Reviewer 1:

This is a very timely review of the therapeutic use of immune checkpoint inhibitors in melanoma. The review focuses on the PD1 antibody pembrolizumab and often compares activity to the CTLA4 antibody ipilimumab. This is a reasonable approach, and very informative, but the authors have ignored important clinical data on nivolumab (a second PD1 drug with advanced clinical data; see Robert et al 2014 NEJM). I think some mention of these new data should be included. I also have several minor comments below to improve the clarity of the text.

Abstract Page 2 clarity would be improved with ‘these signals serve as vital targets for therapeutic intervention’.

Page 3 ‘As it is well known that melanoma tumors express an infinite assortment of genetic alterations and present an abundance of neoepitopes’

This sentence is awkward. Melanomas don’t express an infinite assortment of alterations?

Page 3 ‘Although HD-IL-2 is associated with a 16-23% response rate where 5-10% of patients achieve durable responses lasting upwards of 10 years, severe multi-organ toxicity potential has limited HD-IL-2 use to specific treatment facilities and patients with excellent overall health’.

Sentence needs rewording

Page 5 ‘Although PD-1 does so at a different location and stage in the immune activation cascade, (in the peripheral target site as opposed to the lymphatics and in the effector phase as opposed to the priming phase), the net result similar to that of CTLA-4, is down-modulation of T-cell activity or checkpoint regulation’ Sentence is unclear

Page 6 ‘pembrolizumab is presently indicated in patients with disease progression following ipilimumab or if BRAF V600 mutation positive, targeted kinase pathway inhibiting therapy (vemurafenib, dabrafenib and trametinib alone or in combination)’. Sentence needs rewording to make it clear that pembro is given after BRAF inhibitor failure

Page 7 ‘This phase 1b study evaluated 173 patients with unresectable or metastatic melanoma who experienced disease progression after ipilimumab or in patients with BRAF mutant advanced melanoma, targeted kinase pathway inhibiting therapy.’ Sentence should be reworded

Page 9 ‘Specifically to melanoma patients, rash and pruritus frequently involve eosinophil and lymphocytic infiltration which may progress to vitiligo’. This is unclear, what do the authors mean ‘specifically to melanoma patients’
Reviewer 2:

I think that this is a very interesting and topical review. I have a few comments:

1. Although the review is focused on Pembrolizumab, the authors should also mention another leading PD-1 inhibitor nivolumab, which was approved only 3 months later. Without mentioning other PD-1 inhibitors, the review gives an impression that Pembrolizumab is the only PD-1 inhibitor in clinic.

2. As Nivolumab currently represents the strongest competitor to pembrolizumab, it is important to compare the two antibodies in this review (efficacy and adverse effect), showing the data in a table.

3. Addition of a figure(s) to illustrate the interactions between MHC/TCR, CTLA-4/B7 and PD-1/PDL1 receptors in cancer cells and T cells for the section “Immune Checkpoints and Cancer”.

4. INTRODUCTION:

   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 (missing reference). 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 (missing reference).

5. The manuscript would benefit from language editing to improve the clarity and ease of reading.

Reviewer 3:

In their review Ho et al. give a comprehensive overview of the current data about pembrolizumab. However for a review some major concerns occur:
1) don't cite reviews in your review and use the original literature; PD-1 was described by T. Honjo, PD-L1 by Freeman, PD-L2 by Latchman - I miss their groundbreaking works completely

2) the CTLA-4 literature is also missing the original literature - there is a current review where you can find the original literature by Enk et al. Int Immunol

3) please do not use colorful terms, like T cell awakening etc.

4) please do not copy full sentences from other reviews

5) RECIST stays the current marker of response, if you allow TBP and use then response confirmation RECIST in out of question even in the IT era, thus please adjust

6) if you use the title managing advanced melanoma, then focussing on pembro only is very restricted

(End)