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Dear Mr Boysen

Re: ACD Consultation Ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma [ID74] - Joint reply by the National Cancer Research Institute (NCRI), Royal College of Physicians (RCP), Royal College of Radiologists (RCR), Association of Cancer Physicians (ACP), Joint Collegiate Council for Oncology (JCCO) and Melanoma Focus

We write on behalf of the NCRI/RCP/RCR/ACP/JCCO, who work together to produce joint responses to NICE oncological consultations, and Melanoma Focus. We are grateful for the opportunity to comment on this ACD and wish to submit the following joint comments.

NICE approved ipilimumab for the treatment of metastatic melanoma patients who have received prior therapy in December 2012 (TA 268). Since then the management of patients with advanced melanoma has changed significantly.

There is now strong evidence that a significant proportion of patients treated with ipilimumab go on to be long term survivors. A benefit is seen for all patient groups treated in a series of clinical trials (first and subsequent line, 3mg/kg and 10mg/kg dosing schedules), with a clear plateau on the survival curve around three years, which is maintained up to at least five years. (1)

Whilst there remains no robust predictive biomarker, there is increasing evidence that patients are more likely to benefit from ipilimumab treatment if they have small volume disease, normal LDH level and do not require steroids for control of symptoms. (2, 3, 4)

Patients, clinicians and regulators have recognised this potential for long term survival in a proportion of patients. UK melanoma specialists have changed the recommendations for follow-up of high risk patients to reflect this. We now routinely image high risk patients regularly in order to detect recurrence earlier and maximize the benefit of early immunotherapy. (5) The current raft of registration trials with new immunotherapy agents use ipilimumab 3mg/kg as the comparator in the first line setting: this is now an internationally accepted standard of care. Ipilimumab has been licensed by the FDA and the EMA in the first line setting.

The direct evidence for first line ipilimumab 3mg/kg as a single agent is weak, but what evidence there is all points to it being superior to DTIC and not inferior to its use as second line treatment. There is no precedent for second line therapy to be more effective than the same treatment in the first line that is not explained by selection bias.

There will never be a study comparing DTIC with ipilimumab. The only endpoint that could be used would be progression free survival (PFS), and this is not a surrogate of efficacy for immunotherapy. Overall, survival would be confounded by crossover and subsequent treatment.

It is difficult to calculate the change in ICER in moving from the second to first line, but this is likely to be minimal. At present, clinicians routinely offer the minimum amount of chemotherapy needed to justify switching to ipilimumab, usually 1-2 cycles, so this is closer to the use of ipilimumab up front than the initial MDX-010 study, in which patients were heavily pretreated. The number of patients treated may be slightly higher, but more patients are likely to benefit, and there will be savings in terms of chemotherapy costs, imaging, etc.

The UK melanoma community is a major contributor to clinical trials and this has a positive benefit in potential drug cost savings. (6) In the last year, we conservatively estimate that we have saved more than £7 million on ipilimumab expenditure through enrolling 179 patients in clinical trials who would otherwise have received ipilimumab as a standard of care. We are very aware of the impact of these high cost, but effective, treatments on the NHS budget. We also see an opportunity to collect robust prospective audit data on use, efficacy and health economics.

It is our strong recommendation that ipilimumab be made available as first line treatment for eligible patients with metastatic melanoma.

Yours sincerely

1 Lebbe et al. Long term survival with ipilimumab, 5 year follow-up. Proc ASCO 2013, #9503 (poster)

2 Kelderman et al. Lactate dehydrogenase as a selection criterion for ipilimumab treatment in metastatic melanoma. Cancer Immunology and Immunotherapy 2014 (in press)

3 Hodi et al. Improved survival with ipilimumab in patients with metastatic melanoma. NEJM 2010, 363 (8); 711-723

4 Margolin et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncology 2012, 13 (5); 459-65

5 Larkin et al. http://melanomafocus.com/wp-content/uploads/2014/02/Cutaneous-Melanoma-Follow-Up-Position-Paper-30Jan14.pdf

6 Liniker et al. Treatment costs associated with interventional cancer clinical trials conducted at a single UK institution over 2 years (2009–2010). BJC 2013 DOI:10.1038/bjc.2013.495 (ePub ahead of press)