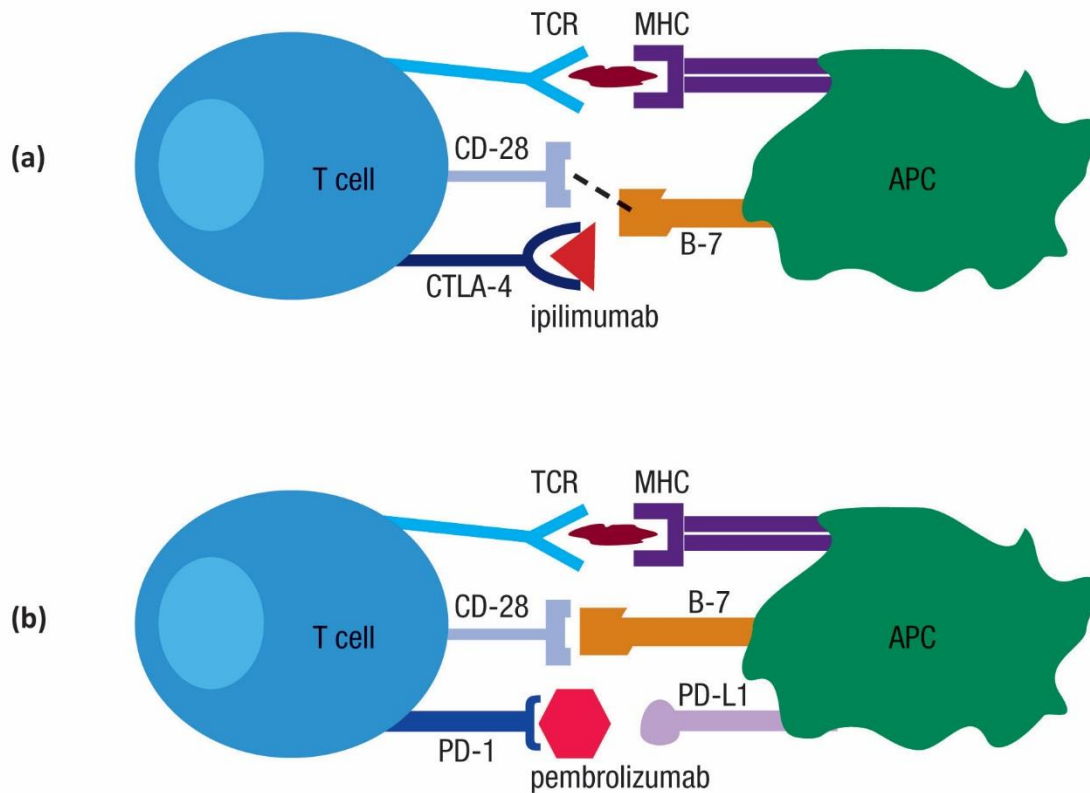
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**Figure 1: T-cell reactivation with checkpoint inhibitors.**

(a) Ipilimumab binds to CTLA-4 to obstruct the receptor from binding to the B-7 ligand on the APC. This instead allows B-7 to bind to CD-28, which continues T cell stimulation (19).

(b) PD-1 and PD-L1, when bound together, halt T cell activation. Pembrolizumab blocks the PD-1 receptor on the T cell to reactivate the immune system (21-23).

typically a curable form of the disease, the prognosis is significantly poor for metastatic melanoma. Conversely, up to 5% of patients initially present with metastatic disease and approximately 20% of all patients with locally advanced melanoma develop metastatic recurrence where median survival has historically been less than 1 year (range of 6 to 18 months) with standard therapy (1-3).

As it is well-known that melanoma tumors express an innumerable assortment of genetic alterations, not limited to a few protein mutations, and present an abundance of neopeptides, immune-based therapeutic intervention would be expected to be an effective treatment strategy in patients with this tumor type (2,7-9). But, the immune therapy concept is not new to cancer therapeutics as it was born over a century ago by William Coley, the first researcher to link the immune system with cancer (10). In the case of

advanced melanoma, initial attempts to improve outcomes focused on the use of high-dose interleukin-2 (HD-IL-2), a cytokine shown to activate T-cells and expand the T-cell population. HD-IL-2 is associated with a 16-23% response rate, and of which, 5-10% of patients achieve durable responses lasting upward of 10 years. Use of HD-IL-2, however, is limited by its severe multi-organ toxicity to specific treatment facilities and to patients with excellent overall health (11). Only recently has an improved understanding of the complexities of immune activation as well as tumor immunology incited the development of immune-targeting therapies aimed to unleash immune restraints that have been exploited or hijacked by cancer cells. These immune restraints are now commonly referred to as "Immune Checkpoints". Today, immune checkpoints represent therapeutic targets for contemporary immune-based therapy as

they play a major role in immune-driven reactivity to cancer cells and the tumor microenvironment (12-15).

### Immune Checkpoints and Cancer

The initiation of an immune response begins when antigen-presenting cells (APCs) process and present malignant cell antigens (12,13). Once processed,

APCs will display antigens on their surface as a peptide/antigen major histocompatibility complex (MHC). Upon encountering a naïve or resting T cell, this complex will interact with the T-cell receptor (TCR). Although a requirement for stimulating T-cells, MHC-to-TCR attachment alone is not adequate to initiate full T-cell activation. Full T-cell activation results only after co-stimulation as a result of an

**Table 1: Overall response rate from trials**

Study	Past Use of Ipilimumab	Intervention	Results	
			RECIST	Immune-related
Part B of KEYNOTE-001 (31)	Includes patients with and without history of ipilimumab treatment	Pembrolizumab 10 mg/kg every 2 weeks	29 (56%) <i>n</i> = 52	32 (56%) <i>n</i> = 57
		Pembrolizumab 10 mg/kg every 3 weeks	16 (36%) <i>n</i> = 45	15 (27%) <i>n</i> = 56
		Pembrolizumab 2 mg/kg every 3 weeks	7 (35%) <i>n</i> = 20	3 (14%) <i>n</i> = 22
		Total	52 (44%) <i>n</i> = 117	50 (37%) <i>n</i> = 135
Expansion cohort of KEYNOTE-001 (32)	Includes only patients refractory to ipilimumab	Pembrolizumab 2 mg/kg every 3 weeks	21 (26%) <i>n</i> = 81	24 (27%) <i>n</i> = 89
		Pembrolizumab 10 mg/kg every 3 weeks	20 (26%) <i>n</i> = 76	27 (32%) <i>n</i> = 84
Preliminary results from KEYNOTE-002 (33)	Includes only patients refractory to ipilimumab <i>(n</i> = 540)	Pembrolizumab 2 mg/kg every 3 weeks	21% ( <i>p</i> < 0.0001)	
		Pembrolizumab 10 mg/kg every 3 weeks	25% ( <i>p</i> < 0.0001)	
		Investigator-choice chemotherapy	4%	
KEYNOTE-006 trial underway (34)	Includes only patients naïve to ipilimumab	Pembrolizumab 10 mg/kg every 2 weeks		
		Pembrolizumab 10 mg/kg every 3 weeks		<i>Estimated completion date: March 2016</i>
		Ipilimumab 3 mg/kg every 3 weeks for 4 doses		

interaction between APC-expressed B7 protein and T-cell-derived CD28 (12-15). When combined, these interfaces (MHC-to-TCR + B7-to-CD28) orchestrate early T-cell activation that produces stimuli appropriate for the strength of the MHC-to-TCR signal. Within 48 hours of early T-cell activation, the T-cell begins transport of an otherwise internalized protein, cytotoxic T-lymphocyte-associated protein (CTLA-4), to its surface (16-18). This protein, with its strong affinity for APC B7 protein, outcompetes T-cell CD-28 for B7 attachment. Once bound to APC B7 protein, CTLA-4 will regulate the amplitude of early T-cell activation thus serving as an early priming signal dampener or more commonly an “immune checkpoint” (16-19). As one of the immune checkpoints, CTLA-4 is therefore thought to be important in the early T-cell priming phase, where it regulates and maintains balanced immune responsiveness while protecting normal tissue from immune-based collateral damage (12-17). As cancers take advantage of early immune-regulated states, early phase checkpoint blockade represents a transformative therapeutic approach that serves to release immune activity restraints. Approved by the US Food and Drug Administration (FDA) in 2011, ipilimumab, under the patent name Yervoy®, is a fully human, immunoglobulin G (IgG) 1 class monoclonal antibody that selectively targets CTLA-4. The prototypical checkpoint inhibitor increases median overall survival (OS) and provides durable response up to 2 years in patients with advanced melanoma (20).

Following this therapeutic breakthrough and further proof-of-concept studies, attention has now turned to additional checkpoint pathways (21-23). One pathway in particular, the Programmed Death (PD-1) pathway, serves to limit T-cell mediated immune reactivity in the periphery, at the antigenic site, closer to the tumor cell and its microenvironment, during the effector phase of T-cell immune activation. As tumors that express PD-1 ligands can be more aggressive carrying a poor prognosis, and because PD-1 is broadly expressed, this pathway represents an additional and therefore extremely important therapeutic checkpoint target (24,25). Prognosis is possibly more than 4 times worse when tumors express a high level of PD-L1 (26).

PD-1 belongs to the CD28 family of T-cell receptors and is expressed by activated T and B cells as well as tumor infiltrating lymphocyte populations

that are actively engaging tumor cells (20,25-27). Its known ligands PD-L1 and PD-L2 undergo cytokine-induced expression on a variety of tissues and cell types (e.g., heart, placenta, skeletal muscle, and lung) in response to chronic inflammatory or immune reactive conditions such as those that occur with chronic viral infection and malignant states (17,18,20,22,25-27). During chronic immune-reactive states it appears that PD-1 activity serves to regulate or balance immune effector activity establishing a state of “self-tolerance,” which reduces auto-immunity risk. Both PD-L1 and PD-L2 are considered inhibitory ligands that limit T-cell proliferation, cytokine production, and cellular adhesion; most of the PD-1 immune-mitigating activity is thought to be derived from its ligation to PD-L1 (28). Consequently, like CTLA-4, the PD-1 pathway results in down-modulation of T-cell activity or checkpoint regulation (Figure 1). The difference is that CTLA-4 regulates T cell activation in the lymphatics during the priming phase, whereas PD-1 predominantly regulates T-cell activity and its duration of response in the peripheral target site during the effector phase (17,18).

Unfortunately, cancer cells have learned to co-opt these immune regulatory response signals to evade immune attack that establishes a state of immune tolerance (15-18,20,25,29). Just as PD-1 expression is increased by active lymphocytes engaging tumor cells, PD-L1 expression is up-regulated on the tumor surface and by its surrounding microenvironment. Recent findings provide evidence that many cancers express high levels of PD-L1 expression. The net result is attenuation of anti-tumor T-cell mediated response that creates a state of T-cell “exhaustion”. Though reversible, ongoing checkpoint imbalance mediated by PD-1 ligation parallels the persistence of a foreign or mutated cellular population that eventually fosters distant metastatic spread. Targeting PD-1 or its ligand PD-L1 therefore limits the activity of a second checkpoint pathway, each representing additional promising targets for immune-based therapeutic intervention.

### **Pembrolizumab in Advanced Melanoma**

Pembrolizumab, formerly MK-3475 and Lambrolizumab, is a humanized monoclonal IgG4 antibody that targets the human cell surface receptor PD-1, expressed on the surface of activated T-cells (18,25,30). Upon binding to PD-1, pembrolizumab

eliminates PD-1 ligation with its known ligands PD-L1 and PD-L2. Once bound to PD-1, the resulting receptor blockade reverses adaptive immune resistance by restoring antitumor T-cell mediated response, reversing T-cell suppression and mitigating the state of T-cell exhaustion. In September of 2014, pembrolizumab became the first anti-PD-1 directed therapy to be approved by the US FDA. Pembrolizumab, given the patent name Keytruda®, received breakthrough therapy designation based on unmet medical need and early study findings supporting efficacy in patients with disease progression after a standard of care therapeutic approach (30). Based on available clinical data, pembrolizumab, at a dose of 2 mg/kg every three weeks, represents an immune-based treatment option for the patients with unresectable or metastatic melanoma. Until further studies demonstrate equality or superiority, pembrolizumab is indicated in patients with disease progression after having tried either ipilimumab or, if BRAF V600 mutation positive, one of the targeted kinase pathway inhibitors (vemurafenib, dabrafenib, and trametinib alone or in combination) (30).

### Clinical Efficacy in Advanced Melanoma

To date, studies have supported both the efficacy and safety of pembrolizumab in advanced melanoma (Table 1). In 2013, Hamid and colleagues published the results of an initial dose escalation study, KEYNOTE-001, that titrated patients to a maximum of pembrolizumab (now, pembrolizumab) 10 mg/kg IV over 30 minutes every 2 weeks (31). The study also included an expansion cohort assigning participants to either 10 mg/kg or 2 mg/kg every 3 weeks. The primary objective of the study was safety with the secondary endpoint being antitumor activity in ipilimumab-naïve and ipilimumab-refractory patients. Eligible patients were at least 18 years of age with measurable metastatic or locally advanced unresectable melanoma. Only those with an ECOG performance status 0-1 and adequate organ function were included. Ipilimumab-naïve patients were included if they had previously received fewer than 2 systemic therapy regimens, while patients with ipilimumab experience qualified only if they were side-effect-free and 6 weeks had lapsed since their last ipilimumab infusion. The investigators also screened patients previously treated for brain metastases to ensure no evidence of central nervous system progression had occurred in the previous 8

weeks. Patients were excluded if their melanoma was of ocular origin, if they had received anti-PD-1 or PD-L1 targeting therapy, if they were on systemic immunosuppressive therapy, or if they presented with active infections or autoimmune diseases.

Combined, 135 patients with advanced melanoma were enrolled in non-randomized cohorts. The mean patient age was 60.4 years; of which, 27% had elevated lactate dehydrogenase, 54% had visceral metastases (stage M1C), and 9% had a history of metastatic spread to the brain. The overall response rate, defined as the proportion of patients with complete or partial response after at least one treatment dose, was evaluated using immune-related response criteria and by an independent central review using Response Evaluation Criteria in Solid Tumors (RECIST). Based on immune-related response measures across all cohorts, 37% of treated patients (95% confidence interval [CI] 29-45) achieved a confirmed objective response, while the confirmed response assessed by RECIST was 38% (95% CI 25 to 44). A composite of immune-related and RECIST response data indicated that the 10 mg/kg every 2 week treatment group achieved the highest confirmed objective response of 56% and 52%, compared to 27% and 27% in the 10 mg/kg every 3 week and 14% and 25% with 2 mg/kg in the every 3 week groups, respectively. The response observed in the 10mg/kg every 2 week group did not differ significantly between patients who had received prior ipilimumab treatment and those who had not. At median follow-up of 11 months, 81% of responders were still receiving treatment where the overall median progression free survival (PFS) extrapolated by Kaplan-Meier analysis exceeded 7 months.

Subsequently, Robert, et al., published the results of an open-label, international, multicenter expansion cohort trial (32). This phase 1b study evaluated 173 patients with unresectable or metastatic melanoma, who have disease progression despite treatment with ipilimumab or, if positive for a BRAF mutation, a targeted kinase inhibitor. Eligible patients were randomized to pembrolizumab 2mg/kg or 10mg/kg intravenously every 3 weeks until progression or intolerable toxicity. Patients with severe immune-related disease, those requiring immunosuppression, and those with a history of severe immune-related adverse effects to ipilimumab were excluded from randomization. The median age of the study population was 61 years, 97% being Caucasian and

40% female. With regard to disease characteristics, 39% had elevated lactate dehydrogenase, 82% had visceral metastatic involvement (stage M1c), 18% were *BRAF* mutation positive, and 9% had brain metastases. The primary outcome, overall response, was evaluated by both RECIST and the investigator-approved immune-related response criteria. Secondary endpoints were evaluation of response duration, PFS and OS. Finally, adverse events were broadly assessed to provide relevant side effect information that could be attributed to immune-based therapy.

At the time of analysis (median of 8 months), 42% of patients were still receiving therapy. Based on RECIST, overall response was 26% in both the 2mg/kg and 10mg/kg treatment arms (difference 0%, 95% CI,  $p=0.96$ ). Exploratory analysis revealed that the rate of response was not different in any subgroup, and that activity was observed across all dose levels, irrespective of prior ipilimumab therapy, performance status, lactate dehydrogenase, *BRAF* mutation status, tumor stage, and number and type of prior therapies. In both treatment arms, time to assessed response was 12 weeks. Median response duration was not reached in either group at the time of analysis but of the 41 participants responding to therapy, 36 (or 88%) were still alive without evidence of progression. Of those who did progress after a complete or partial response, progression occurred between 6 to 37 weeks. By independent central review using RECIST, median PFS was 22 (95% CI 12-36) and 14 weeks (95% CI 12-24) in the 2 mg/kg and 10 mg/kg treatment groups, respectively. However, when assessed by immune-related response criteria, median PFS increased to 31 weeks in the 2mg/kg treatment group and 35 weeks in the 10mg/kg treatment group suggesting that the conventional use of RECIST for assessing immune-based therapeutic response may underestimate actual therapeutic benefits. Kaplan-Meier estimated OS at 1 year was 58% in the 2mg/kg treatment group compared to 63% with higher dose assigned group.

As a condition of accelerated approval, two ongoing multicenter randomized controlled therapeutic confirmatory trials in patients with unresectable or metastatic melanoma were conditional requirements of the FDA. To confirm and maintain approval, one trial will compare pembrolizumab to chemotherapy, the other pembrolizumab to ipilimumab. These trials include the KEYNOTE-002 and the KEYNOTE-006 which

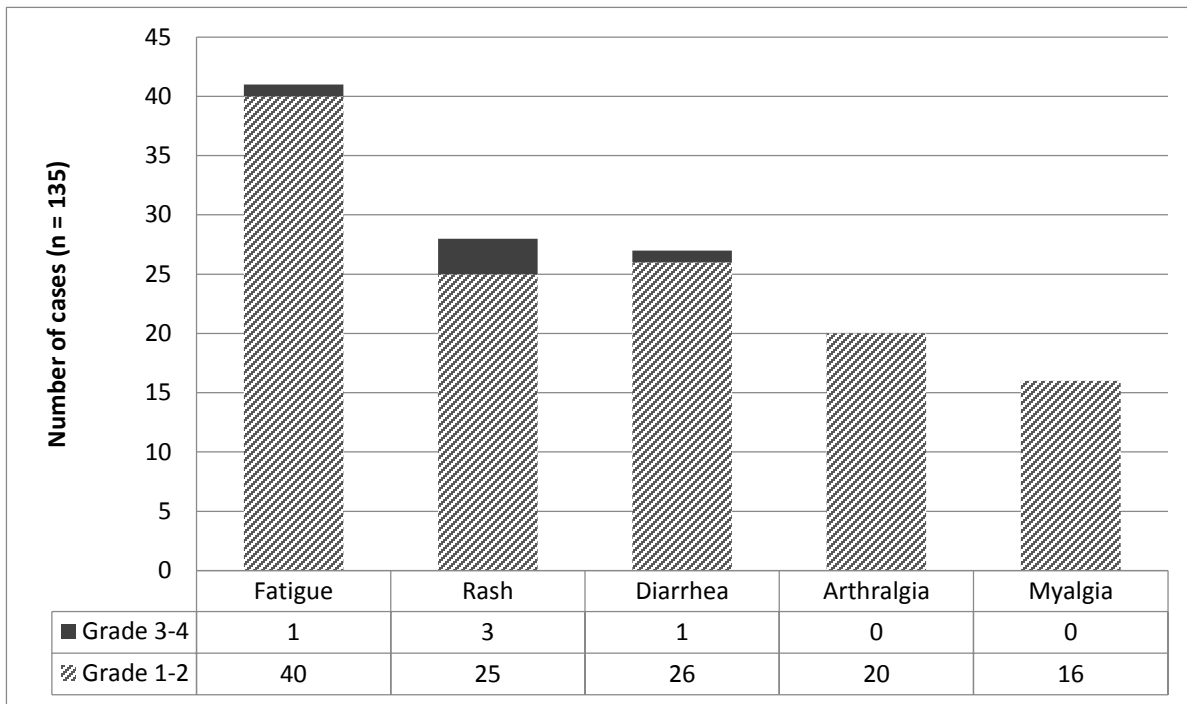
are now closed to new enrollment and currently underway (33,34).

Preliminary data for the KEYNOTE-002 was recently presented at the Society of Melanoma Congress (33). This study, a global phase II study, has enrolled 540 patients who were refractory to ipilimumab. Patients were randomized to pembrolizumab dosed at 2mg/kg or 10mg/kg every 3 weeks or investigator's choice chemotherapy (paclitaxel, carboplatin, alone or in combination, dacarbazine or temozolomide). At 6 months, PFS was 34% and 38% for pembrolizumab 2mg/kg and 10mg/kg, respectively, compared with 16% for patient on chemotherapy. Objective response rate was 21% at 2mg/kg and 25% with 10mg/kg but only 4% in the chemotherapy treated group. Median response duration of 37 weeks was reached in those receiving chemotherapy but had not yet been reached in either of the pembrolizumab-treated groups. Based on this interim data, pembrolizumab at either dose more than doubles PFS in an ipilimumab-refractory patient population compared to chemotherapy. Final results of this trial are expected in March of 2015.

The KEYNOTE-006, estimated to be complete in 2016, is a multicenter, randomized, controlled, three-arm, phase III study designed to evaluate the safety and efficacy of two pembrolizumab dosing schedules compared to ipilimumab in ipilimumab-naïve patients with advanced melanoma (34). The primary objectives of the study seek to evaluate each agent's effect on PFS and OS, while the secondary objective is to assess overall durable response rate out to 2 years. Combined, the results of KEYNOTE-002 and -006 will hopefully answer unresolved clinical questions where further insight will direct clinical treatment decisions affording patients the greatest outcome.

### **Pembrolizumab: Common Adverse Effects and Safety**

Clinical studies have shown that pembrolizumab is generally well-tolerated and that overall safety is similar with low (2mg/kg) and high (10mg/kg) dose therapy (30-32). Although clinical data continue to emerge, pembrolizumab appears to have a toxicity profile that is slightly lower in incidence and different in spectrum from that of therapy targeting CTLA-4. Early data from mouse models predicted less immune related toxicity compared to CTLA-4 blockade and



**Figure 2: Reported pembrolizumab-related adverse events by frequency and severity.**

107 of the 135 participants in an expansion cohort of KEYNOTE-001 reported at least one drug-related adverse event (31). Of which, the most common reactions were fatigue, rash, diarrhea, arthralgia, and myalgia; and were rarely classified as severe or life-threatening.

this has been somewhat mirrored by early human clinical studies. Although associated with an acceptable safety profile, clinical studies report that upwards of 82% of patients experience at least one treatment-related adverse effect but rarely have those been considered serious (31,32).

The most commonly experienced adverse effects occurring in 20 percent or more of patients (Figure 2) include fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, muscle pain, and diarrhea (30-32). Although common side effects, most have been classified as grade 2 or less and have required little intervention (30,35-37). In melanoma patients, rash and pruritus frequently involve eosinophil and lymphocytic infiltration which may progress to vitiligo (36-38). Many experts however consider local dermatologic side effects to be indicative of immune response and therefore indicative of potentially beneficial therapeutic effects. Although grade 3 to 4 toxicities have occurred in up to 13% of patients, they are rarely classified as serious, the most common being fatigue and rash (30-

33). Of greatest concern with immune-based therapy, inflammatory or immune-related adverse effects have been noted but have been very infrequent in occurrence. These have rarely been considered grade 3 or 4, and have included pneumonitis, colitis, nephritis, hypophysitis, and auto-immune hepatitis, which have been sufficiently managed by treatment interruption and/or corticosteroid therapy. Pneumonitis and colitis have generally occurred in the 5<sup>th</sup> or 6<sup>th</sup> month of therapy while nephritis has occurred later around the 11<sup>th</sup> month of therapy (35-38). Hypothyroidism requiring thyroid replacement has also been reported. Safety profiles have thus far been reported as similar in ipilimumab-naïve and previously treated patients where discontinuation because of a drug-related adverse effects in either stratified treatment population has rarely been required. Data from ongoing studies combined with clinical experience and pooled case data will further help clinicians predict and manage anti-PD-1 therapy related adverse effects. As current adverse event data may not reflect what is observed in practice, clinicians must be diligent to assess and evaluate each

patient for treatment related adverse events while keeping in mind that they may or may not be immune-related. Generally immune-related adverse events are manageable with prompt and aggressive intervention which presently includes the use of moderate to high doses of corticosteroids (40 to 60mg per day of prednisone) combined with temporarily withholding therapy (35,36). When considered non-life-threatening, pembrolizumab can be safely restarted when toxicities regress to grade 1 or when prednisone dosing of less than 10mg is needed for immune-related adverse effect management (35,38).

### Future Directions and Considerations

The recent success of immune-based treatment of advanced melanoma is expected to promote the further development and expansion of available immune-based treatment options. However, since not all patients with advanced melanoma respond to immune-based therapies, biomarkers that further define the molecular profile of the tumor are needed to more strategically direct therapeutic intervention. Recently, Tumei and colleagues showed that pre-existing CD8<sup>+</sup> cell levels, especially those located in the invasive tumor margin, were associated with PD-1 and PD-L1 expression (29). If this continues to be true of expanded cohorts, biopsy evaluation of CD8<sup>+</sup> levels might serve as a viable treatment response predictor. These and other biomarkers, if proven to correlate with clinical benefit, would ultimately provide clinicians with the information needed to direct treatment decisions to optimize outcomes. Additionally, considering pre-clinical evidence that suggests synergistic antitumor effect with simultaneous blockade of multiple immune checkpoints, additional prognostic and predictive biomarkers could help to stratify and identify patients who might benefit from single, combination or sequential therapeutic intervention (12,38-40).

Additionally, certain treatment-related questions require resolution including the role of PD-L2, the second known ligand of the PD-1 co-receptor T-cell inhibitory pathway. Although its activity is blocked by pembrolizumab, its overall role in mediating immune tolerance/immune exhaustive states remains to be fully established. Correlation of its effect on clinical outcome therefore requires further investigation and becomes even more relevant as evidence continues to support the effectiveness of antibodies that selectively target PD-L1 in isolation.

As data continues to support selective PD-L1 antibody inhibition, one questions the need to block the ligation of PD-1 by both PD-L1 and PD-L2. Ongoing clinical investigation will hopefully expand our understanding of PD-L2's role in the checkpoint pathway (12).

Finally, standard criteria have been used in clinical studies to evaluate response to anticancer agents. These criteria have been used to promote objectivity and facilitate comparative outcomes between studies. One commonly used response criteria, RECIST, is based on observed response seen with cytotoxic chemotherapy (38,40,41). As immune-based therapy modulates antitumor immune response, its mechanism of action is considered dramatically different from that of chemotherapy which directly mediates cellular cytotoxicity and cellular death. When evaluating response, the typical result observed with cytotoxic chemotherapy includes rather rapid tumor shrinkage noted by subjective and objective assessment. With immune-based therapy, however, some patients experience the onslaught of an inflammatory process where tumor lesions become heavily infiltrated with immune reactive cellular constructs and therefore tumor size remains unchanged and in some cases may increase in size. As may be the case, these lesions are reported as progressive when in fact they are being targeted for immune destruction. Recent reports by Hodi and colleagues presented at the 29<sup>th</sup> annual meeting of the Society for Immunotherapy of Cancer further support these considerations (42). Their data along with other expert opinion further questions the use of RECIST as a sole marker of response and outcome in immune-based therapy trials (40-42). Their presentation focused on data showing that pembrolizumab treated patients experience a unique response pattern that is not fully captured under RECIST criteria. More specifically, their data concluded that with conventional use of RECIST, immune-therapy benefit may be underestimated by as much as 10%. Hence, when evaluating immune checkpoint targeting therapy, the development of updated response criteria aimed at fully capturing the unique response patterns seen with immunotherapy are needed. Future studies should attempt to answer and address these and other treatment related dilemmas which will further enhance our understanding of the immune-therapeutic approach and response, ultimately advancing our position in the fight to cure cancer.



## Conclusion

Since 2011, the treatment of metastatic melanoma has been revolutionized. Pembrolizumab is the sixth agent to receive approval for use in this patient population. It represents a highly selective humanized monoclonal antibody directed against PD-1 receptors that reside on the surface of various activated immune cells. By blocking this receptor, pembrolizumab prevents PD-1 interaction with its known ligands, PD-L1 and PD-L2. Inhibiting the PD-1 pathway reverses adaptive immune resistance and restores antitumor T-cell mediated response. Current evidence demonstrates the efficacy and safety of this agent in advanced melanoma where activity is noted even in patients with very advanced and/or progressive disease. The results of ongoing studies will further establish pembrolizumab's place in therapy, supporting its role as a first or second line agent. In the interim, our foundational understanding of the mechanisms involved in immune regulation will

continue to advance along with strategies that will improve patient outcomes. Other agents targeting the PD-1 pathway are in development while at the same time research continues with the goal of determining markers which will guide therapeutic decisions. Combined, the recent intense effort to develop immuno-therapeutic approaches to cancer is paying off. New agents targeting immune checkpoints are not only effective and well tolerated; they convey new hope to patients with advanced stages of disease.

## Abbreviations:

PD-1	programmed death;
CTLA-4	cytotoxic T-lymphocyte-associated protein 4;
APC	antigen-presenting cell;
RECIST	Response Evaluation Criteria in Solid Tumors.

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