Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Pembrolizumab for treating unresectable, metastatic melanoma after progression with ipilimumab

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

Name of your organisation: NCRI/RCP/RCR/ACP and Melanoma Focus

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Patients with advanced, inoperable melanoma are normally genotyped for BRAF gene mutation status. Although all patients with BRAF mutant melanoma are eligible for BRAF inhibitor treatment as first line, around one third of patients may have low volume, indolent disease and these patients who are otherwise fit and well are more likely to be offered ipilimumab as first line therapy according to NICE guidance (TA xxx). The majority of patients with BRAF wild type advanced melanoma will be offered first line ipilimumab, unless it is clear that they have rapidly growing, high volume disease and/or poor performance status and other co-morbidities which might exclude them – in general, it is assumed that patients need to have at least a 3 month life expectancy to stand a chance of benefiting from ipilimumab. A very small number of patients may still be offered first line cytotoxic chemotherapy with the aim of debulking disease prior to immunotherapy.

For those patients who receive either BRAF inhibitor or chemotherapy as first line therapy, on disease progression, they may be offered second line ipilimumab, according to NICE guidance (TA xxx).

The choice of treatment for patients who have progressed after ipilimumab will depend on a number of factors including what other treatments have been given previously, patient performance status, predicted life expectancy and patient preference. For those patients who received ipilimumab as a first line therapy, they may be offered cytotoxic chemotherapy (dacarbazine), or for BRAF mutant melanoma, BRAF targeted therapy. Alternatively, patients may be considered for clinical trials, while those less fit patients will be offered best supportive care only.

This summary of treatment options is pretty standard across the country. Use of ipilimumab and BRAF inhibitors is standardised in England as a consequence of NICE guidance recommendations.

In the last 2 years, anti-PD1 monoclonal antibodies have become available initially in clinical trials as an option on progression after ipilimumab as well as first line therapy. These international trials involving limited numbers of UK sites have all closed to recruitment currently. In the summer of 2014, Merck opened a compassionate access programme to provide access to pembrolizumab for patients who had progressed after standard therapies including ipilimumab and, where appropriate, BRAF inhibitors. This programme is ongoing and is available to any specialist who approaches them.

Pembrolizumab is a very exciting new treatment for metastatic melanoma patients. As an immune checkpoint inhibitor, it might be considered to be very similar to

ipilimumab. However, it appears to have a much higher response rate and long term remission rate compared with Ipilimumab, while it appears to have a much lower rate of grade 3+ toxicities. It takes effect more quickly, so more patients with higher volume, more aggressive disease might benefit compared with ipilimumab.

This appraisal is addressing the role of pembrolizumab AFTER ipilimumab. Direct standard of care comparators are therefore cytotoxic chemotherapy (dacarbazine) and BRAF inhibitors. For BRAF wild type patients, pembrolizumab is clearly a more active treatment than dacarbazine and would be used in preference to cytotoxic chemotherapy.

For BRAF mutant patients, this might be a difficult choice. For some patients with rapidly progressing, high volume disease and deteriorating performance status, a BRAF inhibitor would remain the treatment of choice. However for others, the hope of long term survival might influence patients and clinicians to prioritise pembrolizumab, since it appears that the duration of benefit with BRAF inhibitors remains limited, at best around 1 year median survival.

There are other treatments on the horizon which will make choice of treatment for metastatic melanoma more complex in the near future – namely, nivolumab, another anti-PD1 McAb currently beginning its appraisal process for first line therapy as well as post ipilimumab. In addition, combinations of BRAF and MEK inhibitors offer significantly greater survival compared with BRAF inhibitor alone and are well tolerated and these are also in the process of being appraised by NICE.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

As described above, around 10% of metastatic melanoma patients have high volume, aggressive disease with rapidly deteriorating performance status who are less likely to benefit from immunomodulators, but if BRAF mutant, could be expected to benefit from BRAF inhibitors at least in the short term.

Melanoma frequently metastasises to the brain and these patients have an extremely poor prognosis. To my knowledge, quality data on the activity of pembrolizumab is not yet available, however, trials have confirmed that Ipilimumab is active in patinets with brain involvement, so there is every reason to assume that pembrolizumab will also benefit these patients.

There are currently no reliable biomarkers for predicting response to Pembrolizumab.

The potential to do harm with this agent is remarkably low.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional

professional input (for example, community care, specialist nursing, other healthcare professionals)?

Pembrolizumab should be prescribed only by specialist melanoma oncologists in secondary care. There are no other routine requirements for additional professional input over and above what already exists for this group of patients. Education of acute oncology services is needed to ensure appropriate management of immune-related adverse events, although the risk of hospitalisation due to this agent is remarkably low.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Specialist melanoma oncologists can currently access pembrolizumab in this indication via a compassionate access programme. Over 30 oncologists have registered in this programme and over 200 patients have been treated in the UK. Pembrolizumab is still awaiting its European licence.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NICE guidelines for melanoma management are currently out for consultation and will therefore predate this technology appraisal

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

The drug is very easy to use, the main issue is the current recommendation to continue treatment once every 3 weeks for up to 2 years in responding patients. This is likely to represent a large volume of work for chemotherapy day unit teams.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

Patients with brain metastases should not be excluded from accessing this treatment.

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Little is known about the benefit of Pembrolizumab in patients with metastatic disease arising from rarer melanoma subtypes other than cutaneous melanoma, but since there is evidence showing that these groups benefit from ipilimumab, patients with metastatic uveal and mucosal melanomas should not be excluded from treatment.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The Keynote 001 and 002 trials were not conducted in the UK, however they are representative of UK practice, involving patients with metastatic melanoma treated in the USA, Australia and other European countries. Keynote 001 was a study to evaluate different dosing schedules (10mg/kg vs 2 mg/kg and 2 vs 3 weekly cycles) of pembrolizumab in both ipilimumab-naïve and ipilimumab-pretreated metastatic melanoma patients. Overall, there was little difference in the various schedules tested. 221 patients were ipilimumb-pretreated, objective response rate in this cohort was 30%, median overall survival 22.9 months and 12 month survival rate was 65%. Grade 3 toxicities occurred in 14% patients.
The Keynote 002 trial was undertaken in ipi-refractory patients only and randomised 540 patients to receive pembrolizumab 10mg/kg q 3 weeks, 2mg/kg q 3 weeks or investigator's choice of cytotoxic chemotherapy. Cross over on progression on chemotherapy was allowed. Only PS 0-1 patients were recruited and they were allowed very minimal use of steroids. Early analysis of the primary end point, PFS, reported hazard ratios of 0.57 and 0.5 in the pembrolizumab arms. Again, toxicity was very manageable. Longer term survival data is needed, however, these data Convincingly show that pembrolizumab is an effective treatment for this disease.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

As already described, both Ipilimumab and pembrolizumab can generate immune-related adverse reactions. For Ipilimumab, the incidence of severe reaction requiring hospitalisation is around 1 in 10 patients treated. In the initial trials, there were a small number of treatment-related deaths, usually due to colitis and these do occur in the real world setting. For pembrolizumb, there have been no treatment-related deaths reported in the trials conducted to date. Immune-related events do occur,but they are usually mild to moderate and easily manageable in the outpatient setting. In my own practice of treating 10 patients with pembrolizumab, we have not recorded anything more than mild toxicities, mainly fatigue.

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

N/A

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NHS staff are already familiar with using Ipilimumab, which is a similar agent and so no additional training will be required. The main issue is the duration of treatment – while Ipilimumab is delivered as 4 intravenous infusions over 12 weeks, pembrolizumab is being offered as a 3 weekly infusion every 3 weeks for up to 2 years in the absence of progression. This will generate a significant amount of additional work to pharmacy and chemotherapy day unit services.

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Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

N/A