

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They also have the right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
<p>Bristol-Myers Squibb</p>	<p>BMS is in receipt of the Appraisal Consultation Document (ACD) for ipilimumab for previously treated unresectable malignant melanoma. We are obviously disappointed that the ACD does not recommend the use of ipilimumab in this indication.</p> <p>Of singular importance, in our view, is the lack of credit that this highly innovative product has been given by the Appraisal Committee. In Section 4.2, the AC recognises that the treatment represents a step change in the treatment of advanced melanoma and that it is the first treatment development in this area for 30 years.</p> <p>Section 4.13 of the ACD considers “...whether the innovative nature of the technology may not have been adequately captured in the QALY measure.” We believe that while the treatment effects have been captured in the QALY measure, the mechanism of action of ipilimumab – which represents a paradigm shift in the treatment of malignant melanoma, and is the essence of the highly innovative nature of ipilimumab – has not been appropriately and comprehensively captured.</p> <p>Innovation is one of the factors that the methods guidance recognises as relevant to whether a product represents a good use of NHS resources, so this is a crucial point. The AC says that it “considered that the magnitude of additional weight that would need to be assigned to the QALY gains...would be too great...to be...a cost effective use of NHS resources”. This implies that it was applying the same end of life cut off point that it has used with other oncology products, many of which have been significantly less innovative than ipilimumab. It is unclear from the ACD what methodology the AC used to reach this conclusion and, in particular, what value it is ascribing to various degrees of innovation to decide what is, and isn't, an acceptable magnitude of additional weight.</p> <p>The end of life criteria allows NICE to recommend treatments with an ICER over £30,000 per QALY if a substantial improvement in overall survival is demonstrated. This captures the unmet need for a treatment. However, society should put additional value on innovation benefits not captured by the QALY and therefore the NHS, as the organisation dealing with the health interests of society, should be willing to pay more for medicines offering a paradigm shift in the treatment of a disease through such non QALY captured benefits.</p> <p>BMS has conducted further work on the value of innovation within the NICE 'End of Life' guidance. This work is set out in Section 1 on page 6 (Valuation of innovation within NICE 'End of Life' guidance) and outlines a method to quantify the level of innovation inherent in an end of life product, defined as the 'innovation ratio'. This work shows</p>	<p>Comments noted. The Committee acknowledged that few advances had been made in the treatment of advanced melanoma in recent years and ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need. Nevertheless, the Committee considered that the clinical benefit of ipilimumab had been fully captured in the QALY calculation and concluded that, with the patient access scheme applied to the cost of ipilimumab, it had been demonstrated to be a cost-effective use of NHS resources for the treatment of advanced (unresectable or metastatic) malignant melanoma for people who have received prior therapy. See FAD section 4.17.</p> <p>Comment noted. This has been amended in</p>

	<p>ipilimumab to be one of the most innovative drugs assessed by NICE under the 'End of Life' criteria. Please note that it is provided as Academic in Confidence (AIC). BMS is clear that this drug has the ability to produce substantial survival benefit in a sizeable group of patients, for whom rapid and painful death would be their only other option. The AC states:</p> <ul style="list-style-type: none"> “...the manufacturer showed a survival advantage for ipilimumab, it was unable to reliably quantify the long-term survival benefit beyond 2 years.” (Section 3.15). This statement is not correct, as the pivotal MDX010-20 study provides outcomes up to 4.5 years. In addition poster presentations are included with this submission, showing survival data from patients in Phase 3 studies. <p>The ACD also states:</p> <ul style="list-style-type: none"> “When the cost of administering the full course (four doses) of ipilimumab in line with the UK marketing authorisation was included in the model, the manufacturer’s base-case ICER increased to £70,200 per QALY gained.” <p>An error has been recognised in the model for this scenario analysis. The model allowed all patients to receive 4 doses of ipilimumab even if they were deceased. Re-running the scenario analysis to allow only living patients to receive a dose of ipilimumab reduces this value to [REDACTED] (commercial in confidence information removed).</p> <p>BMS have also conducted other additional modelling and provided further information to assist the appraisal committee. This is presented below.</p> <ul style="list-style-type: none"> Revision of the modelling methodology in using registry data on long term survival rates (see page 13) <p>BMS recognise the limitations of the original modelling – the ACD states “the ERG considered that the manufacturer’s model is likely to have substantially overestimated the extent of survival benefit associated with treatment with ipilimumab” (Section 3.17), and the inherent positive bias – the ACD also states “The ERG noted that this approach implied that anyone surviving beyond 5 years of second-line systemic treatment was effectively cured” (Section 3.16).</p> <p>In order to model the effectiveness of both ipilimumab and best supportive care, the initial modelling submitted by BMS to NICE used:</p> <ul style="list-style-type: none"> Kaplan-Meier data from months 0 – 18 	<p>the final appraisal determination.</p> <p>Comment noted. .</p> <p>Comment noted. The Committee has considered the manufacturer’s alternative approach, using registry data to model long term survival benefits of ipilimumab treatment, which was provided in response to the appraisal consultation document. See FAD</p>
--	--	--

	<ul style="list-style-type: none"> • Parametric curve fitting for months 18-60 • Background mortality beyond month 60 <p>However, to inform better the cost-effectiveness of ipilimumab, BMS revised its modelling methodology based upon feedback from clinical experts. Rather than assume patients are effectively cured should they survive to month 60, we have used registry data (available for up to 15 years post diagnosis) to predict disease specific mortality for Stage IV melanoma in addition to background mortality. This addresses the issue that patients after 5 years were effectively cured, and uses real world data to support the number of patients dying of relapsed melanoma.</p> <p>The impact of the changes is to increase the ICER from the original model of around [REDACTED], to approximately [REDACTED]. Although the SmPC does not allow for vial sharing of ipilimumab, discussions with clinicians have indicated that vial sharing may occur in a proportion of patients in practice (Appendix 1). BMS endorses the use of ipilimumab as outlined in the SmPC (Appendix 2). However based on the feedback from clinicians BMS is providing ICERs incorporating vial sharing for the Appraisal Committee's consideration. The ICER including 50% of patients sharing vials is [REDACTED] if all patients vial share the ICER lies at [REDACTED] (commercial in confidence information removed).</p> <ul style="list-style-type: none"> • Revised economic model results and sensitivity analyses (see page 21Error! Bookmark not defined.) <p>BMS believes that the revised approach addresses the comments by the ERG and Appraisal Committee on the original modelling, and provides a more realistic estimate of both the effectiveness and cost-effectiveness of ipilimumab. As such, the key results and sensitivities are provided in Error! Reference source not found. (not reproduced), with a full set of results and sensitivity analyses presented later on page23.</p> <p>In the revised model, survival gain is estimated to be 30 months (44.1 months vs. 14.1 months), which generates an ICER of [REDACTED], implementing 50% vial sharing reduces this ICER to [REDACTED] (commercial in confidence information removed).</p> <ul style="list-style-type: none"> • Further information on utilities used in the submission (see page 33) <p>In the Appraisal Committee meeting it was highlighted that BMS should provide further information on the utilities used within the submission. This Section contains a full report on the methods used to value the utility of patients in the MDX010-20 clinical trial, and is also provided as Academic in Confidence.</p> <ul style="list-style-type: none"> • Utility of progressive disease patients (see page 44) 	<p>section 3.18.</p> <p>Comment noted. The Committee considered all of the revised scenario analyses presented by the manufacturer in response to consultation on the appraisal consultation document. See FAD section 4.11 for the Committee's consideration of the vial sharing assumptions.</p> <p>Comment noted. The Committee has considered the revised base-case ICERs presented by the manufacturer, taking into account the patient access scheme. See FAD section 4.10.</p> <p>Comments noted. The Committee heard from the manufacturer that EORTC-QLQ and SF-36 utility data were collected in the MDX010-20 trial. It noted the ERG's concerns that the number of respondents to the questionnaires dropped off significantly after week 12 in the MDX010-20 trial and that there was little difference between the utilities assigned to the progression-free and the progressive disease health states. The Committee noted that additional sensitivity analyses conducted by the manufacturer in response to the appraisal</p>
--	---	--

	<p>In the Appraisal Committee meeting, questions were asked as to whether the pre- and post- progression utilities were appropriate, as only a small decrease was seen between health states.</p> <p>Analysis of the utilities data by time to death highlights that patients do not experience a marked decrease on progression, but do experience a rapid fall in utility immediately prior to death; these values are 0.85 in measurements taken in patients over 400 days from death, but 0.64 in patients experiencing death in the following 50 days.</p> <p>Unfortunately this analysis was conducted too late to be included in the economic modelling, however given the long term survival exhibited by ipilimumab patients (remaining in the post-progression state for longer), this biases the result against ipilimumab, as the post-progression utility reported is artificially low.</p> <p>BMS hopes that the information provided in this response will help to inform best estimates of the value to patients of ipilimumab, the methods by which this value is calculated, and to reinforce the high degree of innovation that ipilimumab shows. We look forward to meeting with NICE on 16th November, and to developing a mutually acceptable way in which to bring this valuable medicine to patients in the NHS.</p>	<p>consultation document showed that the utility assumed for the progressive disease state was not a major driver of cost effectiveness. The Committee concluded that the utility estimates derived by the manufacturer were acceptable. See FAD section 4.8.</p>
<p>ScKIN</p>	<p>About Skcin and Skin Cancer UK National skin cancer charity Skcin (the Karen Clifford Skin Cancer Charity) was founded by Richard Clifford after his wife Karen passed away on New Year's Eve in 2005, after a courageous battle against skin cancer. The charity campaigns to raise awareness of skin cancer, with the emphasis on sun safety education for behavioural change and skin cancer awareness resulting in early detection of the disease. Skcin is also passionate about improving patient care and access to treatment for all affected by skin cancer.</p> <p>Skcin coordinates Skin Cancer UK, a coalition of organisations campaigning for action regarding the alarming increase in the incidence of the disease.</p> <p>General comments We would like to thank the NICE Technology Appraisal Committee for providing Skcin with the opportunity to respond to the Appraisal Consultation Document (ACD).</p> <p>We believe that it is important for organisations such as Skcin to comment on issues affecting people diagnosed with melanoma given the charity's specific interest in skin cancer, skin cancer prevention, and of course, melanoma.</p> <p>We concur with the views of the patient experts who presented evidence to the NICE Technology Appraisal Committee. As outlined in the Evaluation Report, they stated that if</p>	<p>Comments noted. The Committee has taken all the views offered into account during the appraisal process for ipilimumab.</p>

	<p>Ipilimumab is not made available to NHS patients, then they would be denied a therapy that might prolong survival and enable patients to continue their usual activities and maintain quality of life. We therefore urge the NICE Appraisal Committee to reconsider its decision and ensure that it is taking into account all of the evidence and representations received from patients and patient support groups over the past few weeks.</p> <p>In particular, when considering the evidence, we believe that it is important that the Committee acknowledge that melanoma is now often referred to as the ‘skinderella’ of all the cancers. Skcin believes that it is time that greater choice and more treatment options should be made available to the growing number of people diagnosed with melanoma across the UK.</p> <p>We would ask the NICE Technology Committee to consider that in the time between the first Appraisal Committee meeting on 20 September 2011 and the second ACD meeting on 16 November 2011, at least another 318 patients across the UK may have died from advanced melanoma¹ due to the limited treatment options available to them.</p> <p>To conclude, we believe that NICE’s draft negative guidance on Ipilimumab is a devastating blow to patients with advanced melanoma and if not overturned, patients will continue to have very limited treatment options.</p> <p>We would like to respond to a number of the questions asked by NICE’s Technology Appraisal Committee as part of its consultation process:</p> <ul style="list-style-type: none"> • Has all of the relevant evidence been taken into account? <p>Whilst we acknowledge that the NICE Technology Appraisal Committee has considered all evidence presented to it, we do not believe that sufficient consideration has been given to the fact that there are few treatment options available for patients diagnosed with advanced melanoma. Currently, patients can only access Dacarbazine, which is chemotherapy first licensed over three decades ago. As the NICE Technology Appraisal Committee will be aware, melanoma is an extremely aggressive disease and without effective new therapies, the prognosis for patients is poor. It has been suggested that the 5-year survival rate is approximately 5 – 15% and the median survival is 6 to 9 months. 6 months is very little time to get your affairs in order, come to terms with a diagnosis and say goodbye to family and friends. We therefore believe that if patients are given extra</p>	<p>Comment noted. The Committee acknowledged that few advances had been made in the treatment of advanced melanoma in recent years and ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need. Nevertheless, the Committee considered that the clinical benefit of ipilimumab had been fully captured in the QALY calculation and concluded that, with the patient access scheme applied to the cost of ipilimumab, it had been demonstrated to be a cost-effective use of NHS resources for the treatment of advanced (unresectable or metastatic) malignant</p>
--	---	--

¹ 318 figures is estimated on the premise that there are 2000 deaths from melanoma across the UK.

	<p>months and years, with a good quality of life, then this treatment is worth being reconsidered by Appraisal Committee A.</p> <p>Following discussions with a number of leading oncologists and clinical nurse specialists, we also believe that clinicians, as well as patients, should be able to have a choice of a range of treatment options available to them. By issuing negative guidance for Ipilimumab, this only serves to continue to limit treatment prescribing options for clinicians who may believe that their patients would benefit from Ipilimumab.</p> <p>We also believe the NICE Technology Appraisal Committee should reconsider its decision by looking at the innovation behind this therapy. Again, given that this is the first treatment for this patient group to be introduced to the market in over 30 years, the fact that the treatment works in a new way – through immunotherapy – should also be taken into further consideration by the NICE Technology Appraisal Committee.</p> <ul style="list-style-type: none"> • Are the provisional recommendations sound and a suitable basis for guidance to the NHS? <p>The NICE Technology Appraisal Committee has acknowledged in its ACD issued on 14 October that few advances have been made in the treatment of advanced melanoma in recent years and Ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need. Skcin agrees with the Committee’s understanding that this treatment is a “step change” and therefore we do not believe that these provisional recommendations are a sound and suitable basis for guidance to the NHS.</p> <p>On the basis that these provisional recommendations are not a sound and suitable basis for guidance, we urge the NICE Technology Appraisal Committee to reverse its decision. As well as being clearly innovative and a step change in the treatment for people with advanced melanoma, the incidence of melanoma is still rising. In fact, it is set to rise on a devastating scale in the coming decades, proving further the value and worth of this treatment to a growing pool of patients.</p> <p>As the NICE Appraisal Technology Committee will be aware, melanoma is a growing public health problem. We know that over the last 25 years the rate of melanoma has risen faster than any other of the top 10 cancers in the UK and incidence rates in Britain have more than quadrupled over the last 30 years. This is a worrying trend which we know is set to continue.</p> <p>In addition, we urge the NICE Technology Appraisal Committee to recognise that, tragically, melanoma often strikes at a younger ages compared to other cancers.</p>	<p>melanoma for people who have received prior therapy.. See FAD section 4.17.</p> <p>Comment noted. The Committee has acknowledged that few advances had been made in the treatment of advanced melanoma in recent years and ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need. Nevertheless, the Committee considered that the clinical benefit of ipilimumab had been fully captured in the QALY calculation and concluded that, with the patient access scheme applied to the cost of ipilimumab, it had been demonstrated to be a cost-effective use of NHS resources for the treatment of advanced (unresectable or metastatic) malignant melanoma for people who have received prior therapy.. See FAD section 4.17.</p>
--	--	---

	<p>Melanoma is the second most common form of cancer among young adults aged 15-34 years and it is the fastest growing cancer in men and the second fastest in women. It has been estimated that an average 22 years of life is lost from each melanoma death – more than any other cancer. Skcin therefore believes that Ipilimumab, which we understand can prolong survival and help prognosis, will allow patients to return to ‘normal life’ for a longer period of time. Without the positive approval of Ipilimumab by the NICE Appraisal Committee, the contribution by many young melanoma sufferers to the workplace and society will be cut short.</p> <ul style="list-style-type: none"> • Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document? <p>Skcin believes that equal access to treatments for people with advanced melanoma must be considered by the NICE Technology Appraisal Committee. As previously mentioned, Ipilimumab is a significant innovation for a disease with a high unmet clinical need. To demonstrate the extent of this unmet need, we can observe that in the last 10 years, NICE has recommended 81 Single Technology Appraisals for oncology. However, there have been no Technology Appraisals specifically for people with melanoma which, although is beyond the control of NICE, is concerning as it demonstrates that there is a real gulf between the number of treatments available across the spectrum of cancers. In light of this unmet need, we believe that equality between different cancer patients should be taken into account, allowing for the fact that this is the first licensed treatment for this patient group since the 1970s.</p>	<p>Comment noted. The Committee concluded that there is a significant unmet need for effective therapies for people with advanced melanoma. See FAD section 4.2.</p>
<p>Royal College of Pathologists</p>	<p>Please note that the Royal College of Pathologists has no comments to make at this stage of the consultation.</p>	<p>Comment noted.</p>
<p>Royal College of Physicians on behalf of NCRI Melanoma Clinical Studies Group, Royal College of Radiologists, Association of Clinical Pathologists, and the Joint Collegiate Council for Oncology</p>	<p>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.</p> <p>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.</p> <p>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.</p>	<p>Comments noted. The Committee has considered the evidence presented by the manufacturer on the clinical effectiveness of ipilimumab. It noted that the manufacturer derived efficacy data primarily from the MDX010-20 trial, which showed that treatment with ipilimumab led to a statistically significant median overall survival gain of approximately 3.7 months compared with gp100 for people with progressive disease after first-line therapy. See FAD section 4.3</p> <p>The Committee has only considered the use of</p>

	<p>This emphasises the continued importance of developing UK based trials to do this. The calculated costs per QALY are substantial whichever way they are calculated. Vial sharing is a possibility in bigger centres.</p> <p>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.</p> <p>It is important to emphasise that, unlike most drugs NICE considers, this is an immunotherapy, boosting the acquired 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.</p> <p>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.</p> <p>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.</p> <p>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.</p> <p>Patient selection Predicting who is likely to benefit would be good. There is an issue of the lack of bio</p>	<p>the 3mg/kg dose of ipilimumab in this appraisal. The higher (10mg/kg) dose is not currently licensed for use in the UK.</p> <p>The Committee concluded that although the adverse reactions and mortality associated with ipilimumab seen in the MDX010-20 trial were considerable, most adverse reactions, including those that led to hospital admissions, were manageable and would be managed more effectively as clinicians become familiar with ipilimumab's toxicity profile. It also concluded that people may be willing to tolerate significant toxicity if there were potential survival benefits. Adverse-event rates for ipilimumab and best supportive care were estimated from the MDX010-20 trial. The resource costs included in the model were drug acquisition and administration costs, and the cost of the disease, which included costs related to each health state and of treating adverse reactions. See FAD sections 4.5.</p> <p>Comment noted. According to the summary of product characteristics, ipilimumab treatment must be initiated and supervised by specialist physicians experienced in the treatment of cancer. It also requires that liver function tests and thyroid function tests should be evaluated at baseline and before each dose of ipilimumab. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with ipilimumab.</p> <p>Comment noted. The Committee heard that the optimal place for ipilimumab treatment in the clinical pathway for advanced (unresectable or</p>
--	--	---

	<p>markers in the use of this medication. As it stands, treatment cannot be targeted to the potential subgroup of patients who may benefit most.</p> <p>Some centres have suggested that there should be restrictions on the second-line use of Ipilimumab 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.</p> <p>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.</p> <p>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.</p> <p>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.</p>	<p>metastatic) malignant melanoma was still being debated in the clinical community. However, the Committee understood that most clinicians in the UK would use ipilimumab as a second-line treatment in line with its UK marketing authorisation. See FAD section 4.3.</p> <p>Comment noted. The decision whether to initiate or continue ipilimumab treatment is one that should be made by the treating physician together with the patient.</p>
<p>British Association of Dermatologists</p>	<p>The British Association of Dermatologists' Skin Cancer sub-committee supports the decision by NICE not to recommend ipilimumab at this point for the treatment of patients with previously treated advanced (unresectable or metastatic) malignant melanoma.</p> <p>The committee acknowledges that ipilimumab shows some potential to improve the median survival of patients with advanced melanoma and feels that the technology had been fairly appraised. The committee accepts the following factors that may have contributed to the decision by NICE, despite the promising results of the MDX010-20 trial:</p> <ul style="list-style-type: none"> • the toxicity levels, adverse events (including deaths on treatment) and side effects • absence of patient characteristics or biomarkers • reported delayed response in patients • the high cost of the drug <p>The committee agrees that the drug requires further research to identify:</p> <ul style="list-style-type: none"> • the group of patients who will most benefit from it – identification of the small 	<p>Comments noted.</p>

	<ul style="list-style-type: none"> group • who have long-term benefit should form the basis for future reconsideration • the optimal dosage • any achievable reduction in adverse events and side-effects <p>The committee would like to echo the ACD and point out that this decision by NICE does not preclude patients from applying on an individual patient basis, at local level, for funding for the drug.</p> <p>Addressing the questions laid out in the ACD:</p> <ol style="list-style-type: none"> 1. Has all of the relevant evidence been taken into account? <ul style="list-style-type: none"> • The process by which NICE assesses potential improvements in healthcare is thorough, rigorous and evidence-based, with a complete review by experts of current evidence. 2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? <ul style="list-style-type: none"> • The detailed analysis appears balanced and the re-analysis of the manufacturers' data relating to QALYs appears reasonable. 3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? <ul style="list-style-type: none"> • While the current decision does not support the routine provision of ipilimumab for advanced melanoma, trials should be continued. If evidence emerges demonstrating significant benefit in the future, particularly to certain subcategories of people with melanoma, NICE will review their decision, as has been done before with other modalities. It is important that a) there is further study to clarify if there is a definable sub-group of patients who demonstrates much better outcomes with ipilimumab, and b) the NICE guidelines are promptly reviewed if such information is available. 4. Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? <ul style="list-style-type: none"> • The decision has no bearing on individual patient's gender, race, disability, age, sexual orientation, religion or belief. 	
<p>Skcin, Factor 50 and the Myfanwy Townsend Melanoma Research</p>	<p>About Skcin: National skin cancer charity Skcin (the Karen Clifford Skin Cancer Charity) was founded by Richard Clifford after his wife passed away on New Year's Eve 2005, after a courageous battle against skin cancer. Skcin campaigns to raise awareness of skin cancer, with the emphasis on sun safety education for behavioural change and skin cancer awareness resulting in early detection of the disease. The charity is also</p>	

	<p>passionate about improving patient care and access to treatment for all affected by skin cancer.</p> <p>About Factor50: Factor50 is a patient support group working with The Christie. It campaigns for greater awareness about the dangers of malignant melanoma, and also raises money to conduct research into malignant melanoma. It works closely with patients themselves, offering support and guidance to those coping with this aggressive and destructive cancer. Factor50 was formed following the realisation that there were very limited options for advanced melanoma patients other than standard treatments, which were clearly inadequate.</p> <p>About the Myfanwy Townsend Melanoma Research Fund: After Myfanwy Townsend died from melanoma on October 20th 1999, husband Harry and their three sons set up the Charity in her name to raise awareness, educate, publicise, make diagnosis more available (e.g. holding free Walk-In Mole Check Clinics, mobile displays etc.) and help to fund practical research to strive to find a cure. We also publicise nationally Melanoma Awareness Week annually in June.</p> <p>Consultation Response: Are the provisional recommendations sound and a suitable basis for guidance to the NHS? We would like to thank the NICE Appraisal Committee (Appraisal Committee A) for their report on Ipilimumab for previously treated advanced (unresectable or metastatic) malignant melanoma. All three of our organisations work closely with, and for, patients affected by this terrible and aggressive disease and are deeply passionate about any new treatment that comes to the market that may benefit patients with advanced melanoma. This is because we are acutely aware that there have been no new licensed treatments for this group of patients since the 1970s and many patients and clinicians tell us about their frustrations about the lack of treatment options available to them.</p> <p>The introduction of Ipilimumab is an exciting development and breakthrough in the market for patients with advanced melanoma. Therefore, we are extremely disappointed by the provisional decision from NICE to deny many patients across England and Wales access to this new and innovative treatment option, and we do not believe that the provisional recommendations are a sound and suitable basis for guidance to the NHS. We feel that this is a particularly short-sighted decision that the Cancer Drugs Fund in England, which currently allows patients access to this treatment in many areas across the country, is to come to an end by 2013.</p>	<p>Comment noted. The Committee acknowledged that few advances have been made in the treatment of advanced melanoma in approximately 30 years and ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need. See FAD sections 4.2.</p> <p>The Committee accepted that the supplementary advice for appraising a life-extending end-of-life treatment applies, and that the manufacturer's ICER of £42,200 per QALY gained was plausible. The Committee considered that the clinical benefit of ipilimumab had been fully captured in the QALY calculation. Nevertheless, it concluded that, with the patient access scheme applied to</p>
--	---	---

	<p>Our concern about this draft guidance is threefold. Firstly, the incidence of melanoma in the UK is rising and new evidence in the British Journal of Cancer suggests that incidence rates will rise even faster than any other cancer; secondly, we are also concerned because this drug fulfils a real unmet need and gap in the market; and finally, we are disappointed as we believe that this treatment is truly innovative and thus more weight needs to be added by the Committee to this element of the decision. We therefore believe it is imperative that NICE re-evaluates this decision and works with all parties involved to find a solution to ensure that patients will benefit from this new treatment for people with advanced melanoma.</p> <p>Rising incidence: The incidence of melanoma is rising significantly in the UK, and this trend is only set to continue. A recent study published in the British Journal of Cancer (October 2011) revealed that malignant melanoma had the largest projected rate of increase of the cancers studied. It showed that rates are set to rise by an estimated 52% over the next 20 years. The study projects the disease will become the fourth most common cancer in men and the fifth most common in women over the period. This is extremely concerning and we believe that is even more important that an expanding group of patients are able to access established and effective treatments for advanced melanoma in the coming years.</p> <p>We also believe that NICE has failed to apportion enough weight to the fact that this is a disease that affects the young as well as the old. The average age of diagnosis is 50 years and melanoma is the second most common cancer in the 15-34 age groups. Melanoma is an aggressive disease. We know from our experiences – both personally and professionally – the value of having extra months and years with loved ones. Any extension of life for these sufferers is invaluable, particularly given the aggressive nature of the disease with sometimes just months between diagnosis to death. It is therefore encouraging that, in trials, 44 – 46% of those given Ipilimumab were still alive after a year compared with 25% given other treatments. This disease disproportionately affects people of a working age and a number of these patients have young families. We urge NICE to look at the social value of the drug and add appropriate weight to this element of its decision.</p> <p>Unmet need: There has been no licensed treatment brought to the market for this patient group since the 1970's. Currently, the standard treatment of care is Dacarbazine and this provides limited treatment options for both clinicians and patients. We believe that Ipilimumab</p>	<p>the cost of ipilimumab, it had been demonstrated to be a cost-effective use of NHS resources for the treatment of advanced (unresectable or metastatic) malignant melanoma for people who have received prior therapy.. See FAD section 4.16 and 4.17.</p> <p>Comment noted. The Committee agrees that there is a significant unmet need for effective therapies for people with advanced melanoma. See FAD section 4.2.</p> <p>Comment noted. The Committee concluded that there is a significant unmet need for effective therapies for people with advanced melanoma. See FAD section 4.2.</p> <p>Comment noted. See response above.</p>
--	--	--

	<p>fulfils a real gap and unmet need. We are pleased to read that the Committee understands that Ipilimumab addresses a “significant unmet need for effective therapies in this patient population,” and we urge the Committee to add further weight to its consideration of the draft evidence by considering the lack of other treatment options that are available to patients with advanced melanoma.</p> <p>Innovation: We also believe that this treatment is innovative. We understand that Ipilimumab is a form of immunotherapy that works by encouraging the immune system to produce more cancer-killing cells, something that has not previously been available to patients before. We therefore believe that there is a real need to reconsider the clinical evidence and add further weight to the innovation behind Ipilimumab. This, combined with the fact this disease disproportionately affects young people, should be a key feature of discussion when the Appraisal Committee meets again to discuss this draft guidance on 16 November.</p> <p>Over the last 20 days, since the draft guidance was issued by NICE on 14 October, we have continued to work alongside and engage with our supporters about the negative draft guidance issued by the Appraisal Committee. Not only have patients been struck by the innovation behind this treatment but also by the cost. Whilst we feel that we cannot necessarily comment on the cost of Ipilimumab, we hope that the manufacturer, NICE and the Department of Health can work together to do all they can to ensure that the innovation behind this therapy is fully considered so this treatment is made available to these patients who need it the most.</p> <p>Reconsidering the decision: We urge that Appraisal Committee A take into consideration all representations it has received in the last 20 days as part of the consultation process. It is important that the jump in rising incidence is taken into account, as well as the unmet need in this disease area. We are extremely concerned that without a positive decision on Ipilimumab for previously treated advanced (unresectable or metastatic) malignant melanoma, patients will lose out on the chance of a lifeline to have extra months or even years with their loved ones. Many people have told us of their fears and hopes about this treatment being available on the NHS in England and Wales and we hope that the Committee recognise the serious ramifications for choice for patients – and indeed clinicians – if this treatment is not recommended.</p>	<p>Comment noted. The Committee accepted that ipilimumab represents a valuable new therapy and that the mechanism of action is novel. It acknowledged that few advances had been made in the treatment of advanced melanoma in recent years and ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need. The Committee considered that the clinical benefit of ipilimumab had been fully captured in the QALY calculation. Nevertheless, it concluded that, with the patient access scheme applied to the cost of ipilimumab, it had been demonstrated to be a cost-effective use of NHS resources for the treatment of advanced (unresectable or metastatic) malignant melanoma for people who have received prior therapy. See FAD section 4.17.</p>
<p>Factor 50</p>	<p>About Factor 50: Factor 50 is a patient support group working with The Christie Hospital in Manchester. We campaign for greater awareness of the dangers of malignant melanoma, and also</p>	<p>Comment noted.</p>

	<p>raise money to conduct research into the disease. We work closely with patients, offering support and guidance to those coping with this aggressive and destructive cancer. Factor 50 was formed following the realisation that there were very limited options for advanced melanoma patients other than standard treatments, which were clearly inadequate.</p> <p>Our response: We would firstly like to thank NICE for giving us the opportunity to respond to its Appraisal Consultation Document (ACD) on Ipilimumab as a treatment for advanced (unresectable or metastatic) melanoma. In particular we thank the Committee for its recognition that Ipilimumab “may represent a potentially valuable new therapy and that the mechanism of action was novel”. However, it is for this very reason that we are particularly disappointed by the Appraisal Committee’s decision, which we believe is misguided and which we would urge you to reconsider and overturn. As a patient support group we are acutely aware of the impact that this negative decision will have on the lives of the patients and families we help. We feel this decision is particularly short-sighted given the fact that the sharp rise in the incidence of melanoma is set to continue in the coming years and that the Cancer Drugs Fund - currently the only hope for advanced melanoma patients - is set to end in just two years. We are gravely concerned for the future of melanoma patients and also for the doctors who have to treat these patients. They are unable to offer their patients anything other than standard treatments, such treatments that are widely acknowledged as ineffective. We feel it is an unfair and unnecessary burden on our doctors.</p> <p>Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Factor50 does not believe that the provisional recommendations are either sound or a suitable basis for guidance to the NHS. NICE has acknowledged that this drug represents a real step change in the treatment of patients with advanced melanoma since it is the first licensed treatment in over 30 years to actually extend life expectancy in this area. The ACD recognised that Ipilimumab addresses a “significant unmet need for effective therapies in this patient population”, as existing NHS treatments for advanced melanoma are outdated and ineffective. In view of the recognition of the innovation in cancer treatment that Ipilimumab offers, Factor50 feels the Committee’s decision is extremely disappointing and comes as a devastating blow to patients in England and Wales.</p> <p>Costs and benefits Factor50 accepts that Ipilimumab is a high-cost treatment. However, we strongly believe</p>	<p>Comment noted. The Committee acknowledged that few advances have been made in the treatment of advanced melanoma in approximately 30 years and ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need. The Committee considered that the clinical benefit of ipilimumab had been fully captured in the QALY calculation. Nevertheless, it concluded that, with the patient access scheme applied to the cost of ipilimumab, it had been demonstrated to be a cost-effective use of NHS resources for the treatment of advanced (unresectable or metastatic) malignant melanoma for people who have received prior therapy. See FAD section 4.17.</p> <p>Comment noted. See response above.</p>
--	--	--

	<p>that it is a high <i>value</i> treatment that offers genuine survival benefits to patients and hope in a disease area which has seen no such breakthrough for over 30 years.</p> <p>Factor50 acknowledges that unfortunately Ipilimumab cannot be said to provide a cure for patients with advanced melanoma. However, where patients can currently expect to survive for between 6 and 9 months after being diagnosed with this aggressive disease, trials showed that 46% of patients were alive after a year of treatment with Ipilimumab. Furthermore, as a result of our work with patients, at Factor50 we know there are many examples of patients that have achieved significantly longer-term survival benefits through treatment with the drug. We would urge the Committee to remember the evidence it heard directly in September from Richard Jackson, a melanoma patient who, over three years on from completing his course of treatment with Ipilimumab, has been able to maintain a normal family and working life. By his own admission Richard suffered severe side effects but has stated that for the glimmer of hope that this drug gave to him, he was ready to accept any risks and indeed, patients who do not receive any treatment are likely to suffer serious effects in any event.</p> <p>We welcome the Committee's assessment that Ipilimumab is a life-extending, end-of-life treatment and that the trial evidence presented for consideration was robust. We call on the Committee to recognise just how priceless any significant extension of life is for patients suffering with this aggressive disease. At Factor50, we regularly see the devastating impact that a diagnosis of advanced melanoma has, particular when - as is sadly so often the case - it is young patients with young families who receive that diagnosis. The extra months and as Richard's case showed, years, that can be provided by a treatment such as Ipilimumab not only gives patients the opportunity to arrange their affairs but, crucially, can mean the difference between seeing their children's first day at school or first birthday. As Joanne, a melanoma patient aged just 30, told us recently: "I need to live. I <i>have</i> to live for my children. I just want a few more years so that my boys will remember me."</p> <p>The average age of diagnosis for this disease is just 50 and treatments like Ipilimumab can offer a greater amount of time to these patients' family members to come to terms with a diagnosis. This not only benefits those individuals but also society as a whole. NICE decisions on treatments for more long-term degenerative illnesses have take account of the cost to society of the emotional and economic toll taken on family members acting as carers for patients suffering with these diseases. Yet in its decision on Ipilimumab we believe the Committee has failed to take into account the impacts felt across the same areas by individuals struggling to deal with the quick and unexpected loss of a loved one as a result of a disease such as melanoma.</p>	<p>Comments noted. See above.</p>
--	--	-----------------------------------

	<p>Innovation</p> <p>We are also concerned that NICE has failed to appreciate the long-term implications of refusing to recommend Ipilimumab at a time when the incidence of melanoma in the UK is rising alarmingly, a trend that is expected to continue and even accelerate over the next 20 years.</p> <p>A study published this month in the British Journal of Cancer, <i>Cancer in the United Kingdom: projections to the year 2030</i>, claims that though overall cancer rates are projected to be stable over the next 20 years, melanoma incidence is set to rise by 52% in both men and women by 2030. The study projects the disease will become the fourth most common cancer in men and the fifth most common in women over the period.</p> <p>In the light of this information, the Chief Executive of Cancer Research UK, Harpal Kumar, has stated: “As we develop ever more sophisticated ways to detect and treat cancer successfully, health planners must deploy resources more effectively to enable all patients to benefit from the latest developments and cutting edge treatments.”</p> <p>Factor50 believes that the development of Ipilimumab represents an opportunity for NICE and the NHS to make these words a reality. Factor50 is committed to improving awareness of the dangers of melanoma and improving prevention and early diagnosis but it is equally vital to take action on treatment now if we are to improve patient outcomes from a disease whose burden on the NHS will only rise in the coming years. The arrival of Ipilimumab is the first time we have been able to offer real hope to patients. Furthermore, through its novel process of ‘immunopotentialiation’, Ipilimumab could provide a basis for the NHS to use future new effective treatments alone or in combination.</p> <p>Are there any aspects of the recommendations that need particular consideration to ensure NICE avoids unlawful discrimination against any age group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?</p> <p>Factor50 believes that the Committee has failed to fully acknowledge in its report the disproportionate incidence of advanced melanoma in patients aged between 15 and 34 years, a demographic in which it is the second most common cancer in the UK. We believe that a more accurate reflection of the value this drug could bring to the NHS would be achieved by giving a more appropriate weight to this factor within NICE’s decision-making process.</p> <p>Factor50 notes with interest the words of NICE Chief Executive, Sir Andrew Dillon, who</p>	<p>Comment noted. The Committee acknowledged that few advances have been made in the treatment of advanced melanoma in approximately 30 years and ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need. The Committee considered that the clinical benefit of ipilimumab had been fully captured in the QALY calculation. Nevertheless, it concluded that, with the patient access scheme applied to the cost of ipilimumab, it had been demonstrated to be a cost-effective use of NHS resources for the treatment of advanced (unresectable or metastatic) malignant melanoma for people who have received prior therapy. See FAD section 4.17.</p> <p>Comment noted..</p>
--	--	---

	<p>said in announcing NICE's decision in 2010 not to recommend the bone cancer drug mifamurtide: "We understand a diagnosis of cancer is very distressing, and especially so when children and young adults are affected. With this in mind, we are disappointed that the evidence for mifamurtide is not stronger. It is important to remember, though, that other, effective treatments are available in the NHS for treating this condition."</p> <p>This may be true when assessing bone cancer treatment, but unfortunately, the same cannot be said in this case. There simply are no licensed effective treatments in advanced melanoma, a disease which also affects young adults and young people who should have their whole lives ahead of them, and yet NICE has come to the same decision.</p> <p>Each death from advanced melanoma results in an average of 22 years of life lost. It is a disease which often affects people in the prime of their life. In Ipilimumab, patients have been offered for the first time the hope and expectation of a minimum of several additional extra months spent with their loved ones. Factor50 urge NICE to think again before removing that hope.</p> <p>In closing, we believe it would be of great benefit if NICE and the manufacturer were able to work together to ensure that the future of melanoma treatment does not grind to a halt.</p>	
<p>British Association Skin Cancer Specialist Nurses</p>	<p><i>Format of feedback:</i> <i>The BASCSN's overall views following reviewing written evidence.</i> <i>Individual evidence / experience in the care of people affected by this stage of disease.</i> <i>Individual evidence / experience in the care of people who have received Ipilimumab as part of their treatment.</i></p> <p>"NICE have cited a very small gain in overall survival, there are many cases of patients living successfully for up to 33 months following the treatment (the document mentions some surviving up to 9 years) and this is a substantial improvement in both quality of life and survival.</p> <p>It is stated in the document that "approx. 30% of people will experience increased survival with this drug and 10% may have long term benefits" – this should not be ignored by NICE. The NICE committee also accepted that "Ipilimumab met the criteria for being a life-extending, end of life treatment and that the trial evidence was robust"</p> <p>The fact that there has not been any other activity or end of life treatment available for stage 4 melanoma patients over the last 30 years means we need to push for something</p>	<p>Comment noted. The Committee acknowledged that few advances have been made in the treatment of advanced melanoma in approximately 30 years and ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need The Committee considered that the clinical benefit of ipilimumab had been fully captured in the QALY calculation. Nevertheless, it concluded that, with the patient access scheme applied to the cost of ipilimumab, it had been demonstrated to be a cost-effective use of</p>

	<p>to be available for this group of patients”.</p> <p>CNS experience <i>experience in the care of people who have received Ipilimumab as part of their treatment:</i></p> <p>“As health care professionals gain more experience of Ipilimumab. So the adverse event profile improves. With robust treatment algorithms and early intervention most toxicities, are manageable with minimal impact on quality of life. I would say that most of the patients that we treated on the expanded access program tolerated the treatment well”.</p> <p>“From a health care professional's point of view, I had several patients on the early Ipilimumab studies, many of whom gained more time, and good palliation following the treatment. <u>Some of them are still alive now several years on.</u> We are looking at ways to reduce the cost by treating patients on the same day so that we can ‘vial share’ to try to cut down the cost”.</p> <p>“All I can add is that from personal experience of caring for patients with metastatic melanoma who have been treated with Ipilimumab, some have achieved a prolonged response of longer than the quoted median overall survival gain of 3.7 months <u>and one patient with a young family continues to benefit, achieving prolonged response which has allowed him to continue to work and support his wife and child”.</u></p> <p>“Ipilimumab is a step change, whose side effects can be effectively managed, and which does offer significant benefit for this small patient group”.</p> <p>“It seems that at the heart of the NICE Appraisal Consultation document their decision not to recommend Ipilimumab is that despite it representing a significant innovation in the treatment of metastatic melanoma that extends life, the QALY gains are such that they don't consider it to be a cost-effective use of NHS resources”.</p> <p>“We shall still not get away from post code lottery”.</p> <p>Conclusion:</p> <p>The BASCSN's <i>feels that</i> Ipilimumab represents a step change in treatment for advanced melanoma. Has this is the first new treatment available in 30 years. That may offer significant palliation and possible survival gain for people with advance, form of unresectable disease that has progressed after first-line therapy.</p>	<p>NHS resources for the treatment of advanced (unresectable or metastatic) malignant melanoma for people who have received prior therapy. See FAD section 4.17.</p> <p>Comments noted. The Committee concluded that although the adverse reactions and mortality associated with ipilimumab seen in the MDX010-20 trial were considerable, most adverse effects, including those that led to hospital admissions were manageable and would be managed more effectively as clinicians become familiar with ipilimumab's toxicity profile. It also concluded that people may be willing to tolerate significant toxicity if there were potential survival benefits. See FAD section 4.5.</p> <p>Comments noted. See responses above.</p>
--	--	---

	<p>NICE acknowledged that their understanding was that most clinicians in the UK would use Ipilimumab.</p> <p>Additionally, the patient expert described succinctly the reality of late stage disease with regard to the present position re: the patients / families poor quality of life & the financial impact on individual families & society.</p> <p>Considering what has already been pointed out that, Malignant Melanoma has a disproportionate number of young adults & Young adults with young families, for an adult cancer. The impact of survival would be significant regarding return to: normal life, other activities & work.</p> <p>Therefore, we feel there is evidence to say that Ipilimumab will be the first treatment to address & some way improve:</p> <ul style="list-style-type: none"> ➤ Quality of life for patients and their families at this stage of decease. <ul style="list-style-type: none"> ○ Financial impact on patients and their families at this stage of decease. ➤ Financial impact on society at this stage of decease. 	
<p>Royal College of Nursing</p>	<p>The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the four questions on which comments were requested is set out below:</p> <p>i) Has the relevant evidence has been taken into account? There are no comments to add on the evidence considered for this appraisal.</p> <p>ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate? We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by people with melanoma. The preliminary views on resource impact and implications should be in line with established standard clinical practice.</p> <p>iii) Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add.</p>	<p>Comment noted.</p> <p>Comment noted.</p> <p>Comment noted. No action required.</p>

	<p>The RCN would welcome guidance to the NHS on the use of this health technology.</p> <p>iv) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? Are there any equality related issues that need special consideration that are not covered in the ACD?</p> <p>We are not aware of any specific issue at this stage. However, it would be helpful to know if NICE will publish the equality analysis for this appraisal. We would also ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.</p>	<p>Comment noted. It is NICE's policy to publish an equality impact assessment form at each stage of the appraisal process. This can be found on the NICE website. No equality issues were raised during the course of this appraisal which are likely to lead to unequal access to treatment for some patients.</p>
--	--	--

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
<p>Clinical oncologist on behalf of the Skin Care Campaign and Factor 50</p>	<p>3.12 Vial sharing is a real option for larger centres and one we have previously discussed in Manchester. It is not without logistic challenges but our initial thoughts were that potential savings are so great, one could even justify supporting part of the salary of an administrative assistant to facilitate scheduling of patients.</p> <p>4.4 The toxicity associated with Ipilimumab is real and needs to be managed carefully by experienced teams. However the majority of patients do not get severe adverse events and the toxicity rates (not types) are comparable with those of other accepted treatments e.g. taxane or anthracycline-based therapy for breast cancer.</p> <p>4.3.1 Number of treatments administered. I feel the advice in the UK Marketing Authorisation for Yervoy that the majority of patients should receive four cycles of treatment is unhelpful. The MDX020 Study was a rigorously conducted clinical trial in selected centres. In this setting, 35-40% of patients did not receive four cycles of Ipilimumab, primarily due to disease progression. I expect that in main stream practice, the number of patients completing 4 cycles will be lower than in the MDX020 Study. The advice that opinion leaders are currently giving to clinicians internationally is to use 'clinical common sense' in deciding whether patients should continue on treatment.</p>	<p>Comment noted. The manufacturer's summary of product characteristics for ipilimumab does not recommend vial sharing. However, based on evidence presented by the manufacturer and the opinion of a clinical specialist at the committee meeting, the Committee concluded that although vial sharing may lead to cost savings in some specialist centres, this could be associated with additional administrative costs and logistic difficulties, and therefore overall the impact on the cost-effectiveness of ipilimumab was likely to be minimal. See FAD section 4.11.</p> <p>Comments noted. The Committee concluded that although the adverse reactions and mortality associated with ipilimumab seen in the MDX010-20 trial were considerable, most adverse effects, including those that led to hospital admissions, were manageable and would be managed more effectively as clinicians become familiar with ipilimumab's toxicity profile. It also concluded that people may be willing to tolerate significant toxicity if there were potential survival benefits. See FAD section 4.5.</p> <p>Comment noted. The decision whether to initiate or continue ipilimumab treatment is one that should be made by the treating physician together with the patient. The Committee also considered the manufacturer's revised analyses which were based on the assumption that all patients received 3.3 doses of ipilimumab at 3 mg/kg body weight, corresponding with the average number of doses used in MDX010-20. A description of the manufacturer's revised analysis incorporating the patient access scheme is in section 3.16 of the FAD.</p>

Comments received from commentators

Commentator	Comment	Response
<p>Members of Parliament (Parliamentary report)</p>	<p>A report was submitted to NICE which recorded outcomes from a parliamentary meeting attended by 6 MPs, 5 patient representatives, 4 patients, 5 patient organisations, 2 oncologists and 2 professional groups among others.</p> <p>Concerns focused on:</p> <ul style="list-style-type: none"> • Efficacy <ul style="list-style-type: none"> • Examples were given where patients had received ipilimumab and were still alive a number of years later • Social value of people being able to continue working and engaging in family life after ipilimumab • Unmet need <ul style="list-style-type: none"> • No new treatments for advanced melanoma in over 30 years • Innovation <ul style="list-style-type: none"> • NICE should reconsider the ACD decision • Rising incidence <ul style="list-style-type: none"> • Estimated that melanoma will have largest rate of increase of any cancer over the next 20 years • A young person's disease <ul style="list-style-type: none"> • Melanoma is the 2nd most common form of cancer in people ages 15-34 years • Average age of diagnosis is 50 years • Survival rates are concerning • "This is actually a young person's cancer. There are so many people. I mean, I am 30. There are young children. My youngest... this drug could be the difference ... between having memories of me. Without being morbid and trying to be emotional, but I am just one person, and there are thousands of other people who are the same." 	<p>Comment noted. The Committee heard from the clinical specialists that people treated with ipilimumab will have some survival benefit, but only 10% of people may experience long-term benefits. See FAD section 4.3.</p> <p>Comment noted. The Committee acknowledged that there is a significant unmet need for effective therapies for melanoma.</p> <p>Comment noted. The Committee has taken all the views offered during consultation on the appraisal consultation document into account during the appraisal and when making their final recommendation for ipilimumab.</p> <p>Comments noted.</p>

Summary of key themes raised in the 108 comments received from members of the public including patients, family and friends of patients and NHS professionals

Topic	Key theme	Response
Disagreement with provisional recommendation in draft guidance.	All comments disagreed with the provisional recommendation in the appraisal consultation document.	The Committee considered all the comments received through the consultation process.
Impact of melanoma on patients', carers' and families' lives	<p>“I am a 71 year old man with stage 4 melanoma. I had four ipilimumab infusions (3 mg/kg) in April-June of 2010 in the Expanded Use setting. All my tumors (over a dozen) either shrank or disappeared within 20 weeks, and the remainder have remained quiescent in the intervening 16 months, and my health is very good. Since my treatment, I have become a patient advocate for the FDA and for a melanoma support organization (the Melanoma International Foundation). “</p> <p>“Personally I am 41, have two young kids and are a stage IV patient since Nov 2009, if it was not for ipilimumab I would probably not be here today. I have worked and contributed to society a 100% all through my illness.”</p> <p>“I am a 62 year old teacher with metastatic melanoma. Just now I am well.I play football and golf, play with my grandchildren and am still working. I have a wonderful life and the thought of my illness worsening is truly terrifying for myself and my family. Without ipilimumab there is no hope. There is no possibility of growing old and watching my grandchildren grow up. As a 40 year old with 3 small children I am not ready to give up on my life and thanks to ipilimumab surviving is something that I can aim for.”</p> <p>“NICE assessment focuses on patients that have a visible response on the disease and seems to ignore all those who achieve stable disease.I would be very happy with SD since I am currently asymptomatic however I know that without Yervoy I will eventually become symptomatic thus stopping me from being a providing father and husband.I am not unique in this. This is important because of the new promising drugs in the pipeline and moreover combination of drugs will yield even better response rates so buying time here is not in the traditional sense but may well make the difference between life and death.”</p>	The Committee considered all the comments submitted through the web consultation process.

Topic	Key theme	Response
	<p>“My husband has just been diagnosed with advanced melanoma, his is his only hope for an extended life. He has worked his whole life has never been off sick and when he needs help he is being let down. His life will end at 59 years of age because there is nothing else that can give him hope.”</p> <p>“This issue is extremely important to me because my relative is only 30 years old. She has advanced melanoma. She has 4 boys, three of whom are under 5 years old. It is devastating to the whole family and it is so vitally important that she manages with the help of this treatment to have as much time as possible with her 4 boys. She is so young. Please help her. It is devastating that many patients have been left with so little hope.”</p>	
Cost of ipilimumab	Several commentators believe the provisional recommendation in the appraisal consultation document was largely decided on the cost of ipilimumab alone. Commentators emphasised that cost should not be an issue when it comes to funding decisions for ipilimumab.	NICE appraises the clinical and cost effectiveness of technologies. For both legal and bioethical reasons, those undertaking technology appraisals must take account of economic considerations (Social Value Judgements – Principles for the Development of NICE Guidance; principle 5).
Vial sharing	Some commentators suggested that ways of reducing vial wastage should be considered.	The Committee considered additional evidence provided by the manufacturer in its response to the ACD regarding vial sharing but concluded that while vial sharing might lead to cost savings in some large specialist centres, this could be associated with additional administrative costs and logistic difficulties, therefore overall the impact of vial sharing on the cost effectiveness of ipilimumab was likely to be minimal. See FAD section 4.11.
NHS price of ipilimumab	Several patients and NHS Professionals query whether the price of ipilimumab could be negotiated, as they believe the price is too high.	It is not within NICE’s remit to negotiate the price of technologies with the manufacturers. The price paid for treatments provided by the NHS are negotiated by the Department of Health with the manufacturers of those treatments.
Adverse effects of treatment	Several patient commentators who have received ipilimumab through the compassionate use program or in clinical trials stated that they had no side effects or few side effects, all which were manageable.	Comment noted. The Committee noted that although the adverse reactions and mortality associated with ipilimumab seen in the relevant trial were considerable, most adverse reactions were manageable and would be managed more effectively as clinicians become familiar with ipilimumab’s toxicity profile. It also concluded that people may be willing to tolerate significant toxicity if there were potential survival benefits. See FAD section 4.5.
Subgroups	Some commentators pointed out that there is a subgroup of people who	Comment noted. The Committee noted that no patient

Topic	Key theme	Response
	benefit from ipilimumab and suggested that predictive tests should be developed, which would require that ipilimumab continue to be investigated and used. With widespread use more data will be available to derive those who derive greater or lesser benefit.	characteristics or biomarkers have been identified that can identify in advance the minority of people most likely to benefit from receiving ipilimumab. See FAD section 6.1.
Clinical issues	One commentator indicated that ipilimumab is being considered entirely out of context of the recent development in melanoma therapy where the combination of conventional, immuno- and targeted therapy promise for the first time a long-term perspective for stage IV melanoma patients.	Comment noted. Ipilimumab has UK marketing authorisation for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy. Should other melanoma therapies be licensed in future, then NICE will consider them at that time.
Clinical issues	Some commentators noted that there is no mention of re-inductions with ipilimumab in the ACD and the fact that the 10mg/kg + re-inductions showed a long time survival rate of 10% higher than that for 3mg/kg + re-inductions.	Comment noted. Ipilimumab has UK marketing authorisation for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy at a dose of 3 mg/kg body weight administered by IV infusion, repeated every 3 weeks for a total of 4 doses. NICE can only provide guidance in line with the current marketing authorisation. Should the manufacturer seek a license extension to include use of the 10mg/kg dose, NICE would consider whether it should review the current guidance or issue new guidance in accordance with the licence extension.
Review date	Most commentators believe the proposed review date 2015 is too late. Some suggested 2012 as best review date.	Comment noted. NICE guidance is only reviewed if sufficient new evidence becomes available which is likely to impact on the existing recommendations.
Population	Commentators emphasised the disproportionate numbers of young people with melanoma.	Comment noted. The Committee recognised that malignant melanoma can occur in young adults; the average age of diagnosis in the UK is approximately 60 years. See FAD sections 4.2.
Economic analysis	Several commentators noted that the hope given to people who receive ipilimumab whose lives may not be prolonged by it, is a benefit in itself and that it has not been captured in the QALY.	Comment noted.
Content of ACD	Several commentators considered that the ACD was too technical and that it might put people off from responding	Comment noted. The FAD has been amended to ensure a balanced view of the clinical and cost-effectiveness evidence and the patient perspective of the disease is presented.