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Dear Professor Longson

Re: RE: Ipilimumab for previously treated advanced (unresectable or metastatic) malignant melanoma – Appraisal Consultation Document

I write on behalf of the NCRI Melanoma Clinical Studies Group/RCP/RCR/ACP/JCCO in response to the above consultation. The above organisations are grateful for the opportunity to comment and would like to make the following joint response.

General

We note that the Appraisal Committee was satisfied that ipilimumab met the criteria for being a life-extending end-of-life treatment and that the trial evidence presented for this consideration was robust.

Our experts found the document to be comprehensive in scope, detailed in depth and well argued. The conclusion that ipilimumab is not recommended for the treatment of advanced malignant melanoma in patients who received prior chemotherapy is not a surprise to clinicians who work in this area, largely based on the economic evaluation.

All of the relevant evidence available has been taken into account, (including those trials using both 3 mg/kg and 10 mg/kg) but the evidence for this treatment regimen is still limited at present. Most consider that the evidence base needs to be developed further. This emphasises the continued importance of developing UK based trials to do this.

The calculated costs per QALY are substantial which ever way they are calculated.

Vial sharing is a possibility in bigger centres.

Efficacy

The UK now has enough experience to know that there is a small but definite cohort of patients who do gain true survival benefit with this drug.

There do seem to be responses which may be durable. A near-doubling of proportion alive at 1 and 2 years, and continued separation of the curves, is valuable.

It is important to emphasise that, unlike most drugs NICE considers, this is an immunotherapy, boosting the aquired immunity and that 2-3 year survivals may well translate into long term survivals as with the high dose IL-2. With that, perhaps the health economics may look more favourable.

Toxicity

Some believe that the toxicity profile appears to be less of a concern than previously thought. Some centres report favourable experiences to date with 3mg/kg in the EAP and since licensing all toxicity resolved without serious sequelae. It is their opinion that this has been aided by patient education and early recognition of warning symptoms and signs. They note that 3mg/kg is less toxic than 10mg/kg, however, they feel that the experience in the 1st line trial (no toxic deaths on 10mg/kg ipi) is perhaps also relevant.

Others centres have real concern regarding presumed drug-related toxicity incidences. They believe that although the ACD represents reasonable interpretations of the evidence, it does need to be emphasised that Ipilimumab does give a substantial drug cost where previously no active treatment was given. This will have an effect on drug costs and clinical resources as patients will have to be seen more frequently and the toxicities of this treatment managed. They believe that the toxicity profile of this treatment is not inconsiderable. Costing would therefore need to include the cost of treating presumed drug-related toxicity.

We recommend that the involvement of colleagues (eg gastroenterologists, endocrinologists, ophthalmologists) will be vital for patients taking this drug. This is one part of a possible justification for centralisation of treatment, as it is not only oncologists who need experience in managing toxicity.

Patient selection

Predicting who is likely to benefit would be good. There is an issue of thelack of bio markers in the use of this medication. As it stands, treatment cannot be targeted to the potential subgroup of patients who may benefit most.

Some centres have suggested that there should be restrictions on the second-line use of Ipilimumamab because of the drugs toxicity profile. These would include having a good performance status (0/1), not requiring steroid medication or being on minimal maintenance dose and having stable intracranial disease.

Some note that although the Hodi study included PS 2 patients, they represented less than 2% of the total. They therefore do not see the merit of ipilimumab for PS 2 patients.

In the current era of targeted therapy, patients with no detectable driving mutation will be at a disadvantage. Ipilimumab may be their most active option.

Unlawful discrimination & equality

There are no aspects of the recommendations that would suggest discrimination or inequitable access to the drug. However, there may be some older patients, who because of their co-morbidities and performance status might clinically not be deemed fit enough to tolerate this treatment and its potential toxicities. The potential morbidity from this treatment must be considered for all patients about to start on this medication, as there were patient deaths within the trials for this drug.

Yours sincerely