NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ipilimumab for previously untreated 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 are also have 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

Bristol-Myers Squibb Pharmaceuticals Limited	Bristol-Myers Squibb (BMS) welcome the opportunity to comment on the Appraisal Consultation Document (ACD) for the ongoing single technology appraisal (STA) for ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma [ID74]. The ACD recommends ipilimumab for this indication *"only in the context of research as part of a clinical study".*
	We are disappointed with the Committee's decision which will restrict NHS patients' access to a breakthrough treatment in a life-limiting, incurable condition.
	We acknowledge that the Appraisal Committee (AC) understood the European Medicines Agency's (EMA) considerations when extending the marketing authorisation for 3mg/kg ipilimumab to first-line, and that the AC concluded that there is an unmet need for effective therapies in this patient population. The AC also recognised that ipilimumab would be valuable as a first-line treatment option for patients. Given the high unmet medical need in this patient group we feel it is important that a pragmatic approach is taken regarding the uncertainty around the cost-effectiveness results.
	You may be aware that, in January 2014, the National Cancer Drugs Fund (NCDF) panel *"concluded that the best option for patients, NHSE and the CDF would be to seek baseline commissioning for 1st line ipilimumab in advanced melanoma as the funding was already in place [for second-line] and the impact [of extending the treatment recommendation to first-line patients] was considered to be cost neutral."* [14]
	Upon review of the ACD, BMS does not believe that all the relevant evidence has been taken into account by the ERG and then by the AC:
	• We have presented clinical evidence for 3mg/kg ipilimumab monotherapy from two robust observational studies in previously untreated patients and from a pooled analysis of chemo-therapy-naïve patients which compared favourably to dacarbazine (DTIC) in first-line – despite inclusion of patients with poor prognostic factors (e.g. brain metastases) in both observational studies.
	  ○ We emphasised the importance of the above data sets for the licence extension by the EMA - which testifies to the increasing acceptance of the value of real-world data in the scientific community. However, disappointingly, the NICE Economic Review Group (ERG) ruled "it was not as robust as the RCT evidence and the results were similar, therefore, we [the ERG] did not consider that these studies provided additional relevant data."
	  ○ We feel that because of this ERG judgment, the evidence may not have been considered adequately, in particular:
		Comments noted. The Committee acknowledged that some of the studies

Consultee	Comment	Response
	▪ the robustness of long-term data in these studies; ▪ the importance of long-term survival as a benefit to patients with advanced melanoma (given the often terminal nature of this disease); ▪ the existence of historical data from numerous sources which provide evidence to support the long-term benefits of ipilimumab; ▪ the scientific basis on which to extrapolate benefits in previously treated patients (second-line) to those patients with untreated advanced melanoma (first-line).	(MDX010-20 and CA184-024) had long term data, with no crossover and with approximately 10% more patients still alive at 5 years compared with the comparator treatment. See FAD sections 4.2 and 4.3.
	• We asked the Committee to consider the similarity between first- and second-line melanoma patients. For second-line treatment of advanced melanoma, ipilimumab was previously deemed cost-effective by NICE and approved. Given the similarity clinically of first- and second-line patients (separated from each other often by only a few weeks of DTIC chemotherapy, which is generally accepted as being ineffective) we once again ask the Committee to take the relevant evidence from the second-line appraisal (TA268) into consideration for this appraisal.	Comment noted. The Committee considered that the trial data used in the previous appraisal and the updated analysis provided by BMS provided additional relevant evidence for this appraisal. See FAD section 4.2.
	• There is no rationale as to why the efficacy (measured as overall survival) of 3mg/kg ipilimumab in the first-line setting would be inferior to 3mg/kg ipilimumab in the second-line setting (This was confirmed in the EMA's European Public Assessment Report (EPAR): "From a pharmacological or biological point of view it is not rational to suspect a different activity for ipilimumab treatment in the first or the next line setting, because the mechanism of action of ipilimumab is general stimulation of the immune-system, which is rather aspecific.").	Comments noted. The Committee heard from the clinical specialists that treatments would usually be more effective rather than less effective if used earlier in therapy, and that there was no biologically plausible reason for ipilimumab monotherapy at a dose of 3 mg/kg to be less effective when used first-line rather than second-line. See FAD section 4.2.
	• The clinical evidence given to the Committee was very clear in its belief that the two patient populations (first- and second-line) are essentially the same. Furthermore, the earlier the patients initiate treatment with ipilimumab within the path of their disease progression, the more likely it is they will be able to benefit from the entire course of ipilimumab (4 doses) which, in turn, can improve their survival prospects. So the longer the patients are delayed from accessing ipilimumab, whilst using DTIC, where it is known that there is no overall survival (OS) benefit, the more their chance of successful treatment diminishes. This is surely an illogical and undesirable outcome. • We have submitted comparative efficacy data of ipilimumab in previously untreated patients, which proved a significant difference in OS over DTIC. In the EPAR it is acknowledged that "the median OS observed with ipilimumab is consistently at least >2 months longer [vs. DTIC] regardless of the line of therapy used as shown by the results from the pivotal and the supportive studies."	

Consultee	Comment	Response
	• We presented trial data for ipilimumab 3mg/kg showing that more than one in five (20%) of melanoma patients survive long-term (>2 years). • Despite the wealth of clinical evidence presented, the Committee concluded that "although it was possible that the ICERs may be in a range considered to be cost effective [...] it was not possible to come to a conclusion without further evidence on the clinical effectiveness of ipilimumab 3mg/kg alone in the first-line setting." • A Phase 3 trial to provide "exact" comparative clinical efficacy results for ipilimumab 3mg/kg in previously untreated patients is lacking. However, based on the arguments above, the most, and indeed a highly plausible position is that 3mg/kg ipilimumab is a cost-effective treatment in first-line. • As stated in the EPAR, "OS analyses from 3 mg/kg ipilimumab monotherapy (pooled) in previously untreated advanced melanoma demonstrate that 3 mg/kg ipilimumab monotherapy has at least similar OS (median, 1 year and 2 year) to the ipilimumab treated patients in the two randomized Phase 3 studies. Furthermore, in previously untreated patients, the median and long-term OS from 3 mg/kg ipilimumab monotherapy and 10 mg/kg ipilimumab + DTIC are similar and both are numerically higher than DTIC alone (median OS = 9.07 months; 1 yr: 36%, 2 yr: 18%)." • We therefore believe that the Committee's summaries of clinical- and cost-effectiveness do not represent a reasonable and logical interpretation of the evidence. In order to provide the Committee with increased certainty in the incremental cost-effectiveness ratios (ICERs), additional cost-effectiveness analyses have been conducted for this response, using extrapolated data from previously treated patients with the 3mg/kg dose. Since new evidence, relevant to the decision problem and addressing areas of uncertainty, has become available since date of submission (October 2013), these additional data have been provided within this response, with the pre-approval of NICE. In particular, this refers to an update of the follow-up data from the vemurafenib trial (BRIM-3) and independent publications relating to treatment sequencing of ipilimumab and vemurafenib. Our response to the ACD is split into 5 sections: (not reproduced here: *for the full manufacturer's response to the ACD, please refer to the Evaluation report)*	Comment noted. The Committee has considered the manufacturer's alternative approach to modelling and all of the revised scenario analyses presented by the manufacturer in response to consultation on the appraisal consultation document. See FAD section 4.8.

Consultee	Comment	Response
British Association of Dermatologists Therapy & Guidelines sub-committee (BAD)	As the effect of ipilimumab is slow in onset it is logical not to wait until patients have reached the most desperate stages of advanced disease before commencing therapy. For this reason, we believe that the opportunity to use ipilimumab 3mg/Kg as a first line treatment should be offered rather than restricting its availability to use as a second line treatment in patients who have failed dacarbazine treatment which in any event, appears to have only a borderline therapeutic effect. The rationale for the proposed policy of limiting treatment in this way is very difficult for patients to understand or for physicians to explain.	Comments noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document. Ipilimumab is recommended as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma. See FAD section 1.1.
Joint reply by the National Cancer Research Institute (NCRI), Royal College of Physicians (RCP), Royal College of Radiologists (RCR), Association of Cancer Physicians (ACP), Joint Collegiate Council for Oncology (JCCO) and Melanoma Focus	We write on behalf of the NCRI/RCP/RCR/ACP/JCCO, who work together to produce joint responses to NICE oncological consultations, and Melanoma Focus. We are grateful for the opportunity to comment on this ACD and wish to submit the following joint comments. NICE approved ipilimumab for the treatment of metastatic melanoma patients who have received prior therapy in December 2012 (TA 268). Since then the management of patients with advanced melanoma has changed significantly. There is now strong evidence that a significant proportion of patients treated with ipilimumab go on to be long term survivors. A benefit is seen for all patient groups treated in a series of clinical trials (first and subsequent line, 3mg/kg and 10mg/kg dosing schedules), with a clear plateau on the survival curve around three years, which is maintained up to at least five years. Whilst there remains no robust predictive biomarker, there is increasing evidence that patients are more likely to benefit from ipilimumab treatment if they have small volume disease, normal LDH level and do not require steroids for control of symptoms. Patients, clinicians and regulators have recognised this potential for long term survival in a proportion of patients. UK melanoma specialists have changed the recommendations for follow-up of high risk patients to reflect this. We now routinely image high risk patients regularly in order to detect recurrence earlier and maximize the benefit of early immunotherapy. The current raft of registration trials with new immunotherapy agents use ipilimumab 3mg/kg as the comparator in the first line setting: this is now an internationally accepted standard of care. Ipilimumab has been licensed by the FDA and the EMA in the first line setting. The direct evidence for first line ipilimumab 3mg/kg as a single agent is weak, but what evidence there is all points to it being superior to DTIC and not inferior to its use as second line treatment. There is no precedent for second line therapy to be more effective than the same treatment in the first line that is not explained by selection bias.	Comment noted. The Committee acknowledged that some of the studies had long term data, with no crossover and with approximately an additional 10% of patients surviving for the 5 year duration of the trials compared with the comparators. See FAD sections 4.2 and 4.3.

Consultee	Comment	Response
	There will never be a study comparing DTIC with ipilimumab. The only endpoint that could be used would be progression free survival (PFS), and this is not a surrogate of efficacy for immunotherapy. Overall, survival would be confounded by crossover and subsequent treatment.	Comment noted
	It is difficult to calculate the change in ICER in moving from the second- to first-line, but this is likely to be minimal. At present, clinicians routinely offer the minimum amount of chemotherapy needed to justify switching to ipilimumab, usually 1-2 cycles, so this is closer to the use of ipilimumab up front than the initial MDX-010 study, in which patients were heavily pretreated. The number of patients treated may be slightly higher, but more patients are likely to benefit, and there will be savings in terms of chemotherapy costs, imaging, etc.	Comment noted. The Committee heard from the clinical specialists that current practice included administering dacarbazine, usually with early scanning after 1 to 3 courses, before moving to second-line ipilimumab. See FAD section 4.1.
	The UK melanoma community is a major contributor to clinical trials and this has a positive benefit in potential drug cost savings. In the last year, we conservatively estimate that we have saved more than £7 million on ipilimumab expenditure through enrolling 179 patients in clinical trials who would otherwise have received ipilimumab as a standard of care. We are very aware of the impact of these high cost, but effective, treatments on the NHS budget. We also see an opportunity to collect robust prospective audit data on use, efficacy and health economics.	
	It is our strong recommendation that ipilimumab be made available as first line treatment for eligible patients with metastatic melanoma.	Comment noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document. Ipilimumab is recommended as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma (see FAD sections 1.1 and 4.13).
OcuMelUK	Further to our recent appraisal of the consultation document for the above guideline, please ask the committee to consider the following points from OcuMel UK pertaining to patients with ocular melanoma. **Existing guidelines for ocular melanoma** It has been our understanding that NICE will not be producing guidance on ocular melanoma as it is too rare (6/7 per million). Therefore we have been working with a group of experts since April 2012 to create UK guidelines for ocular melanoma. The chair of the group is [redacted]	Comment noted

Consultee	Comment	Response
	[redacted] The process has been funded by Melanoma Focus and the first draft is due to be sent for NICE accreditation on 1st April 2014. **Ocular melanoma is not included in the above NICE guideline** OcuMel UK would like the committee to note that ocular melanoma is an orphan disease with no recognised treatment. It is genetically different to cutaneous melanoma and therefore it is extremely unlikely that a UK ocular melanoma patient will have access to an immunotherapy trial in the near future. We understand that you were not able to include ocular melanoma patients in your guidance as you have to align with the evidence that was presented to you by the manufacturer. However, if you do not mention ocular melanoma at all, it will have a significant impact on ocular melanoma patients. It is very important to OcuMel UK that you are aware of this. If you do not make it explicitly clear that you have not included ocular melanoma patients, a medical oncologist seeing only one or two ocular melanoma patients a year will simply treat them in the same way as he does his cutaneous patients. If you do not make a distinction, the physicians will not make a distinction. However, the drugs company obviously did make a distinction by excluding ocular melanoma patients from latter trials.	Comment noted. The Committee heard from the clinical specialists that even though ocular melanoma is biologically different from cutaneous melanoma, patients are usually offered the same treatment options. See FAD section 4.5.
	Our request OcuMel UK would like to see it specified in the recommendations that ocular melanoma was not considered during the drafting of these guidelines. We would like the recommendation from NICE to be a “common sense” one – i.e. that patients with ocular melanoma should be referred to a medical oncologist specialising in their disease. When the ocular melanoma UK guidelines mentioned above are completed, we would also ask that you make it clear there are alternative guidelines for ocular melanoma patients and provide a link to the relevant guidance.	Comment noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document and concluded that patients with ocular melanoma could be included in the final guidance. See FAD section 4.5.

Consultee	Comment	Response
Representatives of leading professional associations and patient groups	As representatives of leading professional associations and patient groups involved in working with, and on behalf of, patients with advanced melanoma we are writing to urge you to rethink your preliminary decision not to recommend ipilimumab (Yervoy) for the first line treatment of advanced melanoma except in clinical trials. This will be a severe setback to patients who had hoped to have earlier access to ipilimumab. For patients and their families it can be extremely traumatic going through months of first line treatment with dacarbazine when they know that ipilimumab can make a real difference to both their quality of life and their long term chance of survival – and that their chances diminish the longer they have to wait. It is difficult for patients to understand why the NHS will only initiate them onto a more effective treatment once they have gone through unsuccessful treatment with an old, ineffective drug (dacarbazine) – after which both their morale and receptiveness to treatment are much lower. This decision is even more devastating because, as you will be aware, the incidence of melanoma is on the rise in the UK. Over the last 25 years, the rate of malignant melanoma has risen faster than any of the top ten cancers in the UK and it is the second most common cancer in the 15-34 age group. More than 11,700 people are diagnosed with malignant melanoma each year. While the majority of skin cancers are treatable, malignant melanoma kills over 2,000 people each year with an average 22 years of life lost from each melanoma death, more than most other cancers. We urge NICE to reconsider its draft guidance at the Appraisal Committee meeting on 23rd April and issue a positive response to patients across the NHS. We ask you to re-examine the case – reflecting the patient need and the desire from the clinical community to provide early access.	Comment noted. The Committee heard at the first committee meeting, patient experts emphasise that having the choice of ipilimumab as a first-line treatment would be valued by patients and their families and a treatment that prolongs survival could allow people to return to normal life. The Committee concluded that there was an unmet need for effective therapies in this patient population. See FAD section 4.1. The Committee heard from the clinical specialists that current practice included administering dacarbazine, usually with early scanning after 1 to 3 courses, before moving to second-line ipilimumab. See FAD section 4.1. Comment noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document. Ipilimumab is recommended as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma (see FAD sections 1.1 and 4.13).

The Department of Health had no comments on the appraisal consultation document for ipilimumab

Comments received from clinical specialists and patient experts

There were no comments from clinical specialists or patient experts

Comments received from commentators

There were no comments from commentators

Comments received from members of the public

Role*	Section	Comment	Response
Development Director (patient group)	Notes	Conflict – yes We receive some of our funding for skin cancer awareness activities from a number of drugs companies, including the manufacturers of this technology.	
	Section 1	Ipilimumab has proved to be a lifesaving treatment for some patients. Where life expectancy would be between six - nine months on average, when treated with ipilimumab some patients live many years longer. Furthermore, ipilimumab offers patients with the chance of quality survival. We hear from many clinicians who are incredibly frustrated at having to initiate their patients onto an ineffective treatment (dacarbazine) before they are able to offer them ipilimumab, which in their clinical opinion should often be given as a first line treatment. With the clinical community calling for this treatment to be made available as a first line option and with the quality survival it can offer some patients, we believe that NICE should reconsider the evidence available. Given the significant rise in the incidence rate of melanoma, it is vital now more than ever that the best possible treatment is available to patients at the right time. As the Appraisal Committee acknowledged, the current first line treatment for this type of advanced melanoma dacarbazine has never been shown to have survival benefit. The clinical community is unified in this view and both clinicians and patients alike are very aware that this treatment is not effective. This delayed access to ipilimumab means that the patients are less likely to achieve stability in their condition or have the chance of quality survival. Skcin therefore believes that the summaries of clinical and cost effectiveness are not reasonable interpretations of the available evidence. Skcin is very disappointed that the Committee has provisionally	Comment noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document. Ipilimumab is recommended as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma (see FAD sections 1.1 and 4.13).

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
		recommended that patients must first use a treatment which is clinically recognised as having no survival benefit before they are able to access a treatment which is much more effective in some patients. We believe that money spent on treating these patients with dacarbazine is wasted because the treatment is not effective. Furthermore, whilst ipilimumab is more costly than dacarbazine, the only patients who would be able to receive it (if NICE approves it as a first line treatment) would otherwise still receive it as a second line treatment, should they live long enough.	
	Section 4	Skcin believes that the Committee should give more consideration to the evidence relating to ipilimumab and melanoma. It is important to consider that melanoma incidence has the biggest projected increase of any form of cancer. In the last 30 years, rates of melanoma in the UK have risen five-fold. In 2011, the British Journal of Cancer reported that malignant melanoma had the largest predicted rate of increase of cancers studied and added that it was set to rise by an estimated 52 per cent over the following 20 years. Indeed the study went on to predict that melanoma would become the fourth most common cancer in men and the fifth in women. Other findings state that over the next 25 years melanoma rates in the UK will have risen faster than any of the other top ten common cancers. Cancer ResearchUK also advise that more than 13,300 people (37 a day) are diagnosed with melanoma in the UK, young women appear to be most at risk. Like most cancers, skin cancer is more common with increasing age but melanoma rates are disproportionately higher in people aged under the age of 55. Indeed, melanoma is the 2nd most common cancer in young adults, with two young people being diagnosed a day.	Comment noted. The Committee accepted that there was evidence that ipilimumab increased overall survival compared with dacarbazine, agreeing that a mean overall survival gain of 5.7 months for patients had been demonstrated in the ipilimumab arm of the CA184-024 trial. See FAD section 4.3.
	Section 6	We believe that ipilimumab has been clearly demonstrated as a highly effective treatment for BRAF-negative patients with advanced melanoma, which would be even more effective if it was given as a first line option. Indeed, the quality of life for patients with advanced melanoma who receive ipilimumab increases significantly when they receive the treatment earlier. Delaying access simply means that patients are more ill when they begin treatment, less likely to be well enough to receive the full course of ipilimumab and have less chance of achieving stability in their condition. The fact that melanoma disproportionately affects young people should also be considered more carefully. Many patients have families to look after and are of a working age. Often, they also contribute significantly to their local community. We believe that NICE should consider the cost to	Comment noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document. Ipilimumab is recommended as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma (see FAD sections 1.1 and 4.13).

Role*	Section	Comment	Response
		society of allowing these patients to deteriorate on dacarbazine before they are able to have an improved chance of survival with ipilimumab. Melanoma is a very common cancer which has extremely limited median survival time and therefore we believe that it warrants a degree of priority, without delays.	
	Section 8	With significant rise in the incidence rate of melanoma, it is vital now more than ever that the best possible treatment is available to patients at the right time. As the Committee acknowledged, the current first line treatment dacarbazine has never been shown to have survival benefit.? The clinical community is unified in this view and both clinicians and patients alike are very aware that this treatment is not effective. This delayed access to ipilimumab means that the patients are less likely to achieve stability in their condition or have the chance of quality survival. Skcin therefore believes that the summaries of clinical and cost effectiveness are not reasonable interpretations of the available evidence. Skcin believes that NICE cannot wait until 2017 to review their decision to allow ipilimumab to be used as a first line treatment for advanced melanoma; it is vital that patients with advanced melanoma can have earlier access to ipilimumab now, where clinically appropriate, to improve their chances of quality survival. Skcin suggests that the Committee should act on the clinical evidence available and in line with clinical opinion & recommend for 1st line immediately.	Comment noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document. Ipilimumab is recommended as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma (see FAD sections 1.1 and 4.13).
Founder and Key Worker (patient group)	Notes	BMS have assisted Melanoma UK in funding small projects.	
	Section 1	We would like to thank NICE for giving Melanoma UK the opportunity to respond to the Appraisal Consultation Document on ipilimumab as a first line treatment for advanced melanoma. On behalf of patients with advanced melanoma across the country, Melanoma UK strongly disagrees with the Committees provisional decision to only allow ipilimumab to be used as a first-line treatment for advanced melanoma in clinical trials. This decision is deeply concerning for patients and clinicians and signals a step backwards in terms of the adoption of innovative treatments. We urge the Committee to reconsider the evidence and review this provisional decision.	Comments noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document. Ipilimumab is recommended as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma (see FAD sections 1.1 and

Role*	Section	Comment	Response
			4.13)
	Section 4	We do not believe there has been a reasonable interpretation of the clinical & cost effectiveness evidence. The only 1st line treatment currently available for advanced melanoma patients who aren't BRAF positive, is dacarbazine, largely considered to be ineffective. Patients are rightly concerned that the committee is recommending such treatment which clinicians agree has no survival benefit as a 1st line option. This is wholly unsatisfactory for patients & against the weight of clinical opinion. Ipilimumab can make a real difference to quality of life and survival chances and patients struggle to understand why they can only access a more effective treatment, once the ineffective one has failed them. The same patients would receive the drug, but will likely be more ill with a higher burden of disease. To allow progression means the patient stands less chance of having the full course of treatment and therefore is less likely to achieve stability following the delay. We have spoken with patients, they know that to not have the treatment reduces their quality and puts strain on an already burdened NHS.	Comment noted. The Committee heard from patient experts, at the first committee meeting, that having the choice of ipilimumab as a first-line treatment would be valued by patients and their families and a treatment that prolongs survival could allow people to return to normal life. See FAD section 4.1. The Committee considered the comments from consultees and commentators on the appraisal consultation document. Ipilimumab is recommended as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma (see FAD sections 1.1 and 4.13).
	Section 10	Melanoma UK believes that the Committee has failed to fully consider the effect that this decision will have on the patient population with advanced melanoma. Indeed, it is alarming to note that this disease disproportionally affects young people aged between 15 and 34. Melanoma is now the second most common cancer in that age group and the incident rate is rising significantly. To accurately reflect the value that this treatment could bring to the NHS if it was recommended as a first line treatment, it is important that NICE fully considers the value of appropriately treating patients within this age group in a timely manner. Given the extremely aggressive nature of the disease, the age profile of the patient pop becomes even more significant. Having a younger age profile means that patients are often of a working age and many have young families – for these patients the speed of effective treatment is invaluable. More average years of life are lost as a result of melanoma than almost any other tumour type (estimates suggest that, on average, patients lose 22 years). We believe that ipilimumab gives patients with this type of melanoma the best chance of achieving quality survival	Comment noted. Comment noted. The Committee accepted that there was evidence that ipilimumab increased overall survival compared to dacarbazine, agreeing that a mean overall survival gain of 5.7 months for patients had been demonstrated in the ipilimumab arm of the CA184-024 trial. See FAD section 4.3.
NHS Professional 1	Notes	I am a clinician involved in care of patients with metastatic melanoma	

Role*	Section	Comment	Response
	Section 1	Moving from second-line ipilimumab to first-line ipilimumab means that patients who are currently denied ipilimumab (due to deterioration on futile 1st line Dacarbazine) would potentially benefit. Costs associated with futile Dacarbazine use would be avoided. The real-world cost of Ipilimumab is less than modelled because the actual number of cycles received is lower than originally estimated (due to treatment-suspension for toxicity, and early deaths)	Comment noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document. Ipilimumab is recommended as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma (see FAD sections 1.1 and 4.13).
	Section 5	Moving from 2nd line ipilimumab to 1st line ipilimumab means that patients who are currently denied ipilimumab (due to deterioration on futile 1st line Dacarbazine) would potentially benefit. Costs associated with futile Dacarbazine use would be avoided.	Comment noted.
	Section 6	Collect real-world data on true number of cycles of ipilimumab received / patient	Comment noted.
	Section 7	Urgent review of nivolumab data required	
NHS professional 2	Notes	I am an Allied Health Professional	
	Section 1	As a group of health care professionals treating patients with advanced melanoma, we want the best treatments for patients at the best time. We agree that ipilimumab is an important part of the treatment for melanoma and so there is much debate about whether this should move from second line treatment to first line or even as an adjuvant treatment. We know that ipilimumab takes time to work and so it makes most sense to give it to fitter patients, with lower tumour burden, earlier in their treatment pathway. NICE has delayed the Committee discussion by one month after BMS requested to submit new evidence and analyses as part of the ACD consultation. We think this is a positive move and hope that this increased data will confirm that first line treatment with 3mg/kg ipilimumab as a single agent is the best treatment.	Comment noted. Committee heard from the clinical specialists that although it is not possible to identify patients most likely to experience a response with ipilimumab, in some patients whose condition responds to treatment it was associated with a very durable response. See FAD section 4.1. The Committee considered the comments from consultees and commentators on the appraisal consultation document. Ipilimumab is recommended as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma (see FAD sections 1.1 and 4.13).

Role*	Section	Comment	Response
Member of Parliament (Emergency Parliamentary Evidence Sessions report)		A report was submitted to NICE which recorded outcomes from a parliamentary meeting attended by MPs, patient representatives, patients, patient organisations and professional groups among others. Below is a section containing information on the concerns demonstrated over NICE's decision (not reproduced here: *for the full manufacturer's response to the ACD, please refer to the Evaluation report)*. • They considered ipilimumab to be the 'best available option' for patients for BRAF V600 negative patients • A number of the stakeholders considered ipilimumab to be revolutionary • They heard examples of patients who had been treated with ipilimumab first-line and how well they had responded. The attendees thought ipilimumab could increase the quality of life for patients if administered as first-line • A number attendees highlighted that melanoma disproportionally affects young people. • Several attendees gave testimony to the importance of early diagnosis and noted that this has one of the biggest impacts on treatment outcomes. • Attendees noted with concern that the incidence of melanoma has the biggest projected increase of any form of cancer • Healthcare professionals recounted the difficulty of explaining to patients why they had to receive a clinically ineffective treatment first before being able to access a treatment which is known to be extremely efficacious in some patients	Comment noted. The Committee acknowledged that few advances had been made in the treatment of advanced melanoma in recent years and that ipilimumab could be considered a significant innovation for a disease with a high unmet clinical need. See FAD section 4.10. Comment noted. The Committee heard from clinical specialists that for patients who are BRAF V600 mutation-negative, dacarbazine is the only first-line treatment option currently available, and it has never been shown to have survival benefit. See FAD section 4.1. The Committee considered the comments from consultees and commentators on the appraisal consultation document. Ipilimumab is recommended as an option for treating adults with previously untreated advanced (unresectable or metastatic) melanoma (see FAD sections 1.1 and 4.13)

Summary of comments received from members of the public

Topic	Theme	Response
Summary of comments regarding ocular melanoma		
Ocular melanoma has not been taken into account	Several patients noted that ocular melanoma had not been taken into account in this appraisal. One comment said that patients with ocular melanoma are covered under the disability act and that the appraisal had failed to considered people with advanced ocular melanoma.	Comment noted. The Committee considered the comments from consultees and commentators on the appraisal consultation document and concluded that patients with ocular melanoma could be included in the final guidance. See FAD section 4.5
Ocular melanoma is genetically distinct to malignant melanoma	Several commentators said that the diseases and disease responses to treatment are very different. Ocular melanoma progresses more quickly than cutaneous melanoma. They would like to see ocular melanoma described as a separate group to malignant melanoma patients.	Comment noted. The Committee heard from the clinical specialists that ocular melanoma is biologically different from cutaneous melanoma. See FAD section 4.5
Ipilimumab is an effective treatment for ocular melanoma	One patient suggested that this is the only treatment which has been proven in clinical trials to work and several people commented on the effectiveness of the drug. The responses suggested that ipilimumab may only work for some patients but in those patients the drug has resulted in years of extra life. Some patients commented that withdrawal of ipilimumab from first-line treatment would discriminate against ocular melanoma.	Comment noted. The Committee heard from the clinical specialists that, even though ocular melanoma is biologically different from cutaneous melanoma, patients are usually offered the same treatment options. See FAD section 4.5
Small ocular melanoma patient numbers	Several patients commented on the small number of ocular melanoma patients making it very difficult to run a large clinical trial.	Comment noted.
Ipilimumab side effects	One patient suggested the side effects were typically less than other first line treatments. If ipilimumab were not available for first-line treatment then the only treatment would be dacarbazine which has very toxic side effects.	Comment noted.

Topic	Theme	Response
Dacarbazine treatment	Several comments suggested that dacarbazine provides no benefit to ocular melanoma patients and there are no other licenced drugs to treat the disease. One patient said this decision would mean he would undergo treatments which are known not to work before he could have ipilimumab. One patient said the onset of disease is fast and waiting for a treatment to fail in order to move on could prove fatal.	Comment noted. The Committee heard from the clinical specialists that, even though ocular melanoma is biologically different from cutaneous melanoma, patients are usually offered the same treatment options. See FAD section 4.5
Costs	One patient considered that the costs of first-line treatment with ipilimumab could be offset by avoiding the need to treat patients with other 'useless' treatments. The mother of a patient said that her daughter is always concern about funding of the drug.	Comment noted.
Benefit to family members	Several patients explained how their families had benefited because their disease had been treated with ipilimumab	Comment noted.
BRAF mutation status of patients	One of the patients suggested that the BRAF mutation is not relevant to ocular patients. One patient commented on why the mutation status of malignant melanoma patients had been taken into account but ocular melanoma patients had not been considered.	Comment noted. The Committee heard from the clinical specialists that ocular melanoma is biologically different from cutaneous melanoma. See FAD section 4.5
Further research	Many of the commentators said they would like the committee and NICE to look further into the evidence for the use of ipilimumab to treat ocular melanoma. One patient commented that the problem with only allowing patients to receive ipilimumab as part of a clinical trial is that the patient may not be randomised to the ipilimumab treatment group and may miss out on the treatment. One patient requested to know when, where and how ocular melanoma would be incorporated into future trials.	The Committee considered the comments from consultees and commentators on the appraisal consultation document and concluded that patients with ocular melanoma could be included in the final guidance. See FAD section 4.5