NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Bristol-Myers Squibb
   - British Association of Dermatologists
   - British Association of Skin Cancer Specialist Nurses
   - Melanoma Focus
   - Melanoma UK

3. **Comments on the Appraisal Consultation Document from experts:**
   - Diane Cannon – patient expert nominated by Melanoma UK

4. **Comments on the Appraisal Consultation Document received through the NICE website**

5. **Evidence Review Group review of company ACD response**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

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 NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
	Consultee	Bristol-Myers Squibb	Bristol-Myers Squibb submitted additional evidence during the ACD consultation which has been published on the NICE website https://www.nice.org.uk/guidance/indevelopment/gid-ta10286/documents	The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the Evidence Review Group (ERG)'s critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the Cancer Drugs Fund (CDF).
1	Consultee	British Association of Dermatologists	On behalf of the British Association of Dermatologists, thank you for the opportunity to comment on the Appraisal consultation document. The British Association of Dermatologists have no comments. Prof Nick Levell Chair, Therapy & Guidelines sub-committee	Thank you
1	Consultee	British Association of Skin Cancer Specialist Nurses (BASCSN)	BASCSN is disappointed by this decision. Nivolumab has demonstrated that is can increase relapse free survival, which is very important for patients. Patients will be denied treatment while we wait for the data on overall survival.	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the Evidence Review Group (ERG)'s critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the Cancer Drugs Fund (CDF). The committee noted that CheckMate 238 provides evidence that nivolumab improves recurrence-free survival (RFS) compared to ipilimumab (see section 3.3 of the Final appraisal document (FAD))
2	Consultee	BASCSN	If the decision stands, BASCSN would support a further appraisal once the data has matured eg in 2019, rather than at 3 years as proposed.	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the ERG's critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the CDF. The guidance will be reviewed when sufficient data has been collected to address the committee's uncertainties (see section 6.1 of the FAD)
3	Consultee	BASCSN	BASCSN would support access to nivolumab through the	Thank you. The committee reconsidered its initial recommendation

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			CDF now, to enable patients to receive it before they progress. If the data on OS is negative then this decision can be reviewed and the drug removed.	taking account of the additional evidence supplied by the company, the ERG's critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the CDF.
	Consultee	Melanoma Focus	We believe that the initial decision not to approve nivolumab for adjuvant therapy for resected stage 3 or stage 4 melanoma is incorrect and risks compromising outcomes for patients. We have addressed the Committee's comments below:	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the ERG's critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the CDF. Melanoma Focus's specific comments are addressed in the rows below.
1	Consultee	Melanoma Focus	*There are no trials directly comparing adjuvant nivolumab with routine surveillance*. Whilst this is a factually correct statement, we are not aware of a single senior melanoma clinician who is not convinced that the data from the two pivotal studies (CA184-029 and CHECKMATE 238) show beyond any reasonable doubt that nivolumab is superior to placebo/no treatment in terms of relapse-free survival and that ipilimumab is superior to placebo in terms of overall survival. These trials have been publicly reviewed and debated at length at ASCO 2018, ESMO 2017 and many other international meetings, and this has never been raised as a concern. Furthermore, the EORTC 1325/ Keynote-054 study comparing pembrolizumab with placebo in patient with Stage IIIa (>1mm deposit)-IIIc showed a clear benefit in terms of RFS (HR 0.57 for pembrolizumab) entirely consistent with the activity of nivolumab in the adjuvant setting. These drugs are used interchangeably in clinical practice in the treatment of metastatic disease and have identical efficacy and toxicity.	Thank you. The committee recognised that, based on experience with immunotherapy treatments in other cancers, clinical experts expect the observed RFS benefit will translate into an overall survival (OS) benefit (see section 3.5 and 3.6 of the FAD).
2	Consultee	Melanoma Focus	*Differences between the trials in the company's indirect treatment comparison mean the results are uncertain.* Whilst uncertainty does exist, the statement that "unable to conclude that the technology had plausible potential to be cost effective" is itself completely implausible. It is entirely plausible to conclude that given the potentially durable effects of immunotherapy and the large benefit that can accrue in the adjuvant setting nivolumab has the potential to be cost effective. The comment that the ipilimumab scheduling in CHECKMATE 238 was significantly different to that for CA184-069 is only correct in considering planned therapy. This fails to account for	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the ERG's critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee recognised that the company adjusted its approach to the ITC in its updated evidence submission to account for differences in the duration of ipilimumb treatment received by patients in the contributing trials. The committee concluded that the updated ITC is suitable to inform decision making (see section 3.4 of the FAD).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			the fact that the median number of cycles of ipilimumab patients received in the latter study was 4, and that 38.6% of patients had discontinued therapy by 12 weeks. The vast majority of patients did not complete 1 year of treatment, and only 13% the full course.	The committee concluded that adjuvant nivolumab has plausible potential to be cost effective (See section 3.14 of the FAD)
3	Consultee	Melanoma Focus	*Nivolumab may improve RFS compared with routine surveillance but the magnitude of the benefit is unclear.* The relapse-free survival curves for patients with resected stage III melanoma treated with ipilimumab in CHECKMATE 238 and CA184-029 are very similar. This provides the most reliable data from which we infer that nivolumab produces a significant improvement in relapse-free survival as compared to observation. We note the criticisms of the populations used in the company's modelling, but do not agree that the drawing on a population from a trial that happens to use interferon invalidates the approach.	Thank you. The committee recognised that the company adjusted its approach to the ITC in its updated evidence submission to account for differences in the duration of ipilimumb treatment received by patients in the contributing trials. The committee concluded that the updated ITC for RFS for the period between 12 weeks and 10 years is suitable for decision making (see section 3.4 of the FAD). However, the committee also noted that these changes did not have any impact on the methods used to estimate the RFS benefit before 12 weeks or beyond 10 years. The committee concluded that although the extrapolation was reasonable, the size of the benefit with nivolumab over the longer term is still uncertain (see section 3.9 of the FAD).
4	Consultee	Melanoma Focus	*The patient population for CHECKMATE 238 had a worse prognosis than that for CA184-029.* Whilst it is correct that these studies are not directly comparable, subgroup analysis from CA184-069 showed no clear impact of stage/number of nodes involved/microscopic versus macroscopic disease etc. on overall survival benefit with ipilimumab. Therefore we feel that ipilimumab was the appropriate comparator to use for the CHECKMATE 238 study even though this included patients at higher risk of recurrence.	Thank you. It is unclear which section of the ACD this comment refers to. The committee remained concerned that because new treatments for metastatic disease have become available in recent years, this may mean that the results of CA184-029 are not directly comparable to those of CheckMate 238 or to patients being treated in current clinical practice (see section 3.10 of the FAD). The committee has now recommended adjuvant nivolumab for use in the CDF in all patients with completely resected melanoma with lymph node involvement or metastatic disease (i.e. the recommendation is not restricted by stage). The committee remained of the view that CheckMate 238 does not provide any evidence on the relative efficacy of adjuvant nivolumab compared with routine surveillance, which was the comparison of interest for the appraisal (see section 3.3 of the FAD).
5	Consultee	Melanoma Focus	*Difficulty predicting treatment in the metastatic setting and impact on the economic analysis.* We agree that it is difficult to predict accurately treatment that will be used in the metastatic setting. However, within current UK practice: (i) NHS England does not approve combination immunotherapy for patients who had previous adjuvant therapy; (ii) at least 50% of eligible treatment naïve metastatic patients will be treated with combination ipilimumab + nivolumab. This suggests that second-line	Thank you for your comment. The committee recognised the uncertainty about which treatments people would in practice receive on recurrence after adjuvant nivolumab. It also noted that that neither the company's nor the ERG's analyses fully captured the true complexity of the post-recurrence treatment pathway. However, the committee accepted that despite the uncertainty, there was the plausible potential for nivolumab to be cost effective and recommended adjuvant nivolumab for use in the CDF

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			therapy will be relatively more expensive after observation than for those patients who receive adjuvant therapy.	
6	Consultee	Melanoma Focus	*No data on overall survival and impact of salvage therapy on this*. We accept that it is not proven that the relapse-free survival benefit will translate into an overall survival benefit, but are unaware of any adjuvant therapy with an RFS effect of the magnitude reported for checkpoint inhibition that has failed to yield an OS benefit. We also accept that it is unclear what the appropriate treatment to use in the metastatic setting will be in patients relapsing on or after adjuvant therapy. The latter question is being addressed by a randomised clinical trial being setup by the EORTC. However, the utility of adjuvant treatment for patients with resected stage III and IV melanoma has not been sufficiently taken into account. Time without cancer is very important to patients, even when relapse ultimately transpires. This is a population that is at very high risk of relapse and premature death. Although treatment in the advanced setting has had an impact on the quality and length of life, patients value the opportunity to maximise the time they can live without disease and severe disruption to their lives.	Thank you. The committee recognised that, based on experience with immunotherapy treatments in other cancers, clinical experts expect the observed RFS benefit will translate into an overall survival (OS) benefit (see section 3.5 of the FAD). There is currently no evidence to support the assumption that re-challenge with PD-1 immunotherapies would be as effective after 2 years as assumed in the company's model (see section 3.11 and 3.12 of the FAD). However, the committee accepted that despite the uncertainty, there was the plausible potential for nivolumab to be cost effective and recommended adjuvant nivolumab for use in the CDF.
7	Consultee	Melanoma Focus	The approval of dabrafenib and trametinib as adjuvant therapy for patients with BRAF mutated melanoma has demonstrated an immediate interest in this treatment from our patients. There will be inequity if adjuvant therapy is not available for BRAF wild type patients, despite similar RFS effects, given the widespread clinical support for this treatment.	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the Evidence Review Group (ERG)'s critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the CDF so patients will have access to treatment in line with the conditions in the managed access agreement
8	Consultee	Melanoma Focus	**Recommendations** We strongly suggest that there is a significant risk that failing to approve nivolumab at this time will prejudice the outcome for patients. We recommend that the drug is approved on the Cancer Drugs Fund and that this approval is reviewed when the overall survival data are available. This is expected at the end of 2019. This interim funding will also allow us to collect real world data on these patients.	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the Evidence Review Group (ERG)'s critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the CDF.
1	Consultee	Melanoma UK	Melanoma UK represents many melanoma patients and families throughout the UK. There is a huge sense of disappointment that this	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the Evidence Review Group (ERG)'s critique of the company's submissions and comments received from C&Cs and patient and

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			treatment has met with rejection from NICE. Given that a recent treatment was approved, patients are relieved. However, there is a section of patients who will not be eligible for that treatment because they do not have the appropriate gene. The recent decision is disappointing and if the draft guidance not to recommend Nivolumab becomes final guidance without any changes, it will mean that patients in England and Wales with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection will not be able to access nivolumab as adjuvant therapy. Melanoma UK realises that the committee acknowledged that people with fully resected melanoma are still at high risk of disease recurrence and that the potential curative aim of nivolumab represented a substantial benefit to patients. With that in mind, it is disappointing that this decision was made. Watch and wait does not sit well with the patient community.	clinical experts. The committee has now recommended adjuvant nivolumab for use in the CDF.

Web comments

Role	Section	Comment [sic]	Response
Patient Advocate	N/A	As the carer of a stage 4 patient treated at the Marsden in London, I am terribly disappointed at this initial decision. Having opted, with Â« eyes wide open Â» as an informed patient, to the Ipilimumab Adjuvant trial (before the anti PD1s were approved) and been assigned the Placebo arm, I am very aware of the cost to a patient of having NO treatment at high risk stage 3c - we "knew" pretty early on that we were on placebo, as we watched other patients drop off the trial with the toxicities of the ridiculous 10mg Ipi dose - but we were PREPARED to risk this toxicity to avoid progression. We were disappointed to see the Checkmate 238 trial had 10mg Ipi as comparator (but in view of the fact that, although Ipilimumab adjuvant wasn't yet approved in Europe, it was in many other places, this would have been violating equipoise for many if they HAD used the Placebo comparator) Having the opportunity of a relatively low toxicity anti PD1 at adjuvant for only 1 year, at the time we would have JUMPED at the chance. (14% grade 3 and 4 toxicity in a treatment environment that is now MUCH more competent at dealing with immunotherapy AEs than it was at the clinical trial stage) we are immensely grateful to still be around after 7 years at stage 4 , but this has largely been due to luck at the timing of approvals/access and extreme proactivity on our part to "chase" trials through adjuvant, targeted therapies and combination immunotherapy - this has been at a huge cost in travel and in the time we spend informing ourselves of the details of the sometime BRUTAL trial process (balancing protocols, second-guessing the disadvantages of randomisation and being blinded) and assessing the risk/benefit of all these treatments - I realise that it is very difficult to decide at adjuvant , when you feel well and MAY have no tumour left, to take a treatment that could give you permanent side effects, but stage 3c is a sword of Damocles , and we felt there was NO choice except to hope we would be some of the relatively small number (in the case of Ipi adjuvant) of patients who could get benefit over just waiting for the disease to come back in the brain or bone. Nivolumab is much less toxic and the efficacy in the higher risk patients (there were no 3a patients in this trial) much better than the Ipi trial. The rarer permanent toxicities are something that concerns me, but the auto-immune management strategies are so much better now, and the management of the destruction of thyroid/pituitary function is something we learn to manage, and with better multi-disciplinary teams at specialist centres these are picked up earlier. We still dont know WHO will benefit from these treatments at stage 4, because we dont yet have effective bio-markers, but Please dont let this be a criteria for refusing adjuvant treatment - we need access for higher risk patients WHILE we carefully monitor in decent registries, we need well designed trials which force industry to use protocols that are more USEFUL to real world use (and data that is shared),we need excellent information for patients so they can more easily analyse the risk/benefit of a treatment at adjuvant stage, and intelligent risk-sharing agreements between payers and Industry in this time of evidence shortage. I speak to many patients and almost ALL want/would have liked the opportunity to choose a therapy at adjuvant : there are a few that find that the high toxicity reporting from the adjuvant trials (healthy people always report more diligently on	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the Evidence Review Group (ERG)'s critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the CDF

		the impact of a drug on their lives) tempts them to "wait until they know they really need it", others have said they want it at stage 2c (because they know this is frequently a more risky place than most stage 3a). I have spoken to patients who say Â« I was given interferon with almost zero evidence of it working and had a miserable year of side effects/uselessness and I still progressed and yet Nivo is much better Â» Please reconsider this assessment .	
Patient	N/A	As a Stage 3 C Melanoma metastasis patient who has had a lymph node groin dissection , I was hoping that the adjuvant therapy was going to be offered to me to help prevent the more than likely further spread of Melanoma in my body and therefore extend my life expectancy . I have two teenage daughters (17 and 15) and as any father would , I want to see them grow up and share as much time with them as possible . Then of course there is my own life . I appreciate no one can predict the future in terms of accidents etc for ones life expectancy but to have another or others , to decide on my behalf that I will have a reduced amount of time to experience life is a very uncomfortable feeling . I understand that this decision is financially influenced and NICE have concluded that to increase my life expectancy is too expensive - I am not worth keeping alive. I appreciate there are limited financial resources in this current desperation for austerity but I am disappointed that NICE have deemed me to a burden and a drain on these resources .	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the Evidence Review Group (ERG)'s critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the CDF
NHS Professional	N/A	In response to the initial negative appraisal of adjuvant Nivolumab in resected stage III or IV melanoma I would like to comment that this is a group of patients in whom we have been looking for effective adjuvant treatment for decades. NICE have recently approved the use of Dabrafenib and Trametenib as adjuvant therapy for resected BRAF+ stage III melanoma but this group only represents around 35% (real world data is lower than the published BRAF mutation rates, often quoted as around 50%) so there is a large group of patients who are not currently eligible for adjuvant treatment on the NHS. Adjuvant Nivolumab appears to be effective in reducing the rates of recurrence of melanoma (compared to Ipilimumab which is not approved for use in the adjuvant setting in the UK) and I would like to add my support to those asking for this treatment to be available on the NHS. It is recognised that the data from the clinical trial are immature and currently the main evidence of benefit sits with improved relapse free survival - however, in multiple studies, in multiple different cancer types an improved RFS can translate into better overall survival. In general, it is better to prevent relapse than to try salvage treatments when it occurs. I hope the committee can approve this treatment for NHS use in due course. Thank you.	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the Evidence Review Group (ERG)'s critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the CDF
Patient Advocate	N/A	On the understanding that the Committee has decided not to recommend Nivolumab within its marketing authorisation, we would we like to comment on this in an attempt to change the final guidance. We strongly feel it a disservice to patients with later stage melanoma to not provide them with the option access Nivolumab as adjuvant therapy. Patients with fully resected melanoma are still at high risk of disease recurrence and patients are fully aware of that. We believe that the potential curative aim of Nivolumab represents a substantial benefit to patients both in terms of physical treatment and importantly, emotional well-being; knowing there is an option. We believe that raising the possibility of recurrence-free survival is important	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the Evidence Review Group (ERG)'s critique of the company's submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the CDF

		because increasing the length of time before tumours come back could lead to patients living longer and a better quality of life as relapse is associated with advanced disease. The Committee recognised Nivolumab was more effective than Ipilimumab in the clinical trial, the comparison with â€˜watch and waitâ€™ was conducted through an indirect treatment comparison and so the results were noted as uncertain. We believe that the ERG's analysis is overly simplistic and does not reflect UK clinical practice where a mix of treatments are used for disseminated disease.	
NHS Professional	N/A	The patients with resected melanoma have a limited number of options (recognising the recent approval of dabrafenib & trametinib combination for resected BRAF positive stage III disease) - standard 'follow-up' is in my opinion not satisfactory - both for all resected stage 4 disease patients & those stage III BRAF negative have no options. Reducing the risk of disease recurrence of this disease is essential to achieve longer term survival. Smaller benefits in other cancers in this circumstances have been approved previously whilst adding to 'standard' treatment. There is no standard treatment at the moment & as a melanoma Oncologist I believe we need access to this option for the future of this group of patients.	Thank you. The committee reconsidered its initial recommendation taking account of the additional evidence supplied by the company, the Evidence Review Group (ERG)’s critique of the company’s submissions and comments received from C&Cs and patient and clinical experts. The committee has now recommended adjuvant nivolumab for use in the CDF

Bristol-Myers Squibb
Uxbridge Business Park, Sanderson Road, Uxbridge, Middlesex, UB8 1DH

28th September 2018

Dear Helen,

RE: Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1316] ACD - BMS Response

Thank you for giving us the opportunity to comment on the Appraisal Consultation Document (ACD) for the above appraisal. We are disappointed with the Committee's draft recommendation as we believe that nivolumab is a cost-effective treatment that has the potential to maintain patients in a disease-free state. We recognise the uncertainty in the base case ICER and this uncertainty was fully explored with multiple scenario and sensitivity analyses, the majority of which resulted in ICERs below the willingness to pay (WTP) threshold of £30,000/QALY. However, those uncertainties can be further reduced with more evidence on which subsequent therapies are used in clinical practice, further confirming that nivolumab in the adjuvant setting is a cost-effective treatment.

We welcome the Committee's acceptance of nivolumab being a more effective treatment than ipilimumab and acknowledgment that patients with fully resected Stage III and IV melanoma have a high unmet need and would benefit from adjuvant therapy.

However, despite the evidence presented to the Committee on a comparison to routine surveillance and on cost effectiveness, the Committee felt that there was too much uncertainty within the analysis to make a positive recommendation. This uncertainty was focussed particularly on the following:

1. The subsequent treatment pathway in England & Wales and how this effects cost effectiveness
2. The generalisability of the indirect treatment comparison for nivolumab vs routine surveillance
3. The application of administration costs
4. Techniques used to extrapolate the recurrence-free survival (RFS) curves in the company model
5. Application of the hazard ratio from the surrogacy relationship
6. Benefit:risk ratio for patients with a lower risk of relapse.

In this document we consider each topic separately and evaluate the uncertainty in clinical outcomes and cost effectiveness for each subject. We also provide two proposed revised base cases using evidence review group (ERG) analyses:

- One assumes equal effectiveness between ipilimumab and nivolumab within a partitioned survival model structure, and produces a revised incremental cost-effectiveness ratio (ICER) of £18,423 per quality-adjusted life year (QALY) gained.
- One uses treatment pathway data from a variety of relevant sources in the Committee's preferred Markov model structure and produces a revised ICER of £18,018 (range: £16,913 to £18,158).
- Sensitivity analysis on the two revised base cases demonstrate that the ICERs are robust with the majority scenarios under £30,000/QALY (See Appendix 2 and 3).

Despite the minimum 2-year follow up, the CheckMate 238 study demonstrated a statistically and clinically significant reduction of risk of relapse or death which, with the cost of avoiding advanced disease, demonstrates that nivolumab is a cost-effective treatment in the adjuvant setting. Nivolumab remains cost effective in all scenarios presented using plausible estimates of the mix of subsequent therapies used in current practice. We are confident that the most plausible ICER for nivolumab as adjuvant treatment falls below the £30,000 per QALY threshold and believe that the information presented in this response should satisfy the Committee's previous concerns.

Given the robustness of the analyses presented, routine commissioning is the most appropriate route towards making this drug available to patients. We will also consider the Cancer Drugs Fund if the

Committee considers this to be relevant, pending ongoing CheckMate 238 data collection (anticipated timelines of additional data included herein).

These analyses demonstrate nivolumab to be a cost-effective option for routine commissioning. A positive recommendation will ensure that equitable access in effective and tolerable adjuvant treatments is available for all patients and regardless of BRAF status in resected melanoma.

Yours sincerely,

[redacted]

On behalf of Bristol Myers Squibb

Contents

1. CE model changes

Based on the feedback from the Committee and clinicians within the committee meeting we have made further changes to the CE model to allow us to explore more appropriate scenarios. Details of these scenarios are described in Section 5 and 6.

Changes made within the model are detailed within the model itself in a sheet labelled “Post ACD changes”. This sheet outlines each presented scenario and directs the user to the location of the change required.

2. Subsequent treatment usage in England & Wales

Subsequent treatment assumptions following routine surveillance

The Committee highlighted concerns with the estimates used to inform subsequent therapy usage taken from the CheckMate 238 trial. In particular, the use of the ipilimumab arm subsequent therapies to inform routine surveillance estimates and potential underestimation of usage of anti-PD1s post routine surveillance. We have obtained real-world (RWD) data from two different sources to highlight which treatments are actually used in practice to treat metastatic melanoma in England & Wales. The two sources collected data from a large number of UK sites and are therefore considered to be generalisable and reflective of the UK clinical practice for the management of metastatic disease. Table 1 summarises the real-word data sources.

IPSOS utilises a representative panel of UK physicians treating Stage IV melanoma which are asked to review patient charts and provide information on the treatment of patients. BMS obtained melanoma prescribing details via Wilmington Health Care from 173 centres across the UK of which 154 were located with England & Wales. The Trusts were asked to provide the total number of metastatic melanoma patients which received treatment in the last 3 months from March 2018. The survey was conducted in April 2018 and collated in April-May 2018.

COMBI-AD data and the NICE appraisal of dabrafenib+trametinib were also considered for use in the economic model, both of which are supportive of BMS' assumptions on subsequent treatment options, showing a wide variety of treatments being used in the metastatic setting. However, the COMBI-AD source was not considered to be generalisable to the full population of patients who would be treated with adjuvant nivolumab as this data relates to BRAF mutation positive patients only (~ 50% of the UK population) and the treatment options for these patients are greater.[1]

Table 1: Real-word subsequent treatment data sources

Data source	**IPSOS**	**Wilmington Health Care**
Data collection method	Representative physician panels directly reviewing patient charts	Freedom of information across UK NHS trust
Time period	July 2017 – June 2018	3 months from March/April 2018
Country	UK	England & Wales
Lines of therapy included	1L and 2L	All – lines not separated
No. of physicians/centres asked	134 physicians	173 centres across the UK of which 154 covered England/Wales
No. of responders	131 physicians (reporting Stage IV)	150 NHS trusts responded with data (66 trusts treated metastatic melanoma, 60 from England and Wales)
Patient numbers/records	1,560 (1L: 924, 2L: 665,3L+: 3)	Total mMEL patient records in FoI: 2,618 England/Wales mMEL records: 2,348
Centre types	52% comprehensive cancer centre 45% university teaching hospital 2% general hospital 1% private clinic	A list of Trusts responding is provided in Appendix 1.
Key: 1L, first line, 2L; second line; 3L+, third line and beyond; mMEL, metastatic melanoma		

The CheckMate 238 ipilimumab arm was originally used to inform routine surveillance subsequent treatments in the model, based on the recommendation of UK and international clinical experts in melanoma treatment. Table 2 summarises the data on subsequent treatments post routine surveillance obtained from IPSOS and Wilmington Health Care and compares it to the data collected in the CheckMate 238 ipilimumab arm. The two RWD sources are methodologically different but show similar general trends such as high usage of dabrafenib plus trametinib, and of pembrolizumab and further support that BMS' assumptions are likely a true representation of real-world subsequent treatment pattern in England and Wales. The CheckMate 238 ipilimumab trial data also show the same general trends and its values sit between the real-world data sources.

These results show that data collected in CheckMate 238 are generally reflective of clinical practice in England as suggested by clinicians on the UK advisory board[2] and those consulted by the ERG.

The proportion of use of anti-PD1s in the metastatic setting (the Committee's main area of concern) is consistent within the ipilimumab arm from CheckMate 238 trial and data sources from the UK (CheckMate 238 trial = 55.7%, ISPOS data = [redacted] Wilmington data = [redacted] Use of BRAF / MEK inhibitors is also consistent within the trial and UK data sources.

Subsequent ipilimumab usage in CheckMate 238 was lower than ipilimumab usage for metastatic melanoma in real-world data. This is expected since the post-recurrence treatment data from routine surveillance comes from the ipilimumab arm in the CheckMate 238 trial (i.e. clinicians would not be expected to want to repeat ipilimumab for early relapses). However, as ipilimumab in the metastatic setting is the least cost-effective of the novel agents available and the difference between the trial and practice is relatively small this does not have a major impact on results (as seen in the scenario analyses presented in Section 5).

In practice individual clinicians use different treatments and each facility will have different usages; however, the real-word metastatic treatment data suggest that use of the post-recurrence treatment data from CheckMate 238 in the ipilimumab arm as a proxy for routine surveillance is generally reflective of average usage in England and Wales, where there is currently no adjuvant treatment use. We have therefore kept the data from the ipilimumab arm of CheckMate 238 within the model base case post routine surveillance.

Table 2: Subsequent treatment data in the metastatic setting

Treatment	IPSOS			Wilmington	CheckMate 238		
	1L	2L	All	All	Ipi – 1L	Ipi – 2L	Ipi – all
Total immunotherapies	[redacted]						
Anti-PD1s	[redacted]						
Pembrolizumab	[redacted]						
Nivolumab	[redacted]						
Nivolumab + ipilimumab	[redacted]						
Other immunotherapies	[redacted]						

Treatment	IPSOS			Wilmington	CheckMate 238		
	1L	2L	All	All	Ipi – 1L	Ipi – 2L	Ipi – all
Interferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interleukin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BRAF/MEK inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic cancer therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: 1L, first line; 2L, second line; Ipi, ipilimumab.							

The original base case presented to the Committee also used the CheckMate 238 trial data to inform costs for subsequent use for patients who have a local/regional recurrence (see Section B3.5, page 160 in the company submission). However, patients currently do not receive adjuvant therapy in clinical practice; dabrafenib plus trametinib has only recently been approved for use as adjuvant therapy for melanoma[3] and it would be unclear if adjuvant therapy with nivolumab would be used for second relapses; consequently, in our revised base case using the Markov 2 model (Section 6) we have made a conservative decision to remove local/regional subsequent therapy costs. Surgery and radiotherapy costs are still included as they are reflective of the current UK clinical practice.

As a higher proportion of patients in the ipilimumab arm in CheckMate 238 received treatment for local/regional recurrence (used as a proxy for routine surveillance subsequent therapy use) relative to the nivolumab arm therefore a higher total cost for subsequent local/regional recurrences was estimated for routine surveillance relative to nivolumab. Removing these costs therefore increased the ICER (increases from £18,685 [original Markov 2 company base case] to £22,084 - see Section 5).

Subsequent treatment assumptions following nivolumab

It was noted at the Committee meeting and during the clinical interviews conducted for the original submission that decisions about what subsequent therapy to give patients after nivolumab would depend on the timing of the relapse. Patients relapsing later following adjuvant nivolumab treatment were more likely to receive subsequent anti-programmed cell death protein 1 (PD-1) drugs whereas patients relapsing early would either receive ipilimumab or a BRAF/MEK inhibitor (if BRAF mutation +ve). Taking these comments on board we have amended the economic model to base the subsequent therapy distribution after nivolumab treatment on the time of initial relapse.

As experience with adjuvant PD-1 therapy is currently very limited in clinical practice in the UK, clinical experts do not have consensus on when it is beneficial for a patient to be re-challenged with anti-PD-1s. At the Committee meeting, one clinician suggested 2 years; during the clinical consultation conducted for the original submission (in response to a question on the resource use survey), another clinician suggested 6 months based on experience from the adjuvant treatment of breast cancer.

There is some evidence on re-challenge criteria for pembrolizumab and ipilimumab from other trials, which can be used to inform potential time criteria for nivolumab. In the Keynote 054 trial, re-challenge with pembrolizumab is allowed after 6 months.[4] In the MDX010-20 trial, ipilimumab re-challenge was assessed for patients who had stable disease for at least 6 months from baseline.[5, 6]

Based on this information, different time points at which patients may be allowed to be re-challenged with anti-PD1s have been included at 6 months, 1 year and 2 years. The model base case uses 2 years as this gives the most conservative estimates of cost effectiveness (Section 6). However, based on current clinical experience, safety profile and current clinical data (MDX010-20), a 6-month re-challenge with anti-PD-1 would ensure patients relapsing following adjuvant anti PD-1 treatment, are still able to access the most cost-effective treatments already approved for use within the NHS for management of metastatic disease. This not only enhances the cost-effectiveness estimates presented within the submission (Section 6) but also ensures that all patients regardless of BRAF status are able to access anti-PD-1 as systemic treatment.

3. Indirect treatment comparison

The Committee expressed concerns about the generalisability of the results from the indirect treatment comparison (ITC) that compared nivolumab and placebo using the CheckMate 238 and CA184-029 trials. We acknowledge that there are areas of heterogeneity between the two trials, and all efforts have been made to address this, as described below.

The ERG had concerns about the different duration of ipilimumab treatment in the trials. We therefore presented a subgroup ITC in which patients in the ipilimumab arm of the CA184-029 trial were censored after 1 year (if they were still on treatment). This analysis did not substantially change the results of the ITC and made little difference to the ICER when used in the model.

Additionally, we presented Bucher ITCs using the Stage IIIb/c patients from both trials to demonstrate the impact of staging upon the results. Using only Stage IIIb/c patients gave similar results to those obtained using the intention to treat (ITT) populations; this showed that the results of the ITC were consistent across all disease stages and that the differences in inclusion criteria for patient staging were unlikely to impact results.

Table 3 presents the results of the Bucher ITCs that were originally presented in the company submission (Section B2.9, page 77, Table 15) and the Bucher ITCs with ipilimumab censored at 1 year that were provided in response to the ERG's clarification questions.

Table 3: Bucher indirect treatment comparison results

Covariate adjusted	Population	Bucher HR RFS (95% CI) Nivo vs PBO – no censoring	Bucher HR RFS (95% CI) Nivo vs PBO – censored[a]
No	ITT	[redacted]	[redacted]
Yes	ITT	[redacted]	[redacted]
No	Stage IIIb/c	[redacted]	[redacted]
Yes	Stage IIIb/c	[redacted]	[redacted]

Key: CI, confidence interval; HR, hazard ratio; ipi, ipilimumab; ITT, intention-to-treat; nivo, nivolumab; PBO, placebo; RFS, recurrence-free survival.

Notes: [a] CA184-029 trial ipilimumab patients censored at 1 year if on treatment.

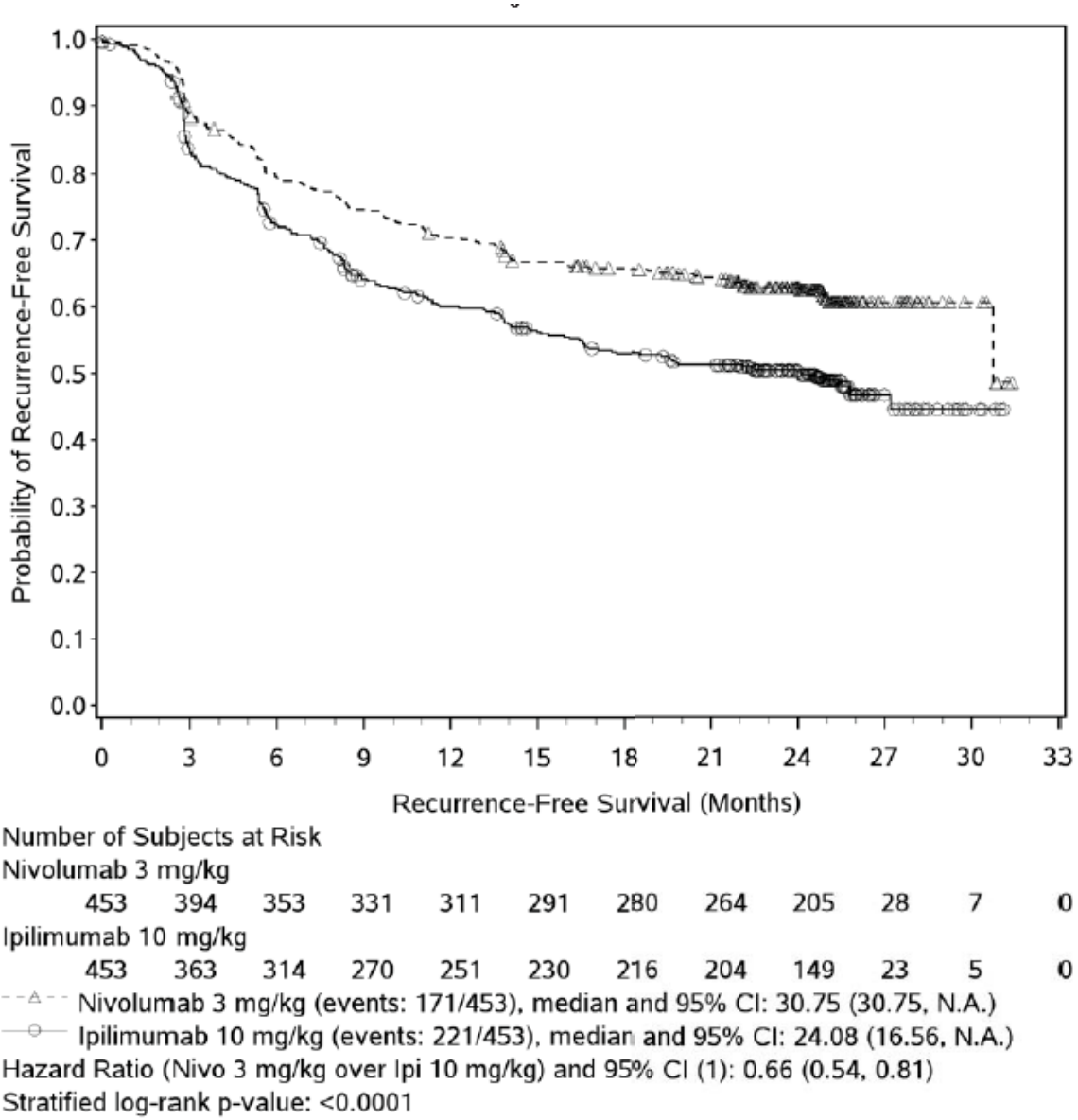
For validation of these outcomes it is possible to look to the KeyNote 054 trial which compares pembrolizumab to routine surveillance in Stage III patients.[4] Pembrolizumab is also a PD-1 inhibitor with a similar mode of action to that of nivolumab, meaning that results would be expected to be reasonably consistent with those shown for nivolumab as they are in the metastatic setting.

All the hazard ratios for nivolumab vs routine surveillance derived from the Bucher ITC are in line with the results of the Keynote 054 trial comparing PD-1 inhibitor pembrolizumab against placebo in a head to head randomised Phase III trial.[4] The results of Keynote 054 show significant benefit of pembrolizumab versus placebo (hazard ratio [HR]: 0.57, 98.4% confidence interval [CI]: 0.43–0.74) and are nearly identical to the covariate adjusted Bucher ITC censoring ipilimumab patients in CA184-029 at 1 year if they were still on treatment [redacted]

Keynote 054 also shows that pembrolizumab has similar outcomes to nivolumab for RFS (72.2% and 72.3% for the Stage IIIb/c subgroup for pembrolizumab and nivolumab, respectively)[7] and that stage is not a treatment effect modifier (p=0.69 for interaction).[4]

As can be seen from the Kaplan Meier data (Figure 1) there is continued separation of the RFS curves post treatment stopping with nivolumab at 12 months, which clinicians expected to continue into the long-term to reflect both the biology of the disease (as the risk of relapse decreases substantially a few years after treatment)[3] and the profile of nivolumab as an immune-oncology treatment.

Figure 1: KM curve for RFS, ITT population, CheckMate 238, 24-month follow-up



Finally, as presented within the original submission the results of the patient-level meta-regression (used in the company base cases) are consistent with the results of the Bucher ITCs (ITT covariate adjusted HR: [redacted] using the exponential curve from the meta-regression).

Taken together these points suggest that the relative benefit of nivolumab compared to placebo would be expected to be similar to that of pembrolizumab versus placebo observed

in a head-to-head RCT (KeyNote-054), and that the results of the ITC are robust and these benefits would be expected to be maintained long-term. The cost-effectiveness estimates presented in Section 6 of this document have been updated to reflect the AC's preferences regarding the ITC methodology.

4. Administration costs

We would like to take the opportunity to respond to point 10 of NHS England's written statement. This point states that:

"NHS England observes that no administration costs for adjuvant therapies appear to have been included in the economic model."

We would like to clarify that administration costs were indeed included in the model for all treatments including subsequent therapies (see company submission, Section B3.5, page 153). The administration cost used in the original submission for adjuvant nivolumab used NHS reference costs code SB12Z (day case and regular day/night £259.76).[8] This equates to an average administration cost of £5,099 per person for adjuvant nivolumab accounting for treatment discontinuation as per the CheckMate 238 trial. The SB12Z NHS reference cost from TA483 was used in the original base case as this reflected the most recent advice received by the ERG suggesting that nivolumab would be infused as a simple parenteral chemotherapy.[9]

However, if the SB13Z NHS reference suggested by NHS England is used as an alternative (£299.68) for adjuvant nivolumab and the subsequent therapies then this equates to an average administration cost of £5,883 per patient with adjuvant nivolumab. This alternative NHS reference cost (SB13Z) has now been applied in the company's revised base case 1 (Section 5) and revised base case 2 (Section 6). Although this increases the ICER, the impact on the cost-effectiveness of nivolumab as adjuvant treatment is minimal.

5. Revised base case 1

Methods

The Committee highlighted key limitations of using a surrogacy relationship to predict overall survival (OS) based on RFS and concluded that the estimated OS benefit was not robust. We acknowledged these limitations in our original submission and made further attempts to explore uncertainty caused by the lack of OS data by including other model options using different data sources. However, during the process of the submission, preliminary descriptive OS data from CheckMate 238 became available, and we therefore presented a scenario in response to ERG clarification questions. In this scenario, the OS curves predicted from the original model base case were adjusted to match the OS Kaplan–Meier data from CheckMate 238 for the nivolumab arm, and a Bucher ITC was used to inform the routine surveillance OS curve.

The ERG presented a similar analysis using the CheckMate 238 OS data but adjusted the curves using the mu parameter in the generalised gamma curve fitted to CA184-029 data, which adjusted the ipilimumab arm so that it matched the CheckMate 238 OS nivolumab Kaplan–Meier curve (see ERG report, Section 6.2.1, page 148). It was then assumed that nivolumab would follow this curve, and hence the difference between nivolumab and routine surveillance would be the same as the difference between ipilimumab and placebo seen in the CA184-029 trial (HR: 0.72, 95% CI: 0.58–0.88).[10] This assumes equal effectiveness between nivolumab and ipilimumab, which can be considered conservative when considering the breadth of clinical evidence form the metastatic setting.

Figure 2 shows the resulting curves for placebo and ipilimumab after adjustment to the mu parameter and the comparison to the CheckMate 238 preliminary OS data.

Figure 2: CheckMate 238 OS Kaplan–Meier data and adjusted CA184-029 parametric curves (assumes equal effectiveness between ipilimumab and nivolumab)

Key: ipi, ipilimumab; KM, Kaplan–Meier; nivo, nivolumab; OS, overall survival.

Given the limitations of the surrogacy relationship and the availability of preliminary OS data from CheckMate 238, we agree with the Committee that using actual data is preferable. Since comparing the CheckMate 238 subsequent therapy profile and real-world subsequent treatment usage has shown that the CheckMate 238 data are reasonably reflective of clinical practice (see Section 1), we would like to present ICERs using the trial OS data for the Committee's consideration. This choice of base case is also based on the following:

- This analysis uses the most recent available data from the trial. Currently, the preliminary OS data from CheckMate 238
- The assumption in this analysis that the difference between nivolumab and routine surveillance would match that of ipilimumab versus placebo in CA184-029 is considered conservative.

- With longer follow up we would expect continued OS gains for nivolumab versus ipilimumab ([redacted]) given the abundance of evidence showing that nivolumab has a greater OS benefit compared to ipilimumab in other settings. For example, evidence from CheckMate 067 suggests that nivolumab has a greater OS benefit compared to ipilimumab with an PFS HR of 0.55 translating to an OS HR of 0.63; as would be expected in the adjuvant setting patients in the trial also went on to receive further treatments upon progression including retreatment with immunotherapies.[11] This shows that early treatment with nivolumab is likely to provide greater benefit in OS compared to ipilimumab (31.3% of patients on nivolumab and 44.4% of patients on ipilimumab received subsequent immunotherapy in CheckMate 067)[12], which is also consistent with clinical opinion. Additionally, the difference between the OS with nivolumab and that with ipilimumab increases over time, from no difference for the first 5 months, to 10% after 12 months, and 18% at 36 months.[11]

- This analysis requires fewer assumptions than the analysis presented in the ERG's preferred base case and revised base case 2 around post-recurrence survival because using the partitioned survival model means that the post-recurrence health state is informed indirectly through OS and RFS which is informed by data collected alongside the CheckMate 238 study, therefore eliminating altogether the need of using the RFS to OS surrogacy relationship to estimate the cost-effectiveness.

In addition to the change in OS curves, based on Committee feedback the revised base case 1 uses the more conservative RFS curves derived from the ITC in which ipilimumab patients in CA184-029 were censored at 1 year if still on treatment.

Lastly, based on the comments in the NHS England written statement on administration costs, the administration cost has been changed from the SB12Z NHS reference cost (£259.76) to SB13Z (£299.68) for adjuvant nivolumab and subsequent treatments.

For this analysis, the subsequent treatments only affect the costs within the model, therefore the original base case subsequent treatment proportions are kept the same so that they are consistent with trial data used to inform the survival extrapolations and as shown in Section 2 are generally reflective of UK clinical practice.

Results

Table 4 presents the results of our revised base case 1. These results are based upon the original partition survival model submitted by the company with the changes described above. Each revision is applied separately from the original submitted base case, and then all changes are applied, providing a revised ICER of £18,423 per QALY gained. This ICER is no longer reliant upon the surrogacy relationship as RFS and OS are modelled based on CheckMate 238. It also uses conservative assumptions regarding the OS profile of nivolumab versus ipilimumab and therefore the ICER would be expected to decrease with longer follow up of OS.

Sensitivity analysis shows consistency with the revised base case ICER with all plausible scenario results under £30,000 per QALY threshold (See Appendix 2).

Table 4: Revised base case 1 (based on original partitioned survival model)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Previous base case using 24 month DBL							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	13.96	[redacted]	[redacted]	[redacted]	[redacted]	£8,882
1. Adjusted CA184-029 OS curves using CheckMate 238 OS data to make adjustment per ERG analysis* (no longer reliant on RFS:OS surrogacy equation)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	17.83	[redacted]	[redacted]	[redacted]	[redacted]	£18,030
2. RFS ITC using censoring at 1 year of ipi treatment in CA184-029							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.68	[redacted]	[redacted]	[redacted]	[redacted]	£9,066
3. Nivolumab admin costs use SB13Z from NHS reference costs*							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	13.96	[redacted]	[redacted]	[redacted]	[redacted]	£9,059
1 + 2 + 3 (all preferred assumptions implemented & no longer reliant on RFS:OS surrogacy equation)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	17.83	[redacted]	[redacted]	[redacted]	[redacted]	£18,423

Key: DBL, database lock; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; LYG, life years gained; OS, overall survival; QALY, quality-adjusted life year; RFS, recurrence free survival.
Notes: *See ERG report Section 6.2.1, page 150, table 65.

Validation of long-term outcomes

One of the limitations in our originally submitted base case was the use of the placebo arm from the CA184-029 trial to estimate OS for routine surveillance. This underestimated the survival gains of patients in clinical practice due to new treatments becoming available upon recurrence. This new analysis resolves that issue by uplifting the curves from CA184-029 using the mu parameter in the generalised gamma curve. By adding 0.5 to the parameter the ipilimumab curve from CA184-029 is uplifted and sits with the CheckMate 238 OS Kaplan–Meier data and used as a proxy for nivolumab OS curve. Routine surveillance is based on the placebo arm in CA184-029 after the uplifted adjustment. Comparing this 'new' routine surveillance curve with external registry data shows that this is much more realistic than previous estimates. Figure 3 shows the routine surveillance estimated OS compared to melanoma registry data. The routine surveillance OS curve is now higher than that of AJCC v7[13] weighted Stage III, which is expected due to advances in melanoma treatment but lower than the data for Stage III from AJCCv8 (as would be expected as our estimates contain Stage IV NED patients as well as Stage III).

Figure 3: External validation of revised base case 1

Additionally, the updated routine surveillance OS curve was compared to the placebo arm in the Phase III trial COMBI-AD looking at adjuvant dabrafenib + trametinib versus placebo for melanoma patients.[14] This trial has a Stage III only population and only considers B-RAF positive patients; however, it is more recent and therefore more generalisable to current practice than the CA184-029 placebo arm. Moreover, B-RAF status was found to be a non-significant prognostic indicator in CheckMate 238 mutant vs wild type patients

Figure 4 presents the placebo Kaplan–Meier curve from COMBI-AD compared to the model routine surveillance OS curve using the model population (Stage III–IV) and to the routine surveillance OS curve after adjusting the corrected group prognosis percentages to reflect the COMBI-AD population (i.e. Stage III and 55% female). This demonstrates the ability of the projections in the model to accurately predict the OS associated with current practice.

The new validation clearly demonstrates that the updated partitioned survival model using KM OS data from CheckMate 238 (and as such no longer reliant upon the surrogacy equation) is a plausible model to inform the cost-effectiveness of nivolumab versus routine surveillance.

Figure 4: Model validation versus COMBI-AD placebo

Key: OS, overall survival; PBO, placebo
Note: COMBI-AD includes only Stage III patients and therefore the OS curve is anticipated to sit higher compared to the routine surveillance OS model population (which used the 029 stage adjusted curve)

6. Revised base case 2

Methods

The Committee concluded that its preferred model was the Markov 2 model because it did not rely on OS assumptions from the surrogacy analysis. Revised base case 1 does not rely on the surrogacy relationship for OS and does not use assumptions from a variety of sources for post-recurrence survival as Markov 2 does. However, given that the ERG and Committee preferred the Markov 2 model we have created a new base case taking in comments on realistic subsequent treatment usage and exploring the uncertainty with realistic scenarios. Consistent with ERG and Committee preference (and our own belief on the most robust of the Markov 2 analyses) we use data from prior NICE appraisals and CheckMate 067 patient level analyses to predict effectiveness for subsequent therapies.

As discussed in Section 2, subsequent treatment data for metastatic melanoma was obtained from real-word data sources, and different subsequent treatment distributions based on time of relapse were explored in the model. Collecting real-word data led to the conclusion that the CheckMate 238 ipilimumab arm post-recurrence treatment data are representative of UK clinical practice and therefore these data were kept in this base case. Scenario analyses are presented using the two real-world data sources which demonstrate consistency between them regarding metastatic melanoma treatments currently used in the UK setting. We understand there may be a question of how this may change if nivolumab is used earlier in the adjuvant setting. Therefore, we discuss this below when we consider assumptions around re-challenge.

Changes to the Markov 2 base case are as follows:

- RFS data were informed by censoring patients in CA184-029 if still on treatment with ipilimumab after 1 year (as per revised base case 1 and in line with the more conservative assumptions preferred by the committee and the ERG).
- The administration cost was revised, using SB13Z NHS reference cost for IV infusion (as per revised base case 1).
- Subsequent treatment data for nivolumab were split by timing of relapse: before 2 years and after 2 years. The 2 year time-point was chosen as the most conservative. BMS's additional analysis looking at progression after next-line therapy in CheckMate 238 suggests an improvement in progression-free survival compared to ipilimumab which demonstrates that it is unlikely that nivolumab in the adjuvant setting effects the efficacy of subsequent treatment including subsequent nivolumab usage.[15] An earlier time point for IO re-challenge at 6 months (in-line with other clinical trial re-challenge)[4, 5] not only improves the cost-effectiveness but also ensures equitable access to highly cost-effective treatment options for managing systemic disease.
    - The data used to inform these estimates were based on the same data used to inform routine surveillance (i.e. the ipilimumab arm from CheckMate 238 in the base case which was shown to be reflective of real-world data in the UK - Table 2).
        - The percentages of subsequent treatment for anti-PD-1s for a relapse before 2 years were excluded and it was assumed that these patients would instead receive ipilimumab. This is based on clinical expert opinion from the committee meeting that the original ipilimumab usage appeared low and that "People relapsing early are likely to have ipilimumab alone".
        - The percentages of subsequent treatments for relapse after 2 years were the same as in the routine surveillance arm, assuming that after this time patients are treated as per current clinical practice including anti-PD-1 agents.

        - Second line treatments were included and assumed to be the same as routine surveillance second line treatments (using the ipilimumab arm from CheckMate 238) and for simplicity these were not split by time of recurrence.
- Local/regional recurrence subsequent therapies costs were removed.
    - In order to represent current UK clinical practice in which no adjuvant therapies are provided, the costs of subsequent treatments in both arms for patients who have a local/regional recurrence were removed (surgery and radiotherapy costs are still accounted for as these remain relevant based on the UK current standard of care). The removal of these costs increases the ICER – see Table 6.

Table 5 presents the subsequent treatment usage used for nivolumab in the revised base case 2. The routine surveillance arm uses the same '1L > 2 years' distribution for any time of recurrence and same 2L+ usage. Figure 5 shows the post-recurrence survival curves used for nivolumab depending on time of recurrence. Using the tunnel states, patients that move into post-recurrence follow the orange curve (≤2 years distribution) and patients who move into recurrence after 2 years follow the blue curve (>2 years distribution).

Table 5: Subsequent treatment usage in revised base case 2 for nivolumab

Subsequent treatments	Previous data used in model*		Used for revised base case (based on 238 ipilimumab arm)		
	1L	2L+	1L ≤2 years	1L >2 years	2L+
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interleukin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Subsequent treatments	Previous data used in model*		Used for revised base case (based on 238 ipilimumab arm)		
	1L	2L+	1L ≤2 years	1L >2 years	2L+
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Key: 1L, first line; 2L+, second line and beyond. **Notes**: *Previous data used in the model was based on subsequent therapy usage from nivolumab arm in CheckMate 238.					

Figure 5: Post-recurrence survival split by time of recurrence

[redacted]

Results

Table 6 presents the results of the new base case for the Markov 2 model; changes are shown applied separately and then all together. The new ICER is £18,018 per QALY gained.

Sensitivity analysis demonstrates constancy with the base case ICER and the majority of scenarios are under £30,000 per QALY threshold (See Appendix 3).

Table 6: Revised base case 2 results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Previous submitted base case with Markov 2 using 24 month DBL ITC							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.08	[redacted]	[redacted]	[redacted]	[redacted]	£18,685
1. RFS using censoring at 1 year of ipi treatment in CA184-029							
Nivolumab	[redacted]	[redacted]	[redacted]				

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	14.19	[redacted]	[redacted]	[redacted]	[redacted]	£18,960
2. Nivolumab admin costs use SB13Z from NHS reference costs							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.08	[redacted]	[redacted]	[redacted]	[redacted]	£19,076
3. Subsequent treatment for nivolumab data split by time of recurrence (2 years) and using ipi arm from CheckMate 238							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.08	[redacted]	[redacted]	[redacted]	[redacted]	£14,661
4. ***No subsequent therapy costs for local/regional recurrence***							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.08	[redacted]	[redacted]	[redacted]	[redacted]	£22,084
1 + 2 + 3 + 4							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.19	[redacted]	[redacted]	[redacted]	[redacted]	£18,018

Key: DBL, database loack; ICER, incremental cost-effectiveness ratio; ipi, ipilimumab; ITC, indirect treatment comparison; LYG, life years gained; OS, overall survival; QALY, quality-adjusted life year; RFS, recurrence free survival.

Scenarios were explored using real-world sources (IPSOS and Wilmington) and a scenario is also presented in which post-recurrence survival and subsequent treatment usage was the same in both treatment arms. Additionally, alternative time points of 6 months and 1 year for allowance of re-challenge with anti-PD1s were also explored. Using the other sources for subsequent treatments the same approach was taken for the nivolumab arm to split the distributions by timing of recurrence. Anti-PD-L1 treatments were removed and applied to ipilimumab before the time point of re-challenge. Table 7 presents the results of each scenario.

Table 7: Markov 2 scenarios

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Revised base case with Markov 2							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.19	[redacted]	[redacted]	[redacted]	[redacted]	£18,018
Scenario 1: subsequent treatment data sources from IPSOS							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.19	[redacted]	[redacted]	[redacted]	[redacted]	£17,488
Scenario 2: subsequent treatment data sourced from Wilmington*							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.19	[redacted]	[redacted]	[redacted]	[redacted]	£18,151
Scenario 3: Subsequent treatment data sourced from CheckMate 238 with same applied in both arms at all time points							

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.19	[redacted]	[redacted]	[redacted]	[redacted]	£16,913
Scenario 4: Alternative time point of 6 months for subsequent treatment distribution switch data sourced from CheckMate 238							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.19	[redacted]	[redacted]	[redacted]	[redacted]	£17,467
Scenario 5: Alternative time point of 1 year for subsequent treatment distribution switch data sourced from CheckMate 238							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.19	[redacted]	[redacted]	[redacted]	[redacted]	£17,737

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year.
Notes: *Assumes the same usage of subsequent therapies across 1L and 2L+ as data was not split by line

Validation of long-term outcomes

The final modelled OS for routine surveillance using Markov 2 produced higher estimates than the original company base case using the partitioned survival model but the predictions were still low compared to what would be expected in clinical practice (See company submission, Appendix N.2 page 125). The revised base case for Markov 2 does not change the original projections of routine surveillance in the original company submission therefore the routine surveillance curve predicts lower outcomes compared to revised base case 1.

Figure 6 presents the routine surveillance OS from the model versus external data sources and Figure 7 presents the routine surveillance OS versus the COMBI-AD placebo OS curve, already reviewed by the AC. This demonstrates that the predicted OS from routine surveillance in Markov 2 is lower than expected and underestimates survival for these patients.

Figure 6: External validation of Markov 2

Figure 7: Markov 2 model validation versus COMBI-AD placebo

Summary of revised base case analyses

Markov Option 2 was originally provided to assess the impact of subsequent treatments on the ICER given the reliance of the partitioned survival model on the surrogacy equation for

RFS and OS and associated uncertainty. However, the revised base case 1 analyses presented no longer rely upon the RFS:OS surrogacy equation and directly reflect survival outcomes based on CheckMate 238 for nivolumab and the predicated routine surveillance arm is consistent with that seen in the more recent trial COMBI-AD.

Whilst subsequent metastatic melanoma treatments exploration is important, scenarios run need to be reflective of current clinical practice. This is not currently the case for the ICER presented within the ACD. This looks more at the melanoma treatment pathway overall and does not account for the fact that subsequent treatments for the management of metastatic melanoma are highly cost-effective and are recommended by NICE.

Our current approach to modelling of subsequent treatments for metastatic disease is plausible, as it uses scenarios for subsequent treatment which are reflective of the UK clinical practice and avoids additional model complexity which otherwise, goes beyond the scope of the STA process itself. The cost-effectiveness of nivolumab as adjuvant therapy following melanoma resection is demonstrated from both of the revised base case options whilst also incorporating the ERG's preferred assumptions following the 1st committee meeting. In conclusion, these analyses demonstrate that nivolumab is cost-effective when clinically plausible scenarios are explored.

7. Complex extrapolation of recurrence-free survival

The Committee highlighted that the methodologies used to estimate RFS for the comparison of nivolumab versus routine surveillance were extremely complex and did not provide a reliable indication of the size of this benefit. This is referring to the use of Kaplan–Meier data for the first 12 weeks and use of the long-term RFS curve to extrapolate RFS beyond 10 years in both treatment arms.

We would like to stress that the methodologies used to extrapolate the RFS curves are common techniques use in prior appraisals for both nivolumab and ipilimumab and were not considered highly complex during those appraisals. Combination of data sources to allow more robust extrapolation to be conducted has been seen in many submissions including previous indications for melanoma[16-18] and the recently appraised dabrafenib + trametinib for adjuvant treatment of melanoma.[3]

The adjustments made were needed to ensure that the data used were comparable between treatment arms, which is a standard and expected methodology. The data used to inform these adjustments were from the best available sources and tested in sensitivity analyses.

As with the majority of melanoma trials, Kaplan–Meier data were used initially in the economic model as a sharp protocol-driven drop was observed around the timing of the first assessment, which could not be fitted to using standard parametric techniques (See Section B2.9, page 58 in the company submission).

The Kaplan–Meier data used for routine surveillance for the first 12 weeks could not be taken directly from the CA184-029 placebo arm as this would give an unfair comparison between nivolumab and routine surveillance. If a naïve comparison were to be made results would have been biased towards nivolumab. Instead, a cox regression was performed on only the ipilimumab arms of CheckMate 238 and CA184-029, in which patients were censored at 12 weeks in order to estimate the trial effect during this period and to make CA184-029 data comparable to CheckMate 238 for the first 12 weeks. This produced a hazard ratio of [redacted] for ipilimumab (CA184-029) vs ipilimumab (CheckMate 238). The uncertainty around this hazard ratio made little difference to the ICER (which ranged from £17,805 to £18,899 per QALY gained if using revised base case 1, or from £21,255 to £26,430 per QALY gained using revised base case 2) and therefore did not impact the cost effectiveness.

The extrapolated data alone produced low estimates of survival compared to long-term sources available; 10-year OS from the CA184-029 placebo arm was estimated to be approximately [redacted] compared to 70% in AJCC version 8[19], 39% in AJCC version 7[20] (weighted stage III curve) and 75% from E1697.[21] Therefore, long-term adjustment was applied to both OS and RFS curves. Long-term melanoma registry data were used as a proxy for RFS because no appropriate long-term RFS data were available. Again, if we had used trial data directly, results would have been considered to be biased in favour of nivolumab. Therefore, in order to estimate a more appropriate long-term RFS curve, a hazard ratio was applied which was based on OS vs RFS. The source used for the hazard ratio in the base case was an interferon trial which had the longest follow-up in the adjuvant setting.[21] Additionally, a hazard ratio derived from the CA184-029 trial was also explored as a scenario. These HRs were subsequently applied on the long term AJCC v8 data to adjust the RFS curve from year 10 onwards.

The hazard ratio estimated from the interferon trial (E1697) was [redacted] and the hazard ratio estimated from the CA184-029 trial was [redacted] Using either source makes little difference to the ICER and using a hazard ratio of 1 (i.e. the

long-term curve directly) also makes little difference. Table 8 presents the ICERs using these different data sources based on the revised base cases.

Table 8: Adjustment to long-term recurrence-free survival curve scenarios

Data used	ICER using revised base case 1	ICER using revised base case 2
E1697 (base case) (HR=[redacted])	£18,423	£18,018
CA184-029 (HR=[redacted])	£18,788	£18,558
Long term curve directly (HR=1)	£17,694	£16,856
Key: HR, hazard ratio; ICER, incremental cost-effectiveness ratio		

Figure 8 and Figure 9 present the model's extrapolated curves at each stage of the curve fitting process and associated ICERs using revised base case 1 for OS and RFS, respectively. For OS, the first curve shows the extrapolated curve directly; this is then adjusted for background general population mortality in the second curve. The third curve shows the extrapolation once the long-term melanoma registry data are applied at 10 years. Similarly, for RFS, the first curve shows the 12-week Kaplan–Meier data directly from CA184-029 with no hazard ratio adjustment plus parametric curve; the second curve shows the adjusted Kaplan–Meier data plus parametric curve; and the third curve shows the long-term adjusted curve applied at 10 years. At each stage of the adjustment, the ICER increased and therefore adjustments applied were based on clinical plausibility and not to favour extrapolated nivolumab benefit.

Figure 8: Model overall survival curves at each adjustment stage

Key: Gen pop, general population; OS, overall survival; QALY, quality-adjusted life year.

Figure 9: Model recurrence-free survival curves at each adjustment stage

Key: KM, Kaplan–Meier; Gen pop, general population; QALY, quality-adjusted life year; RFS, recurrence-free survival
Note: RFS curves meet OS curves at approximately 35 years and 45 years for nivolumab and routine surveillance respectively.

8. Benefit: risk ratio for patients with a lower risk of relapse

The Committee highlighted the risks of adjuvant treatment in patients who have a lower risk of relapse – a potential scenario being that a patient who would not have relapsed without treatment suffers the side effects of adjuvant therapy with nivolumab. Clinicians at the committee confirmed that nivolumab is a very well tolerated drug and serious side effects are generally rare but for Stage IIIA patient's in particular the application of adjuvant treatment would be carefully considered to confirm appropriate risk/benefit. The Committee also concluded that "careful assessment and consideration of the likely benefits of treatment would be important" for clinicians and patients. The risk to benefit ratio was also thoroughly assessed by the EMA and deemed favourable for nivolumab. Clinicians present [redacted]" [22].

We agree that careful assessment would be required for lower risk patients, but would like to reassure the Committee that cost effectiveness remains consistent across all stages of disease.

Although patients with Stage IIIA disease have a lower risk of relapse than those with Stage IIIB, IIIC and IV disease, nivolumab can still provide a benefit in terms of RFS and is still cost effective. In the model, cost-effectiveness analysis by stage subgroup was explored, using the corrected group prognosis on the parametric curves (see company submission, Section B2.9, Page 64) to project survival based on patient characteristics including stage.

For each subgroup, the proportion of patients in each stage was changed to 100% (depending on the subgroup explored). Other patient characteristic distributions – age, sex and weight – were kept the same as in the base case. Table 10 and Table 11 present the results of these analyses. Nivolumab remained cost effective for each disease stage in revised base case 1 and 2.

It should be noted that in the KeyNote 054 trial for pembrolizumab, which is also a PD-1 inhibitor, there was no significant difference seen in treatment effect across stages and no numerical indication of reduced impact in Stage IIIA patients (in fact HR is numerically lower in this group).[4]

The high unmet medical need within Stage IIIA patients as the rate of relapse remains high following resection at around 48%.[23] The results of the cost-effectiveness subgroup by disease stage demonstrate the cost-effectiveness across each Stage III subgroup. This highlights the importance of making this technology available to the overall EMA approved population, which is likely to result in even greater health and societal gains as of a result introducing an effective adjuvant treatment option in the NHS.

Table 10: Subgroup analysis by melanoma stage – revised base case 1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Stage IIIA							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	23.67	[redacted]	[redacted]	[redacted]	[redacted]	£23,076

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Stage IIIB							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	19.56	[redacted]	[redacted]	[redacted]	[redacted]	£18,762
Stage IIIC							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	15.29	[redacted]	[redacted]	[redacted]	[redacted]	£17,782
Stage IV (NED)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	15.29	[redacted]	[redacted]	[redacted]	[redacted]	£17,626
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NED, no evidence of disease; QALY, quality-adjusted life year.							

Table 11: Subgroup analysis by melanoma stage – revised base case 2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALYs)
Stage IIIA							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	16.72	[redacted]	[redacted]	[redacted]	[redacted]	£18,525
Stage IIIB							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.98	[redacted]	[redacted]	[redacted]	[redacted]	£17,736
Stage IIIC							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	13.03	[redacted]	[redacted]	[redacted]	[redacted]	£18,821
Stage IV (NED)							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	13.32	[redacted]	[redacted]	[redacted]	[redacted]	£18,682
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NED, no evidence of disease; QALY, quality-adjusted life year.							

9. The impact of potential data collection within the CDF

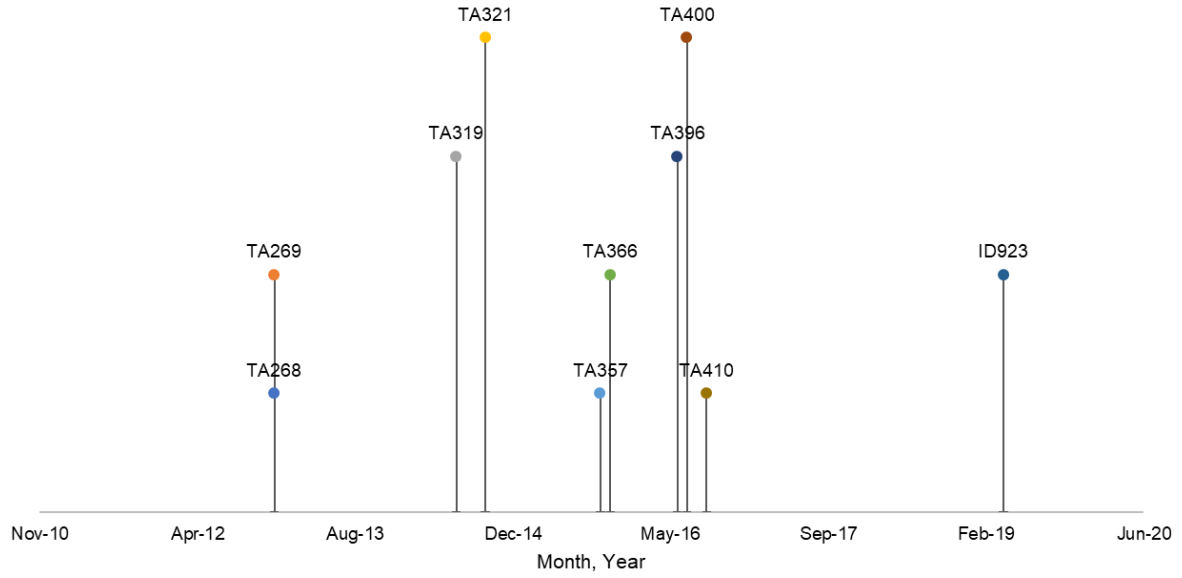
BMS believes nivolumab to be a cost-effective option for routine commissioning, although a CDF recommendation may also be considered if the Committee deems this as an appropriate route in making this innovative drug available to patients.

Waiting for further data collection in CheckMate 238 would further show the magnitude of benefit of nivolumab over ipilimumab, both in terms of RFS and OS. Although further data collection would not solve the lack of a head to head comparison, proving efficacy versus an active comparator (that has itself demonstrated significant benefit over placebo for both RFS and OS) is more challenging. In a global advisory board, melanoma experts noted that the CheckMate 238 study is a well-designed trial and valued the use of a proven efficacious active therapy than being placebo controlled.[24]

However, the patient-level meta-regression which is considered to be the highest standard of ITC was used to attempt solving the heterogeneity between the trials. This showed that different subgroups and comparisons did not make a difference in terms of benefit of nivolumab and provided results that were well supported by the KeyNote 054 trial data for pembrolizumab versus placebo and as such the heterogeneity within the ITC is anticipated to very limited.

Further, the CDF may be restricted in addressing changes in the clinical pathway in the future. More treatments available for patients with unresectable or metastatic melanoma and the management has changed significantly over the last 6 years. Since 2012, nine metastatic melanoma treatments have been accepted by NICE with one more due to be appraised in April 2019 (Figure 12). This change is further substantiated by the introduction of adjuvant therapies; therefore, collection of more data does not solve the matter of changing pathway and expected long-term outcomes.

Figure 12: Metastatic treatment timeline



Key: TA, technology appraisal
TA268 – Ipilimumab (previously treated); TA269 – Vemurafenib; TA319 – Ipilimumab (previously untreated); TA321 – Dabrafenib; TA357 – Pembrolizumab (previously treated with ipilimumab); TA366 – Pembrolizumab (previously untreated with ipilimumab); TA396 – Dabrafenib + trametinib; TA400 – Nivolumab + ipilimumab; TA410 – T-VEC; ID923 – Encorafenib + binimetinib.

Additional data from CM-238 and impact of waiting

If the Committee considers CDF to be a relevant option pending additional clinical data from CheckMate 238 as the study follow up continues, BMS anticipates it could disclose additional clinical data approximately in the dates outlined below.

The anticipated availability of final OS data is expected [redacted] BMS expects that final subsequent treatment data will also be made available in [redacted] Adding an additional [redacted] months for data analysis and re-submission to the above timelines would mean that the earliest nivolumab could be available would be approximately [redacted] years (for OS) and assuming no additional time for the NICE process. Based upon the observed trial data only 3.4 patients have to be treated with nivolumab instead of observation to prevent 1 additional recurrence/death at 24 months.[25]

Moreover, waiting for more data to be collected would incur avoidable costs as of a result of disease recurrence in metastatic setting for patients who would be eligible to receive adjuvant nivolumab. From the budget impact analysis conducted by NICE, it was estimated that 1,365 patients in 2018 and 1,435 patients in 2019 and 1,508 patients in 2020 will be eligible for adjuvant therapy (assuming 5.1% melanoma increase incidence per year). Predicted market shares previously submitted by BMS assuming an uptake of nivolumab which included other adjuvant melanoma therapies recently appraised, suggest that [redacted] of these patients in 2018, [redacted] in 2019 and [redacted] in 2020 would receive nivolumab; this means that in [redacted] years, [redacted] patients would have missed out on adjuvant treatment with nivolumab, resulting in approximately [redacted] avoidable recurrences or deaths. The majority of recurrences would require subsequent metastatic treatment which is associated with higher health care costs due to complex disease management and limited survival outcomes, whereas adjuvant treatment duration is fixed (12 months) and associated with improved survival outcomes as of a result of preventing disease relapse.

10. Conclusion

The new evidence presented for real-word usage of subsequent therapy in the metastatic setting is comparable to the data used to represent the routine surveillance arm from CheckMate 238. Amending the model base case to reflect timing of recurrence and real-world evidence sources demonstrates that nivolumab is a cost-effective treatment in either scenario.

Additionally, we have presented a revised base case using the preliminary OS data, with a conservative assumption that nivolumab and ipilimumab have equal efficacy. This analysis also shows that nivolumab is a cost-effective treatment compared to routine surveillance.

Based on these findings we believe that it is likely that nivolumab will be cost effective and therefore nivolumab should be available for patients with resected Stage III–IV melanoma via routine commissioning to address the current unmet need of these patients, ensuring equitable access to effective adjuvant treatment options regardless of *BRAF* status.

References

1. Ascierto PA, Kirkwood JM, Grob J-J, et al. The role of BRAF V600 mutation in melanoma. *Journal of Translational Medicine*. 2012; 10:85-.
2. Bristol Myers Squibb (BMS). UK advisory board. November 2017 2018. Data on file.
3. National Institute for Health and Care Excellence. ID1226: Dabrafenib in combination with trametinib for adjuvant treatment of resected BRAF V600 positive malignant melanoma. 2018. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10188. Accessed: September 2018.
4. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. LID - 10.1056/NEJMoa1802357 [doi]. 2018; (1533-4406 (Electronic)).
5. Robert C, Hodi FS, O'day S, et al. Re-induction With Ipilimumab, gp100 Peptide Vaccine, Or A Combination of Both in A Phase III Study of Previously-treated Patients With Advanced Melanoma: Update of Clinical Characteristics of Patients. ESMO. Milan, Italy. 8 - 12 October 2010. Poster.
6. Robert C, Schadendorf D, Messina M, et al. Efficacy and safety of retreatment with ipilimumab in patients with pretreated advanced melanoma who progressed after initially achieving disease control. *Clin Cancer Res*. 2013; 19(8):2232-9.
7. Eggermont AMM, Robert C and Ribas A. The new era of adjuvant therapies for melanoma. *Nat Rev Clin Oncol*. 2018; 15(9):535-6.
8. NHS. NHS reference costs. 2017. Available at: https://www.gov.uk/government/collections/nhs-reference-costs.
9. National Institute for Health and Care Excellence (NICE). TA483: Nivolumab for previously treated locally advanced or metastatic squamous non-small-cell lung cancer: Committee papers. 2017. Available at: https://www.nice.org.uk/guidance/ta483/documents/committee-papers. Accessed: April 2017.
10. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in Stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med*. 2016; 375(19):1845-55.
11. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med*. 2017; 377(14):1345-56.
12. Bristol Myers Squibb (BMS). Scientific Advisory Group - Oncology: Breifing document. 18 June 2018. Data on File.
13. Balch CM, Gershenwald JE, Soong S-j, et al. Final Version of 2009 AJCC Melanoma Staging and Classification. *J Clin Oncol*. 2009; 27(36):6199-206.
14. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in Stage III BRAF-mutated melanoma. *N Engl J Med*. 2017.
15. Bristol Myers Squibb (BMS). Response to request for supplementary information. 25 January 2018. Data on file.
16. National Institute for Health and Care Excellence (NICE). [TA268] Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. 2012. Available at: https://www.nice.org.uk/guidance/ta268. Accessed: 28 March 2018.
17. National Institute for Health and Care Excellence (NICE). [TA400] Nivolumab in combination with ipilimumab for treating advanced melanoma. 2016. Available at: https://www.nice.org.uk/Guidance/TA400. Accessed: 28 March 2018.
18. National Institute for Health and Care Excellence (NICE). [TA384] Nivolumab for treating advanced (unresectable or metastatic) melanoma. 2016. (Updated: 18 February 2016) Available at: https://www.nice.org.uk/guidance/ta384. Accessed: 28 March 2018.
19. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017; 67(6):472-92.
20. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009; 27(36):6199-206.

21. Agarwala SS, Lee SJ, Yip W, et al. Phase III Randomized Study of 4 Weeks of High-Dose Interferon-alpha-2b in Stage T2bNO, T3a-bNO, T4a-bNO, and T1-4N1a-2a (microscopic) Melanoma: A Trial of the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network Cancer Research Group (E1697). *J Clin Oncol*. 2017; 35(8):885-92.
22. Bristol Myers Squibb (BMS). Scientific Advisory Group - Oncology: Meeting minutes. June 2018. Data on File.
23. Romano E, Scordo M, Dusza SW, et al. Site and Timing of First Relapse in Stage III Melanoma Patients: Implications for Follow-Up Guidelines. *J Clin Oncol*. 2010; 28(18):3042-7.
24. Bristol Myers Squibb (BMS). Global Advisory board. January 2018. Data on file.
25. Shoushtari AF, M; Betts, K; Gupte-Singh, K; Jiang, S: Du, E: Ritchings, C; Rao, S. Indirect Treatment Comparison of Nivolumab Versus Placebo as Adjuvant Therapy for Resected Melanoma. ASCO. Chicago, USA. June 1–5 2018. 9593.

11. Appendix 1: List of Trusts from Wilmington health care data

The 60 trusts which treated metastatic melanoma patients, from England and Wales are listed below.

□□□

□□□

□□□

□□□

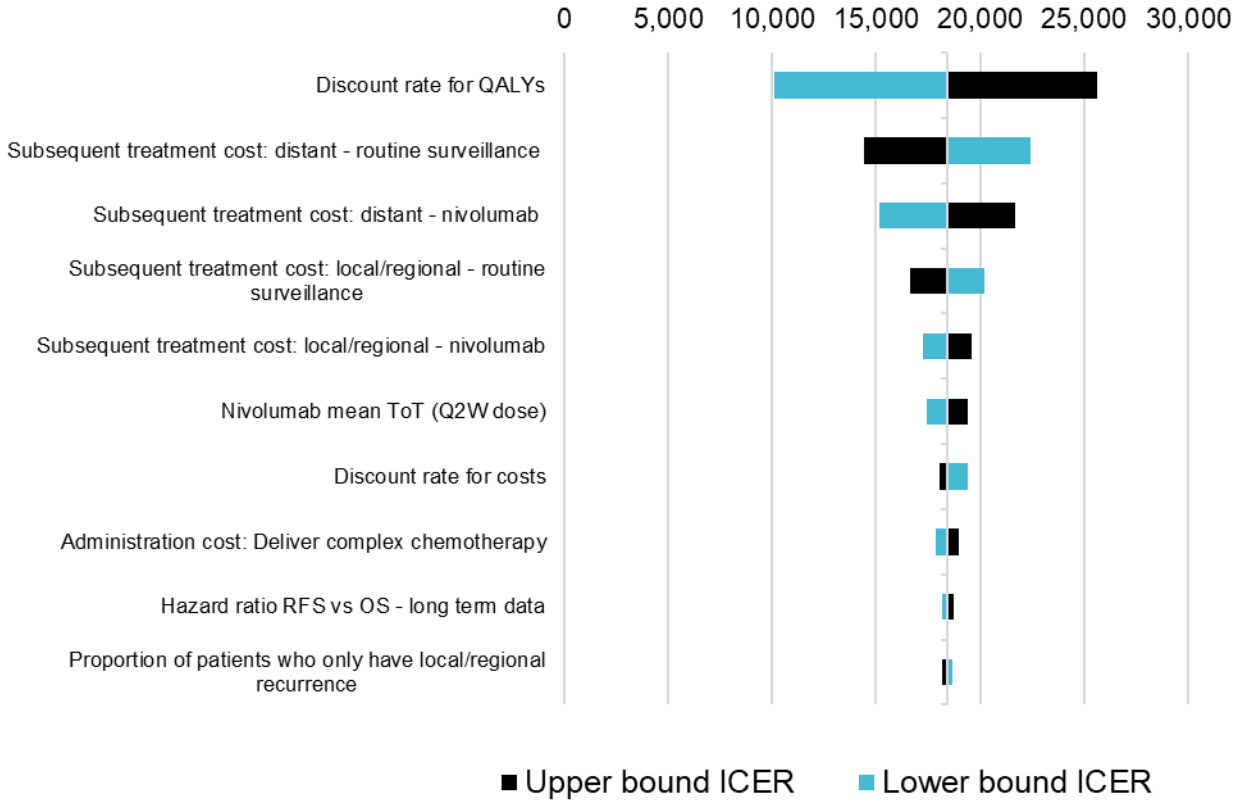
□□□

□□□

12. Appendix 2: Revised base case 1 sensitivity analysis

Deterministic sensitivity analysis

Figure 13: Tornado diagram of the 10 most influential parameters on the ICER – revised base case 1



Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; RFS, recurrence-free survival; ToT, time on treatment.

Probabilistic sensitivity analysis

Table 12: Mean results of PSA (1,000 runs) and comparison with deterministic results – revised base case 1

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	17.83	[redacted]	[redacted]	[redacted]	[redacted]	£18,423
PSA results							
Nivolumab	[redacted]	[redacted]	[redacted]				

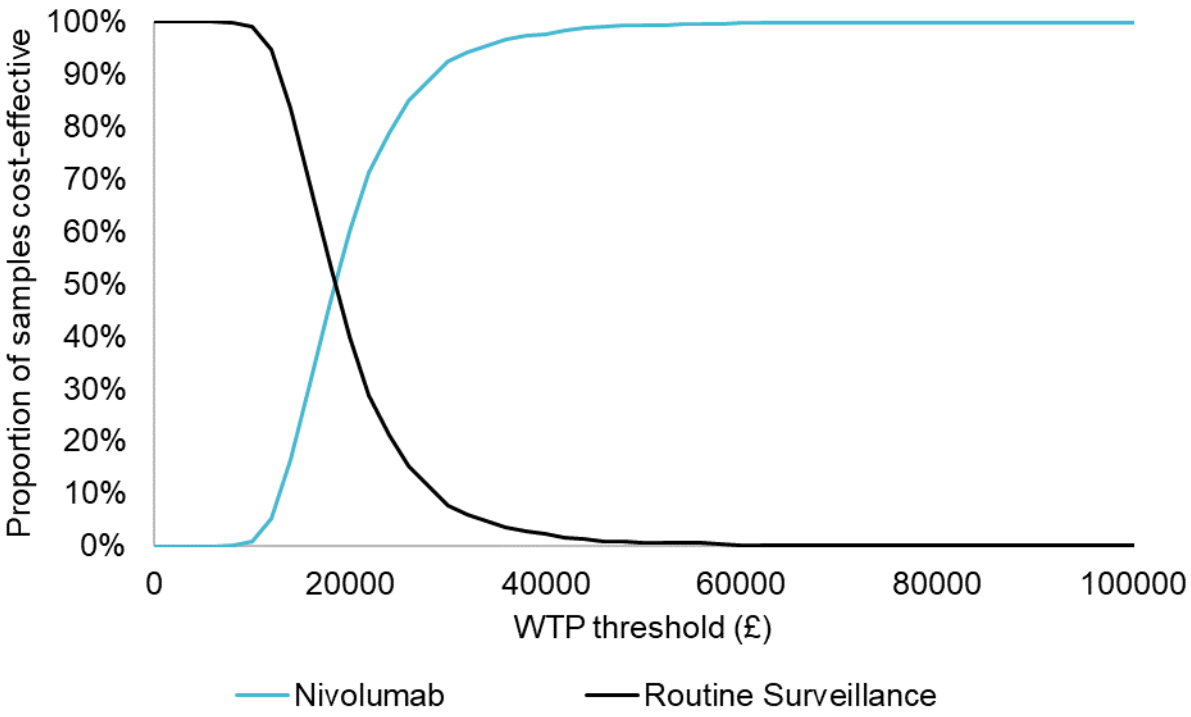
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	18.23	[redacted]	[redacted]	[redacted]	[redacted]	£18,417
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year							

Figure 14: Cost-effectiveness plane – revised base case 1

Key: QALYs, quality-adjusted life years; WTP, willingness to pay.

The probability of nivolumab being cost-effective is 60.0% and 92.4% at willingness to pay thresholds (WTP) £20,000 per QALY and £30,000 per QALY, respectively (Figure 15).

Figure 15: Cost-effectiveness acceptability curve – revised base case 1



Key: WTP, willingness to pay.

Scenario analysis

Table 13: Results of scenario analysis – revised base case 1

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
Base case			[redacted]	[redacted]	[redacted]	18,423
Population	Patient characteristics: (029 and 238) Stage proportions: 029 & 238 adjusted RFS for nivolumab and routine surveillance: ITC (029 and 238)	CheckMate 238 CheckMate 238 Nivo: 238 only, routine surveillance: Bucher ITC	[redacted]	[redacted]	[redacted]	17,103
Half cycle correction	Yes	No	[redacted]	[redacted]	[redacted]	17,770
Time horizon	60 years	40 years	[redacted]	[redacted]	[redacted]	19,063
		50 years	[redacted]	[redacted]	[redacted]	18,548
Weight data	Western European trial data	UK metastatic melanoma	[redacted]	[redacted]	[redacted]	18,359
Vial sharing	Method of moments	Cost per mg	[redacted]	[redacted]	[redacted]	17,546
Subsequent treatment data source	Trial '238 data	Trial '029 data	[redacted]	[redacted]	[redacted]	14,835
RFS distribution (all)	Log-logistic	Exponential*	[redacted]	[redacted]	[redacted]	27,028
		Gompertz*	[redacted]	[redacted]	[redacted]	12,183
		Log-normal	[redacted]	[redacted]	[redacted]	17,637
		GGamma	[redacted]	[redacted]	[redacted]	17,982
		Weibull	[redacted]	[redacted]	[redacted]	19,397
Long-term survival adjustment	Gershenwald, applied after10 years. OS vs RFS HR from E1697	No long-term adjustment	[redacted]	[redacted]	[redacted]	16,669
		Gershenwald, 5 years	[redacted]	[redacted]	[redacted]	23,023
		Gershenwald, 20 years	[redacted]	[redacted]	[redacted]	16,859
		Balch, 5 years	[redacted]	[redacted]	[redacted]	32,029
		Balch, 10 years	[redacted]	[redacted]	[redacted]	21,796
		Balch, 20 years	[redacted]	[redacted]	[redacted]	17,719
		OS/RFS HR from '029 trial	[redacted]	[redacted]	[redacted]	18,788

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
		Balch, OS/RFS HR from '029 trial	[redacted]	[redacted]	[redacted]	22,487
OS for routine surveillance	Generalised Gamma	Exponential*	[redacted]	[redacted]	[redacted]	14,815
		Gompertz	[redacted]	[redacted]	[redacted]	13,273
		Log-normal	[redacted]	[redacted]	[redacted]	17,978
		Log-logistic	[redacted]	[redacted]	[redacted]	18,006
		Weibull*	[redacted]	[redacted]	[redacted]	17,802
Long-term-data curve selection	Gershenwald, GGamma	Balch, Exponential**	[redacted]	[redacted]	[redacted]	30,357
		Balch, GGamma	[redacted]	[redacted]	[redacted]	21,796
		Balch, Log-normal	[redacted]	[redacted]	[redacted]	24,894
		Balch, Log-logistic	[redacted]	[redacted]	[redacted]	24,849
		Balch, Weibull**	[redacted]	[redacted]	[redacted]	26,543
		Exponential**	[redacted]	[redacted]	[redacted]	22,709
		Gompertz	[redacted]	[redacted]	[redacted]	17,912
		Log-normal	[redacted]	[redacted]	[redacted]	20,127
		Log-logistic	[redacted]	[redacted]	[redacted]	20,590
		Weibull**	[redacted]	[redacted]	[redacted]	21,476
End-of life costs	Applied to all deaths	Death from post-recurrence only	[redacted]	[redacted]	[redacted]	18,249
Utilities source	Observed EQ-5D	Include AE disutilities: No	[redacted]	[redacted]	[redacted]	18,386
	Apply same utility to across treatments Separate stage covariate Include AE disutilities: Yes	Mapped EQ-5D Include AE disutilities: No	[redacted]	[redacted]	[redacted]	18,639
		Mapped EQ-5D Include AE disutilities: Yes	[redacted]	[redacted]	[redacted]	18,677
		Middleton et al.	[redacted]	[redacted]	[redacted]	14,016
		Treatment specific utilities	[redacted]	[redacted]	[redacted]	18,760
		Mapped EQ-5D Treatment specific utilities	[redacted]	[redacted]	[redacted]	19,023
		Grouped stage covariate	[redacted]	[redacted]	[redacted]	18,423
		Mapped EQ-5D data, grouped stage covariate	[redacted]	[redacted]	[redacted]	18,677

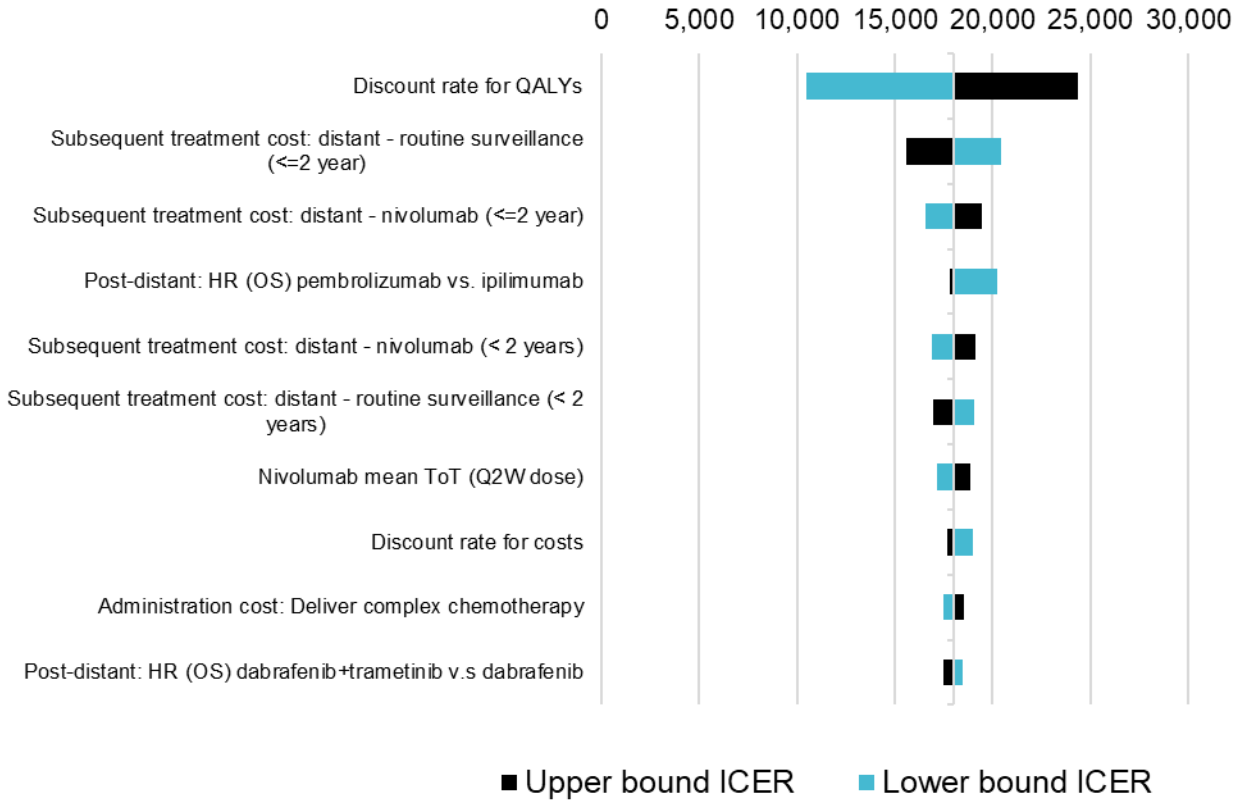
Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
Observation AEs	Assume same as nivolumab	No AEs	[redacted]	[redacted]	[redacted]	18,597

Key: AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; LY, life year; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RFS, recurrence-free survival.
Note: The curve fits that are indicated (*) are those which do not meet the validation criteria as displayed in Table 13 and Table 14 in company submission (**) are those that fit the data poorly.

13. Appendix 3: Revised base case 2 sensitivity analysis

Deterministic sensitivity analysis

Figure 16: Tornado diagram of the 10 most influential parameters on the ICER – revised base case 2



Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; RFS, recurrence-free survival; ToT, time on treatment.

Probabilistic sensitivity analysis

Table 14: Mean results of PSA (1,000 runs) and comparison with deterministic results – revised base case 2

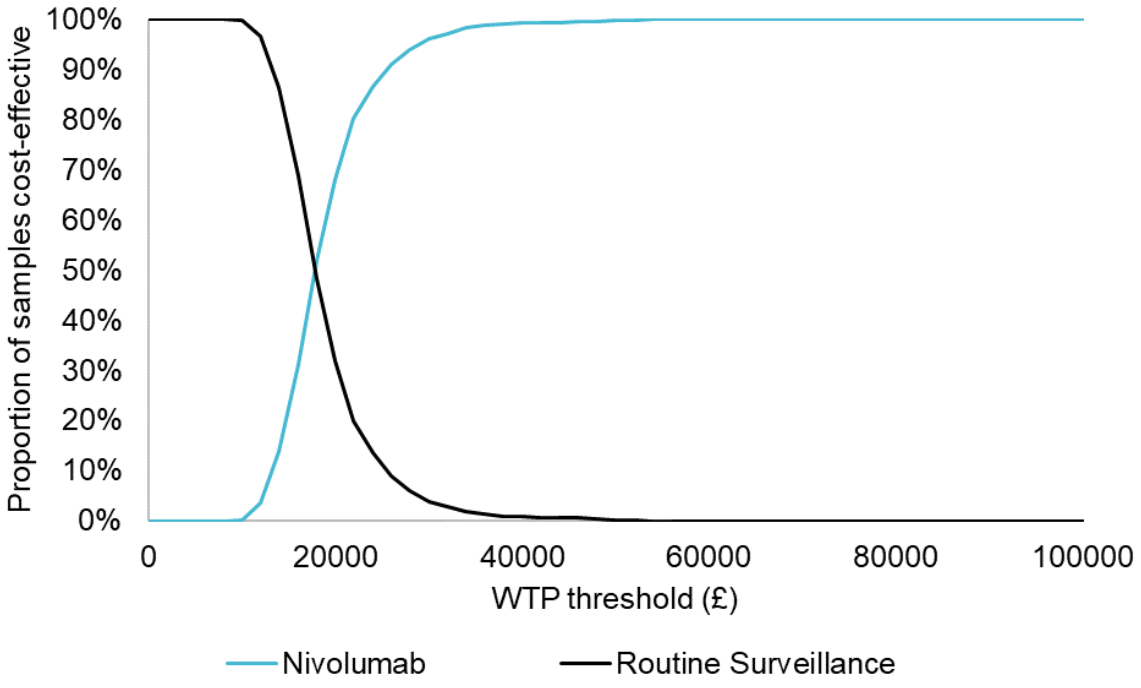
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.19	[redacted]	[redacted]	[redacted]	[redacted]	£18,018
PSA results							
Nivolumab	[redacted]	[redacted]	[redacted]				
Routine surveillance	[redacted]	14.31	[redacted]	[redacted]	[redacted]	[redacted]	£18,027
Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year							

Figure 17: Cost-effectiveness plane – revised base case 2

Key: QALYs, quality-adjusted life years; WTP, willingness to pay.

The probability of nivolumab being cost-effective is 52.1% and 93.4% at willingness to pay thresholds (WTP) £20,000 per QALY and £30,000 per QALY, respectively (Figure 15).

Figure 18: Cost-effectiveness acceptability curve – revised base case 2



Key: WTP, willingness to pay.

Scenario analysis

Table 15: Results of scenario analysis – revised base case 2

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
Base case			[redacted]	[redacted]	[redacted]	18,018
Population	Patient characteristics: (029 and 238) Stage proportions: 029 & 238 adjusted RFS for nivolumab and routine surveillance: ITC (029 and 238)	CheckMate 238 CheckMate 238 Nivo: 238 only, routine surveillance: Bucher ITC	[redacted]	[redacted]	[redacted]	16,974
Half cycle correction	Yes	No	[redacted]	[redacted]	[redacted]	17,609
Time horizon	60 years	40 years	[redacted]	[redacted]	[redacted]	18,469
		50 years	[redacted]	[redacted]	[redacted]	18,111
Weight data	Western European trial data	UK metastatic melanoma	[redacted]	[redacted]	[redacted]	17,960
Vial sharing	Method of moments	Cost per mg	[redacted]	[redacted]	[redacted]	17,250
RFS distribution (all)	Log-logistic	Exponential*	[redacted]	[redacted]	[redacted]	66,977
		Gompertz*	[redacted]	[redacted]	[redacted]	10,980
		Log-normal	[redacted]	[redacted]	[redacted]	16,590
		GGamma	[redacted]	[redacted]	[redacted]	17,263
		Weibull	[redacted]	[redacted]	[redacted]	20,332
Long-term survival adjustment	Gershenwald, applied after10 years. OS vs RFS HR from E1697	No long-term adjustment	[redacted]	[redacted]	[redacted]	17,056
		Gershenwald, 5 years	[redacted]	[redacted]	[redacted]	21,593
		Gershenwald, 20 years	[redacted]	[redacted]	[redacted]	17,099
		Balch, 5 years	[redacted]	[redacted]	[redacted]	29,386
		Balch, 10 years	[redacted]	[redacted]	[redacted]	21,168
		Balch, 20 years	[redacted]	[redacted]	[redacted]	17,962
		OS/RFS HR from '029 trial	[redacted]	[redacted]	[redacted]	18,558
		Balch, OS/RFS HR from '029 trial	[redacted]	[redacted]	[redacted]	22,334
Long-term-data curve selection	Gershenwald, GGamma	Balch, Exponential**	[redacted]	[redacted]	[redacted]	24,886
		Balch, GGamma	[redacted]	[redacted]	[redacted]	21,168
		Balch, Gompertz	[redacted]	[redacted]	[redacted]	17,571

Parameter changed	Base case	Scenario	Incremental results vs Routine surveillance			ICER vs Routine surveillance
			Costs (£)	LYs	QALYs	
		Balch, Log-normal	[redacted]	[redacted]	[redacted]	23,026
		Balch, Log-logistic	[redacted]	[redacted]	[redacted]	23,022
		Balch, Weibull**	[redacted]	[redacted]	[redacted]	23,624
		Exponential**	[redacted]	[redacted]	[redacted]	21,852
		Gompertz	[redacted]	[redacted]	[redacted]	17,022
		Log-normal	[redacted]	[redacted]	[redacted]	19,920
		Log-logistic	[redacted]	[redacted]	[redacted]	20,330
		Weibull**	[redacted]	[redacted]	[redacted]	21,033
End-of life costs	Applied to all deaths	Death from post-recurrence only	[redacted]	[redacted]	[redacted]	17,838
Utilities source	Observed EQ-5D	Include AE disutilities: No	[redacted]	[redacted]	[redacted]	17,986
	Apply same utility to across treatments Separate stage covariate Include AE disutilities: Yes	Mapped EQ-5D Include AE disutilities: No	[redacted]	[redacted]	[redacted]	18,172
		Mapped EQ-5D Include AE disutilities: Yes	[redacted]	[redacted]	[redacted]	18,205
		Middleton et al.	[redacted]	[redacted]	[redacted]	15,341
		Treatment specific utilities	[redacted]	[redacted]	[redacted]	18,250
		Mapped EQ-5D Treatment specific utilities	[redacted]	[redacted]	[redacted]	18,442
		Grouped stage covariate	[redacted]	[redacted]	[redacted]	18,017
		Mapped EQ-5D data, grouped stage covariate	[redacted]	[redacted]	[redacted]	18,205
Observation AEs	Assume same as nivolumab	No AEs	[redacted]	[redacted]	[redacted]	18,171

Key: AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; LY, life year; OS, overall survival; PAS, patient access scheme; QALY, quality-adjusted life year; RFS, recurrence-free survival.
Note: The curve fits that are indicated (*) are those which do not meet the validation criteria as displayed in Table 13 and Table 14 in company submission (**) are those that fit the data poorly.

British Association of Dermatologists
Response to NICE Final appraisal determination
On the Single Technology Appraisal
Nivolumab for adjuvant treatment of resected stage III and IV melanoma
[ID1316]
Appraisal consultation document

British Association of Dermatologists
Therapy & Guidelines and Skin Cancer sub-committees

On behalf of the British Association of Dermatologists, thank you for the opportunity to comment on the Appraisal consultation document.
The British Association of Dermatologists have no comments.

[redacted]
Chair, Therapy & Guidelines sub-committee

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 28/09/18 **via** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	British Association of Skin Cancer Specialist Nurses (BASCSN)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	

Comment number	Comments
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this

Please return to: NICE DOCS

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 28/09/18 **via** NICE DOCS

	table.
Example 1	We are concerned that this recommendation may imply that .....
1	BASCSN is disappointed by this decision. Nivolumab has demonstrated that is can increase relapse free survival, which is very important for patients. Patients will be denied treatment while we wait for the data on overall survival.
2	If the decision stands, BASCSN would support a further appraisal once the data has matured eg in 2019, rather than at 3 years as proposed.
3	BASCSN would support access to nivolumab through the CDF now, to enable patients to receive it before they progress. If the data on OS is negative then this decision can be reviewed and the drug removed.
4	
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 28/09/18 **via** NICE DOCS

Please return to: NICE DOCS

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 28/09/18 **via** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Melanoma Focus
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Melanoma Focus - nil. [redacted] - nil. [redacted] - nil. [redacted] - nil. [redacted] - nil. [redacted] - nil.

Please return to: NICE DOCS

Nivolumab for adjuvant treatment of resected stage III and IV melanoma [ID1316]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 28/09/18 **via** NICE DOCS

Name of commentator person completing form:	[redacted], Consultant Medical Oncologist [redacted], Consultant Medical Oncologist [redacted], Consultant Medial Oncologist [redacted], Professor of Medical Oncologist and Chair of Melanoma Focus [redacted], Consultant Medical Oncologist [redacted], Professor of Clinical Oncology and Chair NCRI Skin Cancer Clinical Studies Group

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	We believe that the initial decision not to approve nivolumab for adjuvant therapy for resected stage 3 or stage 4 melanoma is incorrect and risks compromising outcomes for patients. We have addressed the Committee's comments below:
1.	*There are no trials directly comparing adjuvant nivolumab with routine surveillance*. Whilst this is a factually correct statement, we are not aware of a single senior melanoma clinician who is not convinced that the data from the two pivotal studies (CA184-029 and CHECKMATE 238) show beyond any reasonable doubt that nivolumab is superior to placebo/no treatment in terms of relapse-free survival and that ipilimumab is superior to placebo in terms of overall survival. These trials have been publicly reviewed and debated at length at ASCO 2018, ESMO 2017 and many other international meetings, and this has never been raised as a concern. Furthermore, the EORTC 1325/ Keynote-054 study comparing pembrolizumab with placebo in patient with Stage IIIa (>1mm deposit)-IIIc showed a clear benefit in terms of RFS (HR 0.57 for pembrolizumab) entirely consistent with the activity of nivolumab in the adjuvant setting. These drugs are used interchangeably in clinical practice in the treatment of metastatic disease and have identical efficacy and toxicity.
2.	*Differences between the trials in the company's indirect treatment comparison mean the results are uncertain.* Whilst uncertainty does exist, the statement that "unable to conclude that the technology had plausible potential to be cost effective" is itself completely implausible. It is entirely plausible to conclude that given the potentially durable effects of immunotherapy and the large benefit that can accrue in the adjuvant setting nivolumab has the potential to be cost effective. The comment that the ipilimumab scheduling in CHECKMATE 238 was significantly different to that for CA184-069 is only correct in considering planned therapy. This fails to account for the fact that the median number of cycles of ipilimumab patients received in the latter study was 4, and that 38.6% of patients had discontinued therapy by 12 weeks. The vast majority of patients did not complete 1 year of treatment, and only 13% the full course.

Please return to: NICE DOCS

3.	*Nivolumab may improve RFS compared with routine surveillance but the magnitude of the benefit is unclear.* The relapse-free survival curves for patients with resected stage III melanoma treated with ipilimumab in CHECKMATE 238 and CA184-029 are very similar. This provides the most reliable data from which we infer that nivolumab produces a significant improvement in relapse-free survival as compared to observation. We note the criticisms of the populations used in the company's modelling, but do not agree that the drawing on a population from a trial that happens to use interferon invalidates the approach.
4.	*The patient population for CHECKMATE 238 had a worse prognosis than that for CA184-029.* Whilst it is correct that these studies are not directly comparable, subgroup analysis from CA184-069 showed no clear impact of stage/number of nodes involved/microscopic versus macroscopic disease etc. on overall survival benefit with ipilimumab. Therefore we feel that ipilimumab was the appropriate comparator to use for the CHECKMATE 238 study even though this included patients at higher risk of recurrence.
5.	*Difficulty predicting treatment in the metastatic setting and impact on the economic analysis.* We agree that it is difficult to predict accurately treatment that will be used in the metastatic setting. However, within current UK practice: (i) NHS England does not approve combination immunotherapy for patients who had previous adjuvant therapy; (ii) at least 50% of eligible treatment naïve metastatic patients will be treated with combination ipilimumab + nivolumab. This suggests that second-line therapy will be relatively more expensive after observation than for those patients who receive adjuvant therapy.
6.	*No data on overall survival and impact of salvage therapy on this.* We accept that it is not proven that the relapse-free survival benefit will translate into an overall survival benefit, but are unaware of any adjuvant therapy with an RFS effect of the magnitude reported for checkpoint inhibition that has failed to yield an OS benefit. We also accept that it is unclear what the appropriate treatment to use in the metastatic setting will be in patients relapsing on or after adjuvant therapy. The latter question is being addressed by a randomised clinical trial being setup by the EORTC. However, the utility of adjuvant treatment for patients with resected stage III and IV melanoma has not been sufficiently taken into account. Time without cancer is very important to patients, even when relapse ultimately transpires. This is a population that is at very high risk of relapse and premature death. Although treatment in the advanced setting has had an impact on the quality and length of life, patients value the opportunity to maximise the time they can live without disease and severe disruption to their lives.
7.	The approval of dabrafenib and trametinib as adjuvant therapy for patients with BRAF mutated melanoma has demonstrated an immediate interest in this treatment from our patients. There will be inequity if adjuvant therapy is not available for BRAF wild type patients, despite similar RFS effects, given the widespread clinical support for this treatment.
8.	**Recommendations** We strongly suggest that there is a significant risk that failing to approve nivolumab at this time will prejudice the outcome for patients. We recommend that the drug is approved on

Consultation on the appraisal consultation document – deadline for comments 5pm on 28/09/18 **via** NICE DOCS

	the Cancer Drugs Fund and that this approval is reviewed when the overall survival data are available. This is expected at the end of 2019. This interim funding will also allow us to collect real world data on these patients.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Comments on the ACD received through the NICE Website

Name	[redacted]
Role	Founder of a Melanoma charity
Other role	Founder
Organisation	Melanoma UK
Location	England
Conflict	SInce our inception the manufacturer has assisted us with projects on a ad hoc basis.
Notes	
Comments on the ACD:	

Melanoma UK represents many melanoma patients and families throughout the UK.

There is a huge sense of disappointment that this treatment has met with rejection from NICE.

Given that a recent treatment was approved, patients are relieved. However, there is a section of patients who will not be eligible for that treatment because they do not have the appropriate gene.

The recent decision is disappointing and if the draft guidance not to recommend Nivolumab becomes final guidance without any changes, it will mean that patients in England and Wales with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection will not be able to access nivolumab as adjuvant therapy.

Melanoma UK realises that the committee acknowledged that people with fully resected melanoma are still at high risk of disease recurrence and that the potential curative aim of nivolumab represented a substantial benefit to patients. With that in mind, it is disappointing that this decision was made.

Watch and wait does not sit well with the patient community.

NICE ACM ID1316
Nivolumab for Adjuvant Melanoma Treatment
(following complete resection)

POINTS TO NOTE: information relevant to the 2nd NICE technology appraisal taking place on Tuesday 16 October (Diane Cannon, Melanoma UK)

- MEL UK are so grateful to NICE for the approval of all the treatments that have come along since the days when we had nothing – the patient community recall the days when there was nothing in melanoma apart from dacarbazine and radiotherapy.
- We are extremely grateful for the committee's recent decision to approve the debrafinib / trametinib combination for adjuvant melanoma
- Whilst this is great news for our melanoma patients, there's circa 50% of patients who will still have no treatment option open to them other than watch and wait.
- MEL UK are obviously disappointed that the Committee decided not to recommend NIVO as there remains a huge unmet need across the adjuvant melanoma population. We are keen to represent the patient voice today and would hope the committee will revise the decision and come to one that will help the patients who go find themselves in this position.
- If the treatment is not recommended today, it will mean patients in England & Wales with melanoma (with lymph node disease who have undergone complete resection) will not be able to access this treatment.
- The main unmet needs we hear from patients include uncertainty about their future, lack of information about risk of recurrence, outcomes if melanoma were to spread, fears of cancer returning, what next?
- The current standard of treatment is **NO** treatment - This technology is vital for our patients as it gives them hope and helps them live longer.
- The success of this treatment today could potentially improve a patient's life and although there is a commercial decision to be made, please don't let it all be about the numbers. Most patients do not know the significance of QALY, they are too busy fighting for their life.

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	Carer
Other role	Patient advocate
Organisation	Melanoma Patients Network Europe
Location	England
Conflict	I have submitted this contribution as an individual carer , but I prefer to declare all potential conflict - MPNE has received match funding for its conferences (EQUALLY divided between all the Industry stakeholders in Melanoma) - this includes BMS - but they NEVER have any say over the content or running of our programmes.
Notes	

Comments on the ACD:

As the carer of a stage 4 patient treated at the Marsden in London, I am terribly disappointed at this initial decision. Having opted, with Â« eyes wide open Â» as an informed patient, to the Ipilimumab Adjuvant trial (before the anti PD1s were approved) and been assigned the Placebo arm, I am very aware of the cost to a patient of having NO treatment at high risk stage 3c - we "knew" pretty early on that we were on placebo, as we watched other patients drop off the trial with the toxicities of the ridiculous 10mg Ipi dose - but we were PREPARED to risk this toxicity to avoid progression. We were disappointed to see the Checkmate 238 trial had 10mg Ipi as comparator (but in view of the fact that, although Ipilimumab adjuvant wasn't yet approved in Europe, it was in many other places, this would have been violating equipoise for many if they HAD used the Placebo comparator) Having the opportunity of a relatively low toxicity anti PD1 at adjuvant for only 1 year, at the time we would have JUMPED at the chance. (14% grade 3 and 4 toxicity in a treatment environment that is now MUCH more competent at dealing with immunotherapy AEs than it was at the clinical trial stage) we are immensely grateful to still be around after 7 years at stage 4 , but this has largely been due to luck at the timing of approvals/access and extreme proactivity on our part to "chase" trials through adjuvant, targeted therapies and combination immunotherapy - this has been at a huge cost in travel and in the time we spend informing ourselves of the details of the sometime BRUTAL trial process (balancing protocols, second-guessing the disadvantages of randomisation and being blinded) and assessing the risk/benefit of all these treatments - I realise that it is very difficult to decide at adjuvant , when you feel well and MAY have no tumour left, to take a treatment that could give you permanent side effects, but stage 3c is a sword of Damocles , and we felt there was NO choice except to hope we would be some of the relatively small number (in the case of Ipi adjuvant) of patients who could get benefit over just waiting for the disease to come back in the brain or bone. Nivolumab is much less toxic and the efficacy in the higher risk patients (there were no 3a patients in this trial) much better than the Ipi trial. The rarer permanent toxicities are something that concerns me, but the auto-immune management strategies are so much better now, and the management of the destruction of thyroid/pituitary function is something we learn to manage, and with better multi-disciplinary teams at specialist centres these are picked up earlier. We still dont know WHO will benefit from these treatments at stage 4, because we dont yet have effective bio-markers, but Please dont let this be a criteria for refusing adjuvant treatment - we need access for higher risk patients WHILE we carefully monitor in decent registries, we need well designed trials which force industry to

use protocols that are more USEFUL to real world use (and data that is shared),we need excellent information for patients so they can more easily analyse the risk/benefit of a treatment at adjuvant stage, and intelligent risk-sharing agreements between payers and Industry in this time of evidence shortage. I speak to many patients and almost ALL want/would have liked the opportunity to choose a therapy at adjuvant : there are a few that find that the high toxicity reporting from the adjuvant trials (healthy people always report more diligently on the impact of a drug on their lives) tempts them to "wait until they know they really need it", others have said they want it at stage 2c (because they know this is frequently a more risky place than most stage 3a). I have spoken to patients who say Â« I was given interferon with almost zero evidence of it working and had a miserable year of side effects/uselessness and I still progressed and yet Nivo is much better Â» Please reconsider this assessment .

Name	[redacted]
Role	Patient
Other role	
Organisation	
Location	England
Conflict	
Notes	
Comments on the ACD:	
As a Stage 3 C Melanoma metastasis patient who has had a lymph node groin dissection , I was hoping that the adjuvant therapy was going to be offered to me to help prevent the more than likely further spread of Melanoma in my body and therefore extend my life expectancy . I have two teenage daughters (17 and 15) and as any father would , I want to see them grow up and share as much time with them as possible . Then of course there is my own life . I appreciate no one can predict the future in terms of accidents etc for ones life expectancy but to have another or others , to decide on my behalf that I will have a reduced amount of time to experience life is a very uncomfortable feeling . I understand that this decision is financially influenced and NICE have concluded that to increase my life expectancy is too expensive - I am not worth keeping alive. I appreciate there are limited financial resources in this current desperation for austerity but I am disappointed that NICE have deemed me to a burden and a drain on these resources .	

Name	[redacted]
Role	NHS Professional
Other role	Consultant Clinical Oncologist
Organisation	The Royal Cornwall Hospital
Location	England
Conflict	No- I have previously worked with BMS in an advisory capacity.
Notes	
Comments on the ACD:	
In response to the initial negative appraisal of adjuvant Nivolumab in resected stage III or IV melanoma I would like to comment that this is a group of patients in whom we have been looking for effective adjuvant treatment for decades. NICE have recently approved the use of Dabrafenib and Trametenib as adjuvant therapy for resected BRAF+ stage III melanoma but this group only represents around 35% (real world data is lower than the published BRAF mutation rates, often quoted as around 50%) so there is a large group of patients who are not currently eligible for adjuvant treatment on the NHS. Adjuvant Nivolumab appears to be effective in reducing the rates of recurrence of melanoma (compared to Ipilimumab which is not approved for use in the adjuvant setting in the UK) and I would like to add my support to those asking for this treatment to be available on the NHS. It is recognised that the data from the clinical trial are immature and currently the main evidence of benefit sits with improved relapse free survival - however, in multiple studies, in multiple different cancer types an improved RFS can translate into better overall survival. In general, it is better to prevent relapse than to try salvage treatments when it occurs. I hope the committee can approve this treatment for NHS use in due course. Thank you.	

Name	[redacted]
Role	Healthcare Other
Other role	
Organisation	Melanoma Fund
Location	
Conflict	
Notes	

Comments on the ACD:

On the understanding that the Committee has decided not to recommend Nivolumab within its marketing authorisation, we would we like to comment on this in an attempt to change the final guidance.

We strongly feel it a disservice to patients with later stage melanoma to not provide them with the option access Nivolumab as adjuvant therapy. Patients with fully resected melanoma are still at high risk of disease recurrence and patients are fully aware of that. We believe that the potential curative aim of Nivolumab represents a substantial benefit to patients both in terms of physical treatment and importantly, emotional well-being; knowing there is an option.

We believe that raising the possibility of recurrence-free survival is important because increasing the length of time before tumours come back could lead to patients living longer and a better quality of life as relapse is associated with advanced disease.

The Committee recognised Nivolumab was more effective than Ipilimumab in the clinical trial, the comparison with â€˜watch and waitâ€™ was conducted through an indirect treatment comparison and so the results were noted as uncertain. We believe that the ERG's analysis is overly simplistic and does not reflect UK clinical practice where a mix of treatments are used for disseminated disease.

Name	[redacted]
Role	NHS Professional
Other role	Consultant Medical Oncologist
Organisation	University Hospitals of Leicester NHS Trust
Location	England
Conflict	I am due receive an educational travel grant to attend international conference from this manufacturer.
Notes	
Comments on the ACD:	
The patients with resected melanoma have a limited number of options (recognising the recent approval of dabrafenib & trametinib combination for resected BRAF positive stage III disease) - standard 'follow-up' is in my opinion not satisfactory - both for all resected stage 4 disease patients & those stage III BRAF negative have no options. Reducing the risk of disease recurrence of this disease is essential to achieve longer term survival. Smaller benefits in other cancers in this circumstances have been approved previously whilst adding to 'standard' treatment. There is no standard treatment at the moment & as a melanoma Oncologist I believe we need access to this option for the future of this group of patients.	

Nivolumab for adjuvant treatment of resected stage III and IV melanoma

ERG review of ACD response

October 2018

This report was commissioned by the NIHR HTA Programme as project number 17/156/02

BMJ Technology Assessment Group

1 INTRODUCTION

In response to the Appraisal Consultation Document (ACD), the company submitted two revised cost-effectiveness analyses relating to the analyses preferred by the Evidence Review Group (ERG), which were presented at the first Appraisal Committee Meeting (ACM).

The first of these analyses was to use a partitioned survival approach, assuming equal effectiveness for overall survival (OS) between nivolumab and ipilimumab. This avoids the need to rely on a surrogate relationship between recurrence-free survival (RFS) and OS treatment effects, which the ERG considered potentially unreliable, and assumes the effectiveness observed for the ipilimumab and placebo groups in the CA184-029 trial apply for nivolumab and routine surveillance, respectively.

The second cost-effectiveness analysis was based on the Markov 2 option of the company's original submission, which estimated post-progression survival for those with distant recurrence using data from a range of trials assessing systemic therapies in the metastatic setting. These data were used to fit survival models, which were weighted by the subsequent treatments received in the CheckMate 238 trial[1], with the ipilimumab group assumed to reflect subsequent treatment use following routine surveillance. The ERG was concerned that the subsequent treatments received by patients in the CheckMate 238 trial were not reflective of treatments that would be received by patients in clinical practice. In particular, the ERG considered there to be a lower use of immunotherapies than would be expected, and this was corroborated by clinical expert opinion. To alleviate the Committee's concerns regarding these issues, the company provided results from real-world data (RWD) sources to validate the proportions of each of the subsequent treatments used in the model.

The company also provided discussion around some of the issues raised by the Committee and provided a comparison of long-term outcomes from other sources for validation purposes. Each point presented in the company's response to the ACD is discussed in turn in the following subsections.

2 ERG CRITIQUE

2.1 Subsequent treatments following routine surveillance

The Committee was concerned with the use of data from the ipilimumab group of the CheckMate 238 trial[1] and considered there to be a potential underestimation of the use of immunotherapies, which could underestimate the expected survival of patients who receive routine surveillance as opposed to adjuvant therapy.

To address this issue further, the company obtained RWD from two different sources to determine which treatments were being used in clinical practice in England and Wales. The first of these sources was from IPSOS, who used a representative panel of UK physicians treating Stage IV melanoma who were asked to review patient charts (1,560 patients) and provide information on treatments given to patients between July 2017 and June 2018. The second source was based on a freedom-of-information request of prescribing details obtained via Wilmington Health Care from 173 centres across the UK, of which 154 were from England and Wales. This captured data from 2,348 patients with metastatic melanoma who were treated between March and May 2018. The company also considered COMBI-AD[2] data, but this only relates to BRAF mutation positive patients, therefore only accounting for ~50% of the intended population. The data obtained from the two sources are given in Table 1, alongside the data obtained from the ipilimumab group of the CheckMate 238 trial for comparison.

Table 1. Subsequent treatment data in the metastatic setting (adapted from the company's response to the ACD)

Treatment	IPSOS			Wilmington	CheckMate 238		
	1L	2L	All	All	Ipi – 1L	Ipi – 2L	Ipi – all
Total immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1s	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Interferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	-	-	-	-	[redacted]	[redacted]	[redacted]
Interleukin	-	-	-	-	[redacted]	[redacted]	[redacted]
BRAF/MEK inhibitors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	IPSOS			Wilmington	CheckMate 238		
	1L	2L	All	All	Ipi – 1L	Ipi – 2L	Ipi – all
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic cancer therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Other	-	-	-	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations in table: 1L, first line; 2L, second line; Ipi, ipilimumab.

The company comment on the similar trends observed in the two sources of RWD, noting that [redacted] was shown in the RWD, which the company considers as supportive that the company's analyses are a true representation of real-world subsequent treatment usage in England and Wales. However, the ERG notes that the RWD suggest [redacted] This is not surprising given that the data used were based on the ipilimumab group of CheckMate 238, hence, patients would be more likely to receive an alternative subsequent therapy. The ERG also notes [redacted] in the Wilmington data compared to CheckMate 238 but a [redacted], which is also observed in the IPSOS data.

The ERG considers the Wilmington data may be more reflective of current UK clinical practice compared to the CheckMate 238 data as the Wilmington data are UK specific (CheckMate 238 is based on international data) and more recent (March – May 2018) than the IPSOS data (July 2017 to June 2018). The Wilmington data are also from a wide spread of hospital trusts around the country. One limitation of the Wilmington data, however, is that the data are not split by line of treatment. This meant that the company had to assume these percentages were the same for both first and second line.

The company conducted a scenario analysis to incorporate the alternative data sources and found them to have only a small impact on the results. They considered this to validate their original approach for subsequent treatments and, hence, chose to keep the ipilimumab data from CheckMate 238 in their base case. The company chose to remove the costs of local/regional subsequent therapy as it was uncertain about whether subsequent adjuvant therapy would be used in practice.

The ERG acknowledges that the RWD presented appears to demonstrate that usage of subsequent treatments is not too dissimilar to that observed in the CheckMate 238 trial population, with a few exceptions which were assessed in scenario analyses. However, the ERG is still concerned with the company's approach to modelling, which still uses of a wide range of potentially incompatible studies for OS to inform treatment-specific post-recurrence survival. The company have not reduced this

uncertainty; only the uncertainty in the proportion of subsequent treatments expected in clinical practice.

2.2 Subsequent treatment assumptions following nivolumab

The company commented on the discussion at the first ACM regarding the potential use of PD1 inhibitors in the metastatic setting for patients who have already received nivolumab in the adjuvant setting. At the ACM the company highlighted that one clinician suggested 2 years was a suitable time after which a re-challenge may be beneficial. The company also stated that clinical expert opinion elicited for their original submission suggested a suitable duration between adjuvant nivolumab and a potential re-challenge would be 6 months based on experience in breast cancer treatment. The company also highlight the protocol for the Keynote 054 trial[3], which allowed re-challenge with pembrolizumab after 6 months, and also the MDX010-20 trial[4, 5] in which patients who had stable disease for at least 6 months were re-challenged with ipilimumab.

The company used this information as a basis to provide a range of analyses that assumed re-challenge would be beneficial after 6 months, 1 year and 2 years, respectively. To apply this the company assumed that subsequent treatment usage was the same as the routine surveillance group, i.e. subsequent treatment data form the ipilimumab group of the CheckMate 238 trial, which they considered was validated by the RWD. This was applied directly in the period after the re-challenge threshold, and before this threshold it was assumed that any PD1 inhibitor treatment, i.e. nivolumab, nivolumab plus ipilimumab, and pembrolizumab would have costs and survival rates determined by ipilimumab data for the duration of the set threshold period. The company used this approach for their base case analysis using 2 years as the threshold, which they considered to be conservative.

The ERG is concerned that the company considers this approach to be conservative, as any assumption that a PD1 inhibitor used as a subsequent therapy following adjuvant therapy with nivolumab, is not based on evidence.

2.3 Indirect treatment comparison

The company attempted to reassure the Committee that the indirect treatment comparison (ITC) for RFS between the CA184-029[6] and CheckMate 238[1] trials is robust and fit for decision making. Firstly, by reiterating that the company provided an analysis that censored patients who received ipilimumab beyond the first year in the CA184-029 trial to account for the potential extra benefit received from further treatment, and also by considering the results of the Keynote 054 trial[3] as a way of validating the results. The company note that the results for adjuvant pembrolizumab, the same class of drug as nivolumab, from the Keynote 054 trial[3] compared with placebo produced similar results for RFS to the results from the company's ITC based on the censored analysis of the CA184-029 trial.[6]

The company discussed and presented the data from the ERG's preferred ITC, where the CA184-029[6] study data with 1-year censoring of the ipilimumab patients still on treatment beyond 1-year, were used rather than the unadjusted ipilimumab study population data where patients could have received ipilimumab for up to 3 years. The ERG agrees that the results from this 1-year censored analysis are consistent with the ITC analysis where the ITT population from the ipilimumab arm of CA184-029 are used (Table 2). However, the ERG considers the use of the 1-year censored ipilimumab data from CA184-029 to be most appropriate in the ITC given that ipilimumab was restricted to 1 year in the CheckMate 238 study. This makes the data more comparable between the two trials, thus, making the ITC more reliable.

Table 2. Bucher ITC results for RFS using ITT population and 1-year ipilimumab censoring

Covariate adjusted	Population	Bucher HR RFS (95% CI) Nivo vs PBO – no censoring	Bucher HR RFS (95% CI) Nivo vs PBO – censored[a]
No	ITT	[redacted]	[redacted]
Yes	ITT	[redacted]	[redacted]
No	Stage IIIb/c	[redacted]	[redacted]
Yes	Stage IIIb/c	[redacted]	[redacted]

Key: CI, confidence interval; HR, hazard ratio; ipi, ipilimumab; ITT, intention-to-treat; nivo, nivolumab; PBO, placebo; RFS, recurrence-free survival.
Notes: [a] CA184-029 trial ipilimumab patients censored at 1 year if on treatment.

The company also made a naïve comparison of the results of the ITC to the data from the Keynote 054[3] study of pembrolizumab versus placebo adjuvant therapy in resected stage III melanoma patients. The ERG acknowledges that both nivolumab and pembrolizumab are immunotherapies with similar mechanisms of action as they are both PD-1 inhibitors. However, the ERG has concerns with the naïve comparison as pembrolizumab is not a comparator of interest in this appraisal, there are differences in the population of the Keynote 054 study compared to CheckMate 238 (e.g. CheckMate 238 also includes patients with stage IV melanoma), and there are differences in the confidence intervals presented and compared by the company (98.4% for KeyNote 054 and 95% for the nivolumab ITC). The ERG does, however, acknowledge that the RFS results from KeyNote 054 (hazard ratio [HR]: 0.57, 98.4% confidence interval [CI]: 0.43–0.74) are consistant with the RFS results of the covariate adjusted Bucher ITC with 1-year censoring of ipilimumab for nivolumab versus placebo ([redacted]). The ERG does not consider the comparison of these results to be a validation of the ITC but the results of the Keynote 054 trial at least demonstrate that the results of the ITC for nivolumab versus placebo presented by the company are plausible. Further to this, the comparison of hazard ratios is unreliable given that proportional hazards did not hold for the RFS data in either the CA184-029 or CheckMate 238 trials; however, the ERG considers the company's approach taken to model RFS to be reasonable.

2.4 Administration costs

NHS England submitted a written statement, which was circulated at the first ACM, and in this it raised the issue that administration costs for adjuvant therapies had not been included. The company have responded to this comment by stating that administration costs were actually included based on NHS reference costs code SB12Z for simple parenteral chemotherapy with a cost of £259.76. However, NHS England specified the appropriate cost code as SB13Z for complex parenteral chemotherapy administration, with a cost of £299.68. This increased the average cost of administration from £5,099 per patient to £5,883, thus increasing the ICER. This change was incorporated into the revised base case analyses submitted by the company, which are presented in the company's response to the ACD. The ERG considers this change to be appropriate.

2.5 Revised base case 1: Partitioned survival

Given the Committee's concerns about using an unreliable surrogate relationship to estimate an OS benefit from the observed RFS benefit, the company revised their original base case to use the ERG's scenario, in which the company assumed that nivolumab had the same OS as ipilimumab, hence using the relative benefit from the CA184-029 trial as the basis for OS modelling.

This analysis also included the Committee's preferred modelling for RFS using the CA184-029 trial with the ipilimumab group censored for patients still receiving treatment after a year, and also included the updated administration costs referred to by NHS England.

The company compared the updated OS modelling, based on the adjustment to the scale of the curves to align with the CheckMate 238 trial, with external registry data and determined that the updated OS curve for routine surveillance was more realistic than the previous modelling. They noted that the curve was higher than the AJCC v7 weighted Stage III curve, which is expected due to advancements in treatments, but lower than the data from AJCC v8 for Stage III patients, which would be expected due to the inclusion of Stage IV patients. The company also compared it to the placebo group of the more recent COMBI-AD trial, which also demonstrated similar findings.

2.6 Revised base case 2: Markov Option 2

The company submitted an updated base case for the Markov option 2 model structure, which the Committee considered to be their preferred approach to modelling as it avoided the need to use a surrogate relationship. The company note that the revisions to the first base case, outlined in Section 2.5, mean that the first base case no longer relies on this surrogate relationship. However, the company provided an analysis based on the Markov Option 2 to account for the Committee's preferences and based it on what they considered to be a realistic usage of subsequent treatments.

The company considered the RWD sources to be largely in line with the subsequent treatment usage in the CheckMate 238 trial and, therefore, have kept this trial as the source for the base case, with the RWD sources used to provide scenario analyses to assess the impact. Although the source of data remained unchanged in the company's base case analysis, the company used the ipilimumab group for both adjuvant nivolumab and routine surveillance, and made some changes regarding the time of relapse for both the costs and effects modelled for subsequent treatments.

The company made the assumption that patients who received a PD1 inhibitor as a subsequent treatment in the adjuvant nivolumab group would only receive a benefit after 2 years. The percentage of patients who received subsequent PD1 inhibitors were, therefore, removed and added to the percentage receiving subsequent ipilimumab instead. This means that both costs and benefits for this group of patients were based on ipilimumab treatment for metastatic disease. For patients who relapsed after 2 years, the subsequent treatments were assumed to be the same as in the routine surveillance group, based on the ipilimumab group of the CheckMate 238 trial.

Second line subsequent treatments, for which only the costs are applied, were included and assumed to be the same as routine surveillance second line subsequent therapies, i.e. based on the subsequent therapies received in the ipilimumab group of the CheckMate 238 trial. For simplicity, these were not split by time of recurrence.

The company's other changes to the Markov option 2 base case were the use of censoring applied to the ipilimumab RFS data from the CA184-029 trial for patients treated beyond 1 year, and the updated administration costs for adjuvant nivolumab and relevant subsequent therapies.

2.7 Complex extrapolation of RFS

The Committee raised concerns with the complex extrapolation approach used for RFS and considered it potentially unreliable. The company reiterated its approach and discussed the outcomes and impact on the cost-effectiveness.

The ERG does not consider the use of Kaplan-Meier (KM) data for the first 12 weeks rather than a fully parametric approach to be a major concern, nor the use of a Cox model to estimate the adjustment between ipilimumab groups from the two key trials. This is preferable to using ill-fitted standard parametric curves and the company also demonstrated that using a more flexible spline-based model for the entire time horizon had very little impact on the results.

The other complexities in the survival modelling for RFS and OS using long term data and general population mortality data were shown to result in greater ICERs than a simpler approach using only the extrapolations derived by the parametric models. Although the ERG is reluctant to consider this a

conservative approach, given that the long-term extrapolations of the parametric models alone were not considered plausible, and alternative models may provide a more suitable comparison, the ERG considers this to be a lesser concern in the company's analysis. The company clearly demonstrate the outcomes produced by the model and compare these against various sources of data to assess plausibility.

2.8 Benefit-to-risk ratio for patients with lower risk of relapse

The ERG considers the company's approach to be in line with the approved marketing authorisation, and therefore, the benefit-to-risk ratio has been considered acceptable for approval by the European Medicines Agency (EMA). However, the ERG considers it appropriate to consider the cost-effective of lower risk subgroups separately to be appropriate, and the company have provided analyses for the Committee to consider an optimised recommended.

2.9 The impact of potential data collection within the CDF

The ERG has concerns about the immaturity of the current OS data for nivolumab from CheckMate 238 and notes that the company reported in their clarification response a formal interim analysis of OS was expected to be available in [redacted]. The ERG therefore considers that a CDF recommendation may be beneficial to enable collection of further OS data in CheckMate 238 to help address some of the current uncertainty in the long term clinical effectiveness of nivolumab and the impact of subsequent therapies on OS.

The ERG also considers there to be considerable uncertainty in the current modelling of the routine surveillance group, and in particular, the expected OS in this group. While the ERG acknowledges the data to address this would not be captured through a CDF recommendation for adjuvant nivolumab, or from the ongoing data collection in CheckMate 238 (as routine surveillance is not a comparator in the trial), other data may become available. For example, the ERG is aware that the Keynote 054 study of adjuvant pembrolizumab versus placebo in resected Stage III melanoma has yet to publish OS data. The ERG considers that when OS data are available from the Keynote 054 study, the placebo data could potentially be used to inform the modelling of OS for routine surveillance to help inform the comparison of nivolumab versus routine surveillance (possibly via a matched-adjusted indirect comparison [MAIC] with CheckMate 238).

3 ERG ADDITIONAL ANALYSES

3.1 ERG preferred base case

Based on the currently available data, the ERG considers the Markov option 2 structure to be preferable given that it can account in some way for the inaccuracies regarding subsequent treatment use and the downstream consequences of these. However, the ERG is still concerned with this approach given the wide range of potentially incompatible studies for OS used to determine treatment-specific post-recurrence survival.

The ERG prefers the use of the Wilmington Health Care data source for subsequent treatments as it comes from a larger, more recent data set from a wide range of hospital trusts around the country, which were disclosed by the company in an appendix. The ERG notes that this data has limitations in that it is not split by line of treatment.

The ERG is also concerned that the company's model assumes all patients who survive beyond 2 years of subsequent treatment, and are receiving nivolumab, will have a survival benefit based on patients who received nivolumab in the metastatic setting. The ERG prefers a more conservative approach by assuming that these patients no longer receive a benefit after adjuvant nivolumab. The results of the ERG's preferred base case are given in Table 3.

Table 3. Updated ERG base case ICER

Results per patient	Nivolumab	Routine surveillance	Incremental value
Company's base case 2 (Markov Option 2)			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	14.19	[redacted]
ICER			**£18,018**
Using Wilmington Health Care subsequent treatment data			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	14.12	[redacted]
ICER (compared with company ICER)			**£18,151**
ICER with all changes incorporated			**£18,151**
Assuming that re-challenge never becomes beneficial			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	[redacted]
LYs	[redacted]	14.12	[redacted]
ICER (compared with company ICER)			**£18,863**
ICER with all changes incorporated			**£19,129**
Abbreviation used in the table: ICER, incremental cost-effectiveness ratio; LY, life-year; QALYs, quality-adjusted life years; RFS, recurrence-free survival.			

The ERG base case resulted in an ICER of £19,129 per QALY gained, but this remains highly uncertain based on the disparate data sources used to inform the OS benefit for patients who receive post-recurrence treatments.

3.2 ERG scenario analyses around company's base case 1

The ERG also performed some scenario analyses around the company's base case 1, based on the partitioned survival model structure. The first scenario applied was to assume no difference in OS by setting the routine surveillance OS curve equal to the nivolumab curve. The second was a threshold analysis, which set the OS gain (by adjusting the routine surveillance curve) to the minimum benefit required for the ICER to be less than £30,000 per QALY. The routine surveillance curve was adjusted as there is currently no reliable way to account for the potential OS benefit of current post-recurrence therapies in this group. The placebo scaling factor for the generalised gamma curve was changed from [redacted] to [redacted] to achieve the £30,000 per QALY threshold, which resulted in a mean survival gain of [redacted]. The results are summarised in Table 4. A comparison of the resulting OS curves for the company's base case 1 and the threshold analysis providing the gain of [redacted] can be seen in

Figure 1 and Figure 2, respectively.

Table 4. ERG scenario analyses around company's base case 1

	Results per patient	Nivolumab (1)	Routine surveillance (2)	Incremental value (2-1)
0	**Company's base case 1 (Partitioned survival)**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	17.83	[redacted]
	ICER			**£18,423**
1	**Setting routine surveillance OS equal to nivolumab**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	20.77	[redacted]
	ICER (compared with base case)			**£80,401**
2	**Threshold for OS gain for nivolumab to be cost-effective (adjusting only placebo OS scale)**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	LYs	[redacted]	19.26	[redacted]
	ICER (compared with base case)			**£29,832**
	Abbreviation used in the table: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PRS, post-recurrence survival; QALYs, quality-adjusted life years.			

Figure 1. OS curves in company's base case 1 (partitioned survival)

Figure 2. Scenario 2: Minimum OS gain for nivolumab to be cost-effective (adjusting only placebo OS scale)

4 CONCLUSION

The ERG notes that the main issue addressed by the company since the first ACM is the uncertainty regarding the proportion of subsequent treatments expected to be received by patients following routine surveillance. This does not, however, reduce any of the uncertainty in the treatment-specific post-recurrence OS estimates applied in the Markov 2 model option. This may not be an issue that the company can resolve at the moment, but it must be noted that this is not a robust method and the impact this has on the results is unclear.

The uncertainty in the partitioned survival approach remains as per the ERG's analysis previously presented to the Committee. This has been updated to include NHS England's concerns about the inaccurate administration costs for nivolumab, which had minimal impact on the results. The key concerns in this approach to modelling, therefore, still remain.

Although the survival curves were adjusted to match the nivolumab group of CheckMate 238[1], with the assumption of equivalent OS between ipilimumab and nivolumab, the treatment effect is still derived from the CA184-029 trial. This means that the difference in subsequent treatments received in the CA184-029 trial partly drives the difference in OS, and therefore, the benefit is likely to be overestimated in favour of nivolumab because of the lack of effective immunotherapies used in the placebo group of the CA184-029 trial[6].

This uncertainty can only be reduced further if mature OS data from the CheckMate 238 trial demonstrates a benefit over ipilimumab or, better still, if a robust comparison can be made between the CheckMate 238 trial (for nivolumab) and the Keynote 054 trial[3] (for routine surveillance) when more mature OS data becomes available which would include currently available subsequent treatments for post-recurrence.

The results of the analyses presented in this document based on the confidential patient access schemes for the comparator treatments are provided in a separate confidential appendix.

5 REFERENCES

1. Weber J, Mandala M, Del Vecchio M, Gogas HJ, Arance AM, Cowey CL, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *N Engl J Med* 2017; **377**: 1824-35.

2. Long GV, Hauschild A, Santinami M, Atkinson V, Mandala M, Chiarion-Sileni V, et al. Adjuvant dabrafenib plus trametinib in Stage III BRAF-mutated melanoma. *N Engl J Med* 2017.

3. Eggermont AMM, Blank CU, Mandala M, Long GVA-Ohoo, Atkinson V, Dalle S, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. LID - 10.1056/NEJMoa1802357 [doi]. 2018.

4. Robert C, Hodi FS, O'day S, Peschel C, Ottensmeier C, Trefzer U, et al. Re-induction With Ipilimumab, gp100 Peptide Vaccine, Or A Combination of Both in A Phase III Study of Previously-treated Patients With Advanced Melanoma: Update of Clinical Characteristics of Patients. ESMO. Milan: Italy; 2010.

5. Robert C, Schadendorf D, Messina M, Hodi FS, O'Day S. Efficacy and safety of retreatment with ipilimumab in patients with pretreated advanced melanoma who progressed after initially achieving disease control. *Clin Cancer Res* 2013; **19**: 2232-9.

6. Eggermont AMM, Chiarion-Sileni V, Grob J-J, Dummer R, Wolchok JD, Schmidt H, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. *N Engl J Med* 2016; **375**: 1845-55.