NICE National Institute for Health and Care Excellence

Cancer Drugs Fund Review

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CANCER DRUGS FUND REVIEW

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (CDF review of TA558) [ID1681]

Contents:

The following documents are made available to consultees and commentators:

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 [ID1681]

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
1	Consultee	Bristol-Myers-Squibb - company	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 have demonstrated nivolumab is a cost-effective treatment option that has the potential to maintain patients with adjuvant melanoma in a disease-free state. The uncertainty in the base case ICER was fully explored with multiple scenario and sensitivity analyses, resulting in ICERs below the £30,000 per QALY threshold. We welcome the Committee's acceptance of nivolumab improving recurrence-free survival and clinical expectation that this will be reflected in overall survival. However, despite the additional evidence presented to the Committee on the clinical value in comparison to routine surveillance and on cost effectiveness, the Committee felt that there was too much uncertainty within the cost-effectiveness results, which are impacted by the survival estimates. This uncertainty was focused particularly on the following: • Immature overall survival data • Subsequent treatments post-adjuvant therapy • Appropriateness of censoring the CA184-029 trial in the indirect treatment comparison • Preferred model structure • Modelling approach to estimate extrapolated overall survival In this document, BMS consider these topics and evaluate the appropriateness of the assumptions surrounding the current ICER ranges presented at the committee meeting. BMS provide a range of plausible ICERs based on least conservative to most conservative, clinically-plausible assumptions. These scenarios range from £14,301 to £29,011 and we are confident that the most plausible ICER for nivolumab as adjuvant treatment falls below the £30,000 per QALY threshold. BMS believe the information presented in this response should satisfy the Committee's previous concerns over the cost-effectiveness estimates. These ranges demonstrate nivolumab as a cost-effective option for routine commissioning by the NHS. A positive recommendation will ensure that equitable access in effective and tolerable adjuvant treatments is available for all patients who are at high risk of recurrence in England regardless of BRAF status, and including Stage IV patients, for whom no other adjuvant treatment is available in resected melanoma. Sincerely,	Thank you for your comments. Nivolumab is now recommended, please see FAD section 1.1 for more details.

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			Sophia Ho On behalf of Bristol-Myers-Squibb [see comments on ACD from Bristol-Myers Squibb for more detail on Bristol-Myers Squibb analyses]	
2	Consultee	NCRI-ACP-RCP-RCR	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.	Thank you for your comment. No action needed.
3	Consultee	NCRI-ACP-RCP-RCR	**Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (CDF review of TA558) [ID1681**] As a group of consultant oncologists from across the UK who lead on the treatment of patients with advanced malignant melanoma, we are writing to express our objection to the NICE recommendation to not support the NICE TA558 guidance and hence discontinue CDF funding of adjuvant nivolumab in high risk resected malignant melanoma. Treatment of patients with resected melanoma at high risk of relapse (resected stage III & IV) has been an area of significant unmet need for many years, since approximately 40-60% of patients with resected stage III and 80-90 % of stage IV melanoma will die from their melanoma within 5 years of their surgery. The demonstration of significant improvement in relapse-free survival with adjuvant therapy has been a milestone in melanoma treatment and has led to adjuvant therapy being the standard of care for resected high-risk melanoma in all developed countries. The adjuvant melanoma Checkmate 238 trial comparing nivolumab with ipilimumab demonstrated a significant improvement in recurrence-free survival, with an acceptable toxicity profile. Based on these results, nivolumab was licenced as adjuvant treatment and is recommended as standard of care in all evidence-based international melanoma patient management guidelines. Across the UK, virtually all patients with resected stage III or stage IV melanoma will have the risks and benefits of adjuvant therapy discussed with them routinely. The revaluation of NICE guidance and a reversal of the recommendation for CDF funding of adjuvant nivolumab (TA558) appears to be based on: • review of updated data on the 906 patients in the Checkmate 238 study data & on new real-world SACT data from PHE/CDF comprising 284 patients prescribed adjuvant nivolumab • an appraisal of overall survival and cost of patients receiving adjuvant treatment • appraisal of how survival and cost without adjuvant treatment might be affected by use of subsequent treatments for advanced melanoma and hence the magnitude of beneficial effect of nivolumab being given as an adjuvant. **Nivolumab clearly reduces the risk of recurrence.** The new updated data on Checkmate 238	Thank you for your comments. Nivolumab is now recommended, please see FAD section 1.1 for more details.

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			(Ascierto, Lancet Oncology, Nov2020) show that the recurrence-free survival (RFS) data remains robust with a 4 year RFS of 51.1 months following adjuvant treatment with nivolumab and an overall 4 year survival of 77.9%. There is no direct comparison with a placebo/no treatment arm in this study. However, indirect comparisons have been made with the outcomes of the placebo arm in other adjuvant studies and real-world data. These comparisons of RFS are still valid, as there is no indication that the rate of recurrence has changed significantly over time in non-treated patients. Therefore, the magnitude of beneficial effect of effect of nivolumab in preventing recurrence is still robust. The hazard ratio is in the region of 0.5-0.6, which is among the best for any systemic adjuvant therapy in cancer reported to date. This beneficial effect is supported by the updated 3 year follow results of the EORTC 1325/Keynote054 trial of 1019 patients comparing adjuvant pembrolizumab to placebo (Eggermont ,J Clin Onc Nov 2020). Pembrolizumab is another anti-PD1 antibody, equivalent to nivolumab. The 3 year results of EORTC 1325/Keynote 054 confirm a large benefit of adjuvant pembrolizumab in preventing recurrence in resected high risk stage III disease. RFS at 3 years is 63.7% in the pembrolizumab group vs 44.6% in the placebo group with a hazard ratio of 0.56. The data on overall survival are too premature to be able to assess effect on overall survival. [Figure was removed here, please see the NCRI-ACP-RCP-RCR response for more details] Currently, the additional, real-world data from PHE/CDF are too immature to be helpful for making decisions on efficacy. The cohort of treated patients is very small, 72% of patients are still on treatment and there is no robust overall survival data available. The recommendation of the NICE committee with steer from the Evidence Review Group appears to be driven by the potential effects on survival of (the new) systemic treatments in recurrent advanced disease, and the premise that this is so great that it negates the benefit of adjuvant therapy to prevent recurrence. This is based on selection of a model that uses a pessimistic projection resulting in an unfavourable incremental cost effective ratio (ICER). it appears that the uncertainty on OS has been addressed by giving weight to the most pessimistic models and/or assumptions largely on the basis that they are more conservative. Using these to define the QALY cost as too high becomes essentially a self-fulfilling argument. NICE's guide of course require the ERG and committee to 'take into account the degree of certainty'. However, we feel they have inappropriately interpreted this and have taken most conservative rather than most likely scenario. There are clearly other models that are equally valid that show a very different and more favourable ICER. Essentially, uncertainty arises because the models are based on data that are immature, and without sufficient follow-up. **We would like to assert that it is premature and inappropriate to reverse a decision to fund adjuvant nivolumab at this stage; this would lead to significant potential harm to patients with high risk melanoma**. **We therefore request that funding continue until more robust data are available.** We recognise the need to revaluate the efficacy of drugs as more information comes to hand, but for this setting, ie the adjuvant therapy for melanoma, it is clearly too early, at this stage, to come to such conclusions. The data will be forthcoming with further follow-up in ongoing studies	

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			and as real-world data mature. **The harm to patients of stopping funding of adjuvant therapy is the significantly increased risk of recurrence of melanoma and the consequences of this, which includes high chance of death, despite access to treatment options for advanced melanoma**. In the absence of adjuvant therapy, the majority of patients with resected stage III/IV melanoma will experience disease recurrence. Treatment of advanced disease offers only median survivals of around 3 years, so most will die from metastatic melanoma and experience the increased morbidity of living with and dying from cancer. The physical and psychological burden of developing metastatic disease for patients and carers is significantly worse following recurrence, even if patients are fortunate enough to have a very good long-term survival with subsequent treatments. Of particular concern is the withdrawal of adjuvant nivolumab funding for the resected stage IV patients. These patients, although relatively small in number, are the ones at highest risk of recurrence. Nivolumab is the only adjuvant treatment currently licenced for this indication with 4 year recurrence free survival of 48.6% in the Checkmate 238 study. Support of this benefit in resected stage IV melanoma is seen in the IMMUNED randomised phase II study showing a 2 year RFS of 42% with adjuvant nivolumab vs only 14% in a placebo group (Zimmer et al Lancet May 2020) Withdrawal of funding for adjuvant nivolumab will cause significant harm to this patient group. **In summary** • **The recommendation to discontinue adjuvant nivolumab funding is based on uncertainty of the resulting QALYs generated by immature treatment outcome data.** • **More data will be forthcoming,** • **Withdrawal of funding will cause significant harm to patients.** **Therefore, we urge the committee to reconsider and to commend continued CDF funding of nivolumab in resected high risk melanoma.** This statement has been reviewed and endorsed by 55 consultant melanoma specialists working across the UK.	
4	Consultee	Melanoma UK	Melanoma U.K. is a patient support organisation working with melanoma patients and families who are suffering melanoma - from early stage, right up to late stages. We fully appreciate that NICE has a very difficult role when it comes to technology appraisal. We are aware that over the last few years, the lives of many patients and families have been helped enormously by decisions made. However, we feel that in this case, the decision really is not in the best interest of the patient community. Adjuvant treatment in melanoma is extremely important for patients. There is a very clear unmet medical need for stage four patients and this treatment is the only approved and reimbursed treatment for this section of patients. We are concerned that this recommendation would be extremely traumatic for the patient community and a backward step in the treatment of melanoma.	Thank you for your comments. Nivolumab is now recommended, please see FAD section 1.1 for more details.

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			Some of the feedback we have received includes: • "Utter devastation" • "Please don't take away the hope" • "This decision is breaking my heart" • "This could be the difference between life & death" • "This is now another worry – what about my children?" • "Just reading this news is having a huge psychological impact on me" • "I am sick to my stomach" • "This will remove a lifeline for so many patients" • "This drug is currently keeping me alive" We must not take any backward steps in the treatment of this brutal disease. Melanoma U.K., along with the patients it represents, urge the committee to review this decision and listen to the views of not only clinicians, but the patient community as a whole.	
5	Consultee	Melanoma UK	**Patient quote:** *It breaks my heart to think newly diagnosed patients in my position would not be given the same chance I had. It gave me hope.* *I was given the statistics and of course jumped at the chance to have adjuvant therapy no matter the risks. Anything to prolong my life.*	Thank you for your comment. Nivolumab is now recommended, please see FAD section 1.1 for more details.
6	Consultee	Melanoma UK	**Patient quote:** *I am horrified to learn that this decision of this magnitude has been made on the strength of just two years data. As a patient who was turned down for a trial of adjuvant therapy at an early stage of the disease and then progressed to stage IV fewer than twelve months later, I have spent many sleepless nights wondering whether my current incurable diagnosis could in fact have been prevented. There are so few treatment options for metastatic melanoma as it stands why must we take away a potentially powerful adjuvant immunotherapy option without allowing adequate time for the data to mature?*	Thank you for your comment. Nivolumab is now recommended, please see FAD section 1.1 for more details.
7	Consultee	Melanoma UK	**Patient quote:** *It's devastating news. I'm stage 4 braf mutant with metastatic melanoma, could be the difference between life and death literally.*	Thank you for your comment. Nivolumab is now recommended, please see FAD section 1.1 for more details.
8	Consultee	Melanoma UK	**Patient quote:** *I'm a stage 3 patient currently on adjuvant treatment for 12 months. I have been so grateful to have this treatment to improve the chances of my cancer not coming back. Since diagnosis I have been acutely aware that just a few years ago this would not have been an option for me, I would have just had to watch and wait. Adjuvant treatment gives hope for a return to some normality and is such a recent improvement to the overall treatment options in melanoma. The thought that this could be taken away again would devastate those with this awful disease, myself included. Please don't take away the hope.*	Thank you for your comment. Nivolumab is now recommended, please see FAD section 1.1 for more details.
9	Consultee	Melanoma UK	**Patient quote***:* *Probably means that in a few months there will be no treatment possible for my condition and so my life expectancy will be less than 1 year*	Thank you for your comment. Nivolumab is now recommended, please see FAD section 1.1 for more details.
10	Consultee	Melanoma UK	**Carer quote**: *I am the wife of a melanoma patient. Without NICE approved treatment for my husband last*	Thank you for your comment. Nivolumab is now recommended, please see FAD

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			year, I would now be a widow.	section 1.1 for more details.
11	Consultee	Melanoma UK	The above patient testimonials are just a few to show their reaction to this devastating news. Melanoma UK represent the patient voice, but we urge the committee to read the rest of what the melanoma community have to say (see attached supporting patient comments). [Please see Melanoma UK appendix with patients' testimonials for more information.]	Thank you for your comments. Nivolumab is now recommended, please see FAD section 1.1 for more details.
12	Public (web) comment	Melanoma Focus	**Are the recommendations sound and a suitable basis for guidance to the NHS?** I have stage III melanoma and have recently completed a year of adjuvant treatment. Prior to treatment, I had a proactive discussion with my oncologist where we discussed the evidence of the approved treatment options. I can continue to lead my very active life knowing I have had treatment to reduce the likelihood of my melanoma returning. It is really important for people living with melanoma to have access to adjuvant treatments with the potential to prevent the development of metastatic disease. I understand that nivolumab went into the Cancer Drugs Fund so that further patient information could be observed and that patients in the original trial would have also been followed up for a longer period. 284 people had nivolumab treatment via the Cancer Drugs Fund and 72% patients were still having treatment when the data was reviewed which indicates a short follow-up, particularly in the adjuvant setting. It greatly concerns me as someone fortunate to have adjuvant treatment that patients will be refused this option. It seems that on this basis both adjuvant immunotherapies could suffer the same fate and so only patients with a BRAF mutation could have adjuvant treatment offered to them. After citing an unmet need in TA558, it is difficult to understand the process. We are also in the predicament that the licences for the various adjuvant treatments vary and nivolumab is the only treatment available for resected stage IV patients so this subset will no longer be eligible for treatment in England. In Scotland, the treatment will still be permitted causing inequity between the devolved nations which will be an appalling situation. As a patron for melanoma charities (Melanoma Focus and Melanoma UK), I feel duty bound to express my deepest concern with the NICE recommendation to not approve nivolumab for adjuvant treatment. Adjuvant treatments are a critical choice for melanoma patients and I urge you to reconsider the outcome.	Thank you for your comments. Nivolumab is now recommended, please see FAD section 1.1 for more details.
13	Public (web) comment	patient	As a Melanoma stage 3 patient receiving adjuvant Nivolumab this consultation shocks me to the core. I was diagnosed in April. During lockdown. I'm lucky enough to be have private healthcare or I worry that covid would have delayed my diagnosis and treatment. I would hate to thing that having had the cancer and lymph nodes removed, that I was reliant on scans alone. By the time a scan would have found a tumour, it's already establised and therefore much harder to try and shrink. Microscopic cells are targeted with Nivolumab and this is much more reassuring. I am 38. I don't have cancer because I went on sun beds. I hate the sun. I am just very unlucky. I have two children aged 7 and 4. I wake up everyday and think thank god I am still alive and receiving Nivolumab as I hope beyond hope that this means I will be able to live, see my	Thank you for your comments. Nivolumab is now recommended, please see FAD section 1.1 for more details.

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			children grow up and enjoy a long life with my husband. There are more younger people being diagnosed with Melanoma. These people and myself deserve a chance. This is not an old persons disease. You're not talking about giving a person a few more years. At 38, I hope that I would live a lot longer. Please reconsider. Give time for evidence to show that it does work to reduce recurrence.	
14	Public (web) comment	East Midlands Skin Cancer Expert Clinical Advisory Group (ECAG)	I am commenting as Chair of the East Midlands Skin Cancer Expert Clinical Advisory Group (ECAG). As a group of clinicians we are deeply troubled by this plan to end access to adjuvant Nivolumab based on a small cohort of patients in SACT data who have not yet completed their follow up. You comment yourselves that you only have estimates on cost effectiveness. You also comment that recurrence free survival is improved but it is "uncertain" if overall survival is improved. My colleagues and I are very concerned that you appear in this uncertainty to presume that it is not cost effective despite not having all the necessary data yet, and are assuming it does not significantly improve overall survival but do not know yet whether it does? Where the clinicians in the field feel strongly that this drug is of great benefit, and there is evidence of significant benefit in recurrence free survival, it would surely be better to continue to allow access to the drug until greater clarity is achieved? If we were to discover in a few years time when the data has matured and more patients have completed follow up, that actually it was cost effective and did improve overall survival it would be a bitter pill to swallow for the families who missed out during the period of your uncertainty. We are deeply concerned about this approach to change what in many units is the standard of care, on small amounts of uncertain data. We would request that you reconsider your recommendation until you have stronger evidence to suggest changing course. Yours sincerely, Mr Jonathan Pollock Consultant Plastic & Reconstructive Surgeon Chair East Midlands Skin Cancer Network	Thank you for your comments. Nivolumab is now recommended, please see FAD section 1.1 for more details.
15	Public (web) comment	Consultant medical oncologist	I am a consultant medical oncologist with 20 years of experience managing melanoma patients and have been involved in the clinical trials of immunotherapy both in metastatic disease as well as in the adjuvant setting. I chaired the NCRI skin cancer group between 2012 and 2017. I am a trustee of the national melanoma charity, MelanomaFocus and I am the clinical lead for melanoma in our region. I am also a member of the CCIG, which oversees the SACT dataset. Working with PHE colleagues, I co-led and published a project to evaluate the introduction of immune checkpoint inhibitors as treatment for metastatic melanoma by analysing the SACT dataset (Board et al, Int J Cancer 2020). I am therefore very familiar with the strengths and weaknesses of the SACT data. I am deeply concerned with this proposed recommendation. It appears to be based on analysis of a small dataset of 284 treated patients, 72% of whom remain on treatment at the time of analysis. Not surprisingly as this is an adjuvant cohort, there is no survival data available. The SACT real world dataset has many flaws particularly when it comes to data accuracy . It comes into its own when analysing large numbers preferably in their thousands and there is a hard end point such as survival available. Neither of these are available for this analysis. It is not	Thank you for your comments. Nivolumab is now recommended, please see FAD section 1.1 for more details.

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			surprising that the outcome is a wide variation in ICERs generated by different models and therefore widely varying QALYs. The response to this uncertainty must be to allow access to continue while more data is collated. Not as is the case here, to remove access. The recommendation to remove access flies in the face of all that we know about now a series of RCTs evaluating adjuvant immunotherapy in resected stage III/IV melanoma, which have generated one of the biggest hazard ratios favouring treatment every recorded for any funded adjuvant therapy. How can it be that we will soon be telling our patients that a treatment that literally halves their chance of recurrence will no longer be available to them, but instead they can only be treated when their cancer returns? How can it be that we will be telling our patients in England that if they lived in Scotland they could have this potentially life-saving treatment. The committee must reconsider this unreasonable recommendation that flies in the face of everything we know about prevention being better than palliation. Dr Pippa Corrie Consultant and Associate Lecturer in medical oncology, Cambridge University Hospitals NHS Foundation Trust **Are the summaries of clinical and resource savings reasonable interpretations of the evidence?** No, they are not. They demonstrate uncertainty because the dataset is so small with limited follow-up and the interpretation of this should therefore be to allow access to continue to build a bigger dataset and longer follow-up. **Has all of the relevant evidence been taken into account?** It's difficult to imagine that the committee has truly taken into account all the adjuvant randomised clinical trial data because they consistently show a halving of risk of recurrence with treatment. The only conclusion taking this data into account would be to recommend continuation of access. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No, they are completely unsound (see comments above and below). **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** The outcome of the proposed recommendation will generate completely unacceptable discrimination against patients with melanoma living in England, since treatment will be available in other devolved nations.	
16	Public (web)	55 Consultant	**Are the summaries of clinical and resource savings reasonable interpretations of the**	Thank you for your comments.

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	comment	Melanoma Oncologists	**evidence?** Please see joint submission from 55 Consultant Melanoma Oncologists from across the UK **Has all of the relevant evidence been taken into account?** As a group of consultant oncologists from across the UK who lead on the treatment of patients with advanced malignant melanoma, we are writing to express our objection to the NICE recommendation to not support the NICE TA558 guidance and hence discontinue CDF funding of adjuvant nivolumab in high risk resected malignant melanoma. Treatment of patients with resected melanoma at high risk of relapse (resected stage III & IV) has been an area of significant unmet need for many years, since approximately 40-60% of patients with resected stage III and 80-90 % of stage IV melanoma will die from their melanoma within 5 years of their surgery. The demonstration of significant improvement in relapse-free survival with adjuvant therapy has been a milestone in melanoma treatment and has led to adjuvant therapy being the standard of care for resected high risk melanoma in all developed countries. The adjuvant melanoma Checkmate 238 trial comparing nivolumab with ipilimumab demonstrated a significant improvement in recurrence-free survival, with an acceptable toxicity profile. Based on these results, nivolumab was licenced as adjuvant treatment and is recommended as standard of care in all evidence-based international melanoma patient management guidelines. Across the UK, virtually all patients with resected stage III or stage IV melanoma will have the risks and benefits of adjuvant therapy discussed with them routinely. The revaluation of NICE guidance and a reversal of the recommendation for CDF funding of adjuvant nivolumab (TA558) appears to be based on: • review of updated data on the 906 patients in the Checkmate 238 study data & on new real-world SACT data from PHE/CDF comprising 284 patients prescribed adjuvant nivolumab • an appraisal of overall survival and cost of patients receiving adjuvant treatment • appraisal of how survival and cost without adjuvant treatment might be affected by use of subsequent treatments for advanced melanoma and hence the magnitude of beneficial effect of nivolumab being given as an adjuvant. Nivolumab clearly reduces the risk of recurrence. The new updated data on Checkmate 238 (Ascierto, Lancet Oncology, Nov2020) show that the recurrence-free survival (RFS) data remains robust with a 4 year RFS of 51.1 months following adjuvant treatment with nivolumab and an overall 4 year survival of 77.9%. There is no direct comparison with a placebo/no treatment arm in this study. However, indirect comparisons have been made with the outcomes of the placebo arm in other adjuvant studies and real-world data. These comparisons of RFS are still valid, as there is no indication that the rate of recurrence has changed significantly over time in non-treated patients. Therefore, the magnitude of beneficial effect of effect of nivolumab in preventing recurrence is still robust. The hazard ratio is in the region of 0.5-0.6, which is among the best for any systemic adjuvant therapy in cancer reported to date. This beneficial effect is supported by the updated 3 year follow results of the EORTC 1325/Keynote054 trial of 1019 patients comparing adjuvant pembrolizumab to placebo (Eggermont ,J Clin Onc Nov 2020). Pembrolizumab is another anti-PD1 antibody, equivalent to nivolumab. The 3 year results of EORTC 1325/Keynote 054 confirm	Nivolumab is now recommended, please see FAD section 1.1 for more details.

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			a large benefit of adjuvant pembrolizumab in preventing recurrence in resected high risk stage III disease. RFS at 3 years is 63.7% in the pembrolizumab group vs 44.6% in the placebo group with a hazard ratio of 0.56. The data on overall survival are too premature to be able to assess effect on overall survival. Currently, the additional, real-world data from PHE/CDF are too immature to be helpful for making decisions on efficacy. The cohort of treated patients is very small, 72% of patients are still on treatment and there is no robust overall survival data available. The recommendation of the NICE committee with steer from the Evidence Review Group appears to be driven by the potential effects on survival of (the new) systemic treatments in recurrent advanced disease, and the premise that this is so great that it negates the benefit of adjuvant therapy to prevent recurrence. This is based on selection of a model that uses a pessimistic projection resulting in an unfavourable incremental cost effective ratio (ICER). it appears that the uncertainty on OS has been addressed by giving weight to the most pessimistic models and/or assumptions largely on the basis that they are more conservative. Using these to define the QALY cost as too high becomes essentially a self-fulfilling argument. NICE's guide of course require the ERG and committee to 'take into account the degree of certainty'. However, we feel they have inappropriately interpreted this and have taken most conservative rather than most likely scenario. There are clearly other models that are equally valid that show a very different and more favourable ICER. Essentially, uncertainty arises because the models are based on data that are immature, and without sufficient follow-up. We would like to assert that it is premature and inappropriate to reverse a decision to fund adjuvant nivolumab at this stage; this would lead to significant potential harm to patients with high risk melanoma. We therefore request that funding continue until more robust data are available. We recognise the need to revaluate the efficacy of drugs as more information comes to hand, but for this setting, ie the adjuvant therapy for melanoma, it is clearly too early, at this stage, to come to such conclusions. The data will be forthcoming with further follow-up in ongoing studies and as real-world data mature. The harm to patients of stopping funding of adjuvant therapy is the significantly increased risk of recurrence of melanoma and the consequences of this, which includes high chance of death, despite access to treatment options for advanced melanoma. In the absence of adjuvant therapy, the majority of patients with resected stage III/IV melanoma will experience disease recurrence. Treatment of advanced disease offers only median survivals of around 3 years, so most will die from metastatic melanoma and experience the increased morbidity of living with and dying from cancer. The physical and psychological burden of developing metastatic disease for patients and carers is significantly worse following recurrence, even if patients are fortunate enough to have a very good long-term survival with subsequent treatments. Of particular concern is the withdrawal of adjuvant nivolumab funding for the resected stage IV patients. These patients, although relatively small in number, are the ones at highest risk of recurrence. Nivolumab is the only adjuvant treatment currently licenced for this indication with 4 year recurrence free survival of 48.6% in the Checkmate 238 study. Support of this benefit in resected stage IV melanoma is seen in the IMMUNED randomised phase II study showing a 2 year RFS of 42% with adjuvant nivolumab vs only 14% in a placebo group (Zimmer et al Lancet	

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
			May 2020) Withdrawal of funding for adjuvant nivolumab will cause significant harm to this patient group In summary • The recommendation to discontinue adjuvant nivolumab funding is based on uncertainty of the resulting QALYs generated by immature treatment outcome data. • More data will be forthcoming, • Withdrawal of funding will cause significant harm to patients. Therefore, we urge the committee to reconsider and to commend continued CDF funding of nivolumab in resected high risk melanoma. This statement has been reviewed and endorsed by 55 consultant melanoma specialists working across the UK. The full list of consultants is supplied below. Signatories to Joint statement objecting to potential withdrawal from the Cancer Drug Fund of adjuvant Nivolumab for resected high risk malignant melanoma – Nov 2020 [For full list of names please see the public web responses.]	
17	Public (web) comment	- Skin Cancer Special Interest Group BAPRAS (British Association Plastic Reconstructive Surgeons	**Has all of the relevant evidence been taken into account?** I write on behalf of the Skin Cancer Special Interest Group BAPRAS (British Association Plastic Reconstructive Surgeons) as our Chair. in essence this proposed recommendation is wrong for our melanoma patients. The advent of adjuvant therapy for these patients has been a game changing moment for all of us involved in the care of highly vulnerable patients. With recurrence rates approaching 50% , being able to make significant in roads with a highly favourable side effect profile has been profound. This recommendation appears to be based on a 'worse case scenario' set of data' rather than something akin to real world data and risks depriving patients from an overall small cohort in current trials with immature data receiving treatment that on balance clearly improves their survival. As a committed oncological surgeon and academic it worries me profoundly that biased date are being presented that will impact the lives of our patients without due full sight of the facts. At the very leat we anticipate a pause to consider all available data before looking to answer these essential questions on behalf of both patients and their care givers. Sincerely Prof Rowan Pritchard Jones FRCS Plast) MD(Bris) MRCS(Eng) St Helens & Knowsley NHS Trust **Has all of the relevant evidence been taken into account?** The evidence is both immature in time and low on overall patient numbers to make a decision on withdrawing care that is currently available. **Are the recommendations sound and a suitable basis for guidance to the NHS?** No	Thank you for your comments. Nivolumab is now recommended, please see FAD section 1.1 for more details.

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
			These seem unreasonable pessimistic and would NOT have my professional support. **Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?** Not discriminatory in law, but of concerning academic quality.	
18	Public (web) comment	Melanoma Focus	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Melanoma Focus is a national charity that supports both professionals, patients and carers by commissioning and funding innovative research, while providing support and information on all stages of melanoma. We wholeheartedly support the professional body -coordinated by the NCRI melanoma CSG - who are collectively objecting to the recommendations. We agree that the assessment does appear flawed. The approach to base a decision on the ERG's flawed modelling is unfair and unreasonable. If there are two modelling approaches, neither of which is fit for purpose, perhaps there should be a recommission of this work? The criticism of Checkmate 238 as not having an NHS standard of care control arm is unreasonable. The control arm in the study, ipilimumab, has already been shown to be superior to observation alone in a large EORTC study (Eggermont et al. November 10, 2016 N Engl J Med 2016; 375:1845-1855). Furthermore, given the Keynote-054 and COMBI-AD data showing superior outcomes for pembrolizumab and targeted therapies compared to placebo, we strongly believe that observation is no longer the UK standard of care. In addition, all recent trials now include this as the control arm (Checkmate 915 which has completed accrual of nearly 2000 patients compared combination immunotherapy with nivolumab, and the EORTC proposal for sequential treatment in Stage III also had a PD-1 inhibitor as standard of care. The fact that BMS did not use competitor data in their model prevented the Committee from adequately considering these clinically highly relevant datasets. Whilst we support further data collection via the CDF; such data for adjuvant treatments require significant follow up, and therefore with 72% patients on treatment at the time of the data review, a negative recommendation at this juncture is not justified. We feel that this negative outcome sets a precedent as there will likely be a similar result for pembrolizumab when this is later reviewed and therefore, we could be in the dreadful position where no immunotherapies are available for patients with stage III and resected stage IV disease. These are the only adjuvant treatment options for the 60% of patients with BRAF wildtype melanoma. Melanoma is the 5th most common cancer and its incidence is related to age, however, there is a large increase in incidence (7-8 fold) in the 15-24 year age group and it is the second most common form of cancer in the 15-34 age group. There is therefore a growing population of melanoma patients who are younger in age with the majority of their life ahead of them: they want to increase the possibility of seeing their children grow up and reaching important milestones.	Thank you for your comments. Nivolumab is now recommended, please see FAD section 1.1 for more details.

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
			We canvassed the opinions of patients at a Patient Workshop and they informed us that their biggest fear is stage IV disease. Being told that the melanoma has spread scares patients more than the risk of having treatment. Patients have informed us that they would rather have treatment when they are fit and healthy and have single agent immunotherapy rather than combination immunotherapy if they were diagnosed with metastatic disease. Given a diagnosis of high-risk melanoma we believe that the vast majority of the committee would want this treatment available for themselves or their loved ones. Melanoma Focus would be delighted to work with NICE to provide real world data drawing together clinicians and patients in a common purpose.	

Bristol Myers Squibb™

25 November 2020

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (CDF review of TA558) [ID1681] ACD - BMS Response

Dear [redacted],

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 have demonstrated nivolumab is a cost-effective treatment option that has the potential to maintain patients with adjuvant melanoma in a disease-free state. The uncertainty in the base case ICER was fully explored with multiple scenario and sensitivity analyses, resulting in ICERs below the £30,000 per QALY threshold.

We welcome the Committee's acceptance of nivolumab improving recurrence-free survival and clinical expectation that this will be reflected in overall survival. However, despite the additional evidence presented to the Committee on the clinical value in comparison to routine surveillance and on cost effectiveness, the Committee felt that there was too much uncertainty within the cost-effectiveness results, which are impacted by the survival estimates. This uncertainty was focused particularly on the following:

- Immature overall survival data
- Subsequent treatments post-adjuvant therapy
- Appropriateness of censoring the CA184-029 trial in the indirect treatment comparison
- Preferred model structure
- Modelling approach to estimate extrapolated overall survival

In this document, BMS consider these topics and evaluate the appropriateness of the assumptions surrounding the current ICER ranges presented at the committee meeting. BMS provide a range of plausible ICERs based on least conservative to most conservative, clinically- plausible assumptions. These scenarios range from £14,301 to £29,011 and we are confident that the most plausible ICER for nivolumab as adjuvant treatment falls below the £30,000 per QALY threshold. BMS believe the information presented in this response should satisfy the Committee's previous concerns over the cost-effectiveness estimates. These ranges demonstrate nivolumab as a cost-effective option for routine commissioning by the NHS.

A positive recommendation will ensure that equitable access in effective and tolerable adjuvant treatments is available for all patients who are at high risk of recurrence in England regardless of BRAF status, and including Stage IV patients, for whom no other adjuvant treatment is available in resected melanoma.

Sincerely,

[redacted]
On behalf of Bristol-Myers-Squibb

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Contents

1. Immature overall survival data

When nivolumab entered into the CDF in November 2018, the estimated study completion date was [redacted] with all subjects having a minimum follow up of 48 months. This formed the rationale for ending the CDF data collection period and beginning the CDF review process, as stated in the Managed Access Agreement. At the time of the CheckMate 238 trial, no adjuvant treatments were available in clinical practice, and without adjuvant therapy, ≥60% of patients were expected to relapse,[1] leading to extremely poor 5-year survival rates.[2] Therefore, the trial observed a slower than anticipated rate of death[3], and future plans for subsequent database locks and study completion were revised, with a further data cut with a [redacted]

At the recent appraisal committee meeting (ACM), the committee expressed concerns with the updated CheckMate 238 trial data, in that the 4-year follow-up data still showed immature overall survival (OS). As stated in Ascierto et al, 2020, fewer deaths had occurred than were expected at 4 years in the Checkmate 238 study (211 deaths were observed out of the expected 302 events); median OS was not reached (N.A. in either treatment arm), considering 77.9% (n=353/453) of patients are still alive at 48 months in the nivolumab arm.[3] The committee also acknowledged that given the indication is in the adjuvant setting, it is positive that OS is still immature, reflecting the fact that patients are surviving longer, though this does mean that waiting for mature OS data could take some time.

During the committee meeting, clinical experts explained that treatments that showed a statistically significant and clinically meaningful recurrence-free survival (RFS) or progression-free survival usually resulted in a statistically significant OS benefit. In addition, the draft ACD states, “The clinical experts explained that usually if a treatment has a clinically meaningful difference in recurrence-free survival then it was likely that this would be reflected in overall survival”. In the 4-year data cut, over half of patients who received nivolumab were still recurrence-free (RFS rate: 51.7% at 48 months).[3] Nevertheless, despite this opinion, the committee concluded it is not known “*if nivolumab increases the length of time people live, or by how much”, because the survival data are still immature.* This appears as a contradictory conclusion with clinical opinion for for the committee to reach as this in essence penalises nivolumab for performing better than expected.

Evidence from CheckMate 238

BMS acknowledge the immaturity of the OS data and agree with the committee opinion that this is considered positive for patients as it means the majority of patients (77.9%) in the trial are still alive for at least four years after initiating adjuvant nivolumab therapy. Treatments that improve survival and other clinically meaningful aspects, such as increased time to recurrence, or other patient-relevant outcomes like increased time to distant metastases or first-line metastatic treatment, should not be penalised for patients remaining alive.

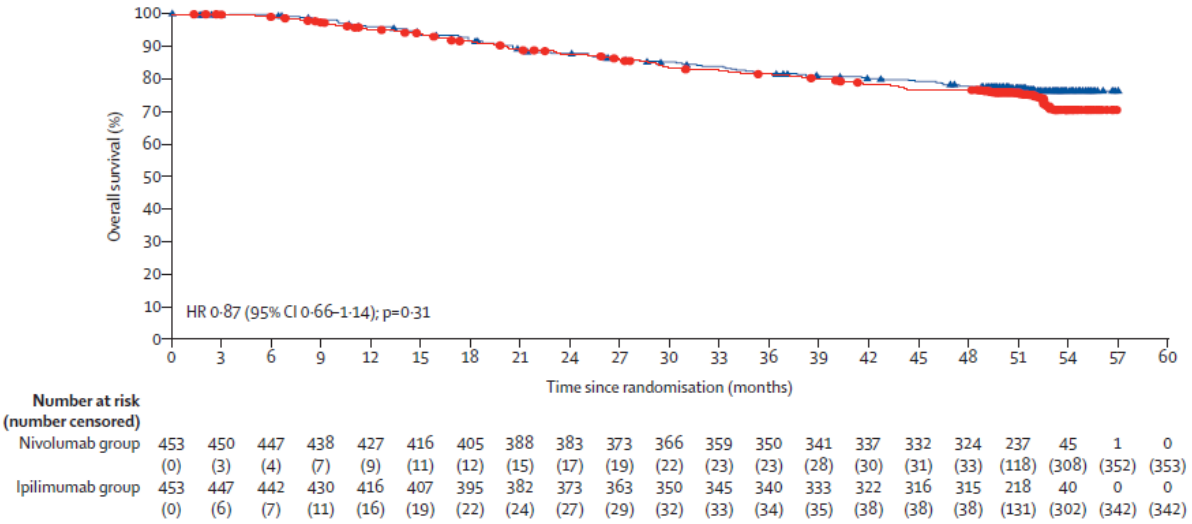
A lack of recommendation for nivolumab adjuvant therapy would lead to denial of an active treatment that will delay or prevent recurrences and offer the possibility of long-term survival. Such denial would impart access inequity on many patients in England and Wales, especially Stage IV patients, who have no access to alternative adjuvant therapy. BMS would also like to remind the committee that despite the data being immature, it does not mean that the CheckMate 238 data lack any useful or clinically meaningful information on the benefits in terms of recurrence, distant metastasis and survival.

Overall survival

As a reminder, due to the low number of events, the Kaplan-Meier OS curve shows overlap between nivolumab and ipilimumab until around 40 months, where nivolumab begins to

show improved survival (company submission, Section A.6.1, Page 14 and Figure 1). Compared to the 24-month data cut, the 48-month data cut has an additional 100 events (55 additional events for ipilimumab and 45 additional events for nivolumab) and shows an improvement in the trend in survival for nivolumab compared to ipilimumab (HR: 0.96 [95% CI: 0.66-1.39] from the 24-month data cut versus HR: 0.87 [95% CI: 0.66-1.14] from the 48-month data cut.

Figure 1: CheckMate 238 OS (48-month minimum follow-up) – Ascierto et al 2020[3]

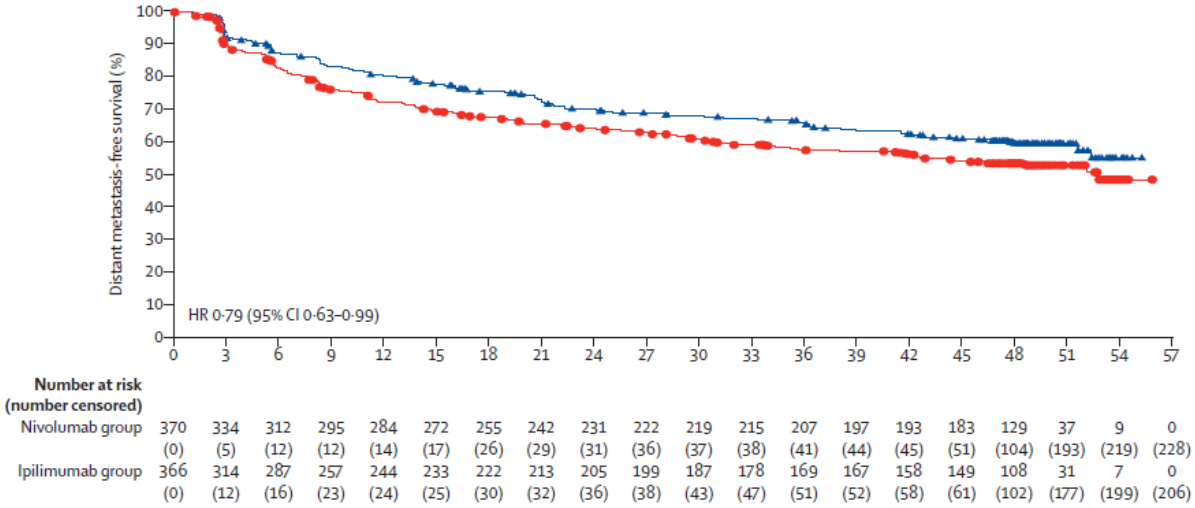


Key: CI, confidence interval; HR, hazard ratio; OS, overall survival

Distant-metastasis free survival

In addition to sustained, significant benefits for nivolumab versus ipilimumab in recurrence-free survival (HR: 0.71 [95% CI: 0.60-0.86])[3], significant benefits have also been shown in distant-metastasis free survival (DMFS) for patients (exploratory endpoint for stage III patients), where the HR for nivolumab versus ipilimumab is 0.79 (95% CI 0.63-0.99)[3] – see Figure 2. At 48 months, nearly 60% of patients in the nivolumab arm are still free from distant metastases (48-month DMFS: 59%) compared with 53% in the ipilimumab arm. These data further demonstrate that the trend is showing improved survival for nivolumab in comparison to ipilimumab, which matches the opinion of the clinical experts in the committee meeting.

Figure 2: CheckMate 238 DMFS (48-month minimum follow-up) – Ascierto et al 2020[3]



Key: CI, confidence interval; DMFS, distant metastasis free survival; HR, hazard ratio

Time to second progression

Nivolumab has also demonstrated [redacted] of progression on next-line therapy (PFS2) compared with ipilimumab [redacted] and [redacted] of time to next line systemic therapy [redacted] (first-line metastatic therapy). In addition, nivolumab also [redacted] of time to second next systemic therapy [redacted] (second-line metastatic therapy) compared with ipilimumab, with [redacted] over the follow-up period for all three outcomes (HR for time to next line systemic therapy: [redacted] HR for time to second next line systemic therapy: [redacted] (see Figure 4 - Figure 5). Literature suggests that PFS2 has a positive correlation with OS in solid tumours, and though there is limited data in melanoma to suggest a relationship, it is very likely to still hold.[4] Nivolumab has demonstrated clear benefits in terms of these outcomes that would be meaningful for patients compared to ipilimumab which has already been proven to be superior to placebo.

Figure 3: Kaplan-Meier curve for PFS2 by treatment arm – CheckMate 238 (48-month minimum follow-up)

Figure 4: Kaplan-Meier curve for time to next line systemic therapy (1L metastatic therapy) by treatment arm – CheckMate 238 (48-month minimum follow-up)

Figure 5: Kaplan-Meier curve for time to second next line systemic therapy (2L metastatic therapy) by treatment arm – CheckMate 238 (48-month minimum follow-up)

[redacted]

Evidence of nivolumab versus placebo

Observed data

BMS reinforce that the NICE scope does not include ipilimumab as a relevant comparator as this submission is evaluating nivolumab versus routine surveillance. An OS benefit of ipilimumab versus placebo has been previously demonstrated, at the median follow-up 6.9 years, the CA184-029 trial demonstrated significantly and substantially better OS for ipilimumab versus placebo (HR: 0.73; 95% CI: 0.60-0.89).[5] In TA553, the clinical experts perspective states that there is evidence that ipilimumab improves overall survival and that anti-PD1 treatments are superior to ipilimumab (Public AC slides, slide 8).[6] Consequently, despite the uncertainty remaining in the CheckMate 238 trial, if the committee conservatively assume that nivolumab and ipilimumab are associated with the same risk of death (BMS note such an assumption is clinically unlikely given the trend of the evidence favouring nivolumab) then there is still ample evidence that nivolumab would have improved OS compared with routine surveillance based on the results of the CA184-029 trial alone.[5]

In addition, the benefit of active adjuvant treatment over routine surveillance has been widely acknowledged by clinical experts in other adjuvant melanoma assessments (TA553[6] and TA544[7]). The KEYNOTE-054 trial shows that at the 3-year minimum follow-up, pembrolizumab demonstrates significantly better RFS versus placebo (HR: 0.56, 95% CI: 0.47-0.68)[8] which is [redacted] results of the ITC of nivolumab versus placebo when the Bucher analysis was performed on the ITT population (HR: [redacted]). The results of RFS from KEYNOTE-054 are expected to also translate to DMFS and OS after longer follow-up data is available.[8] Given [redacted]

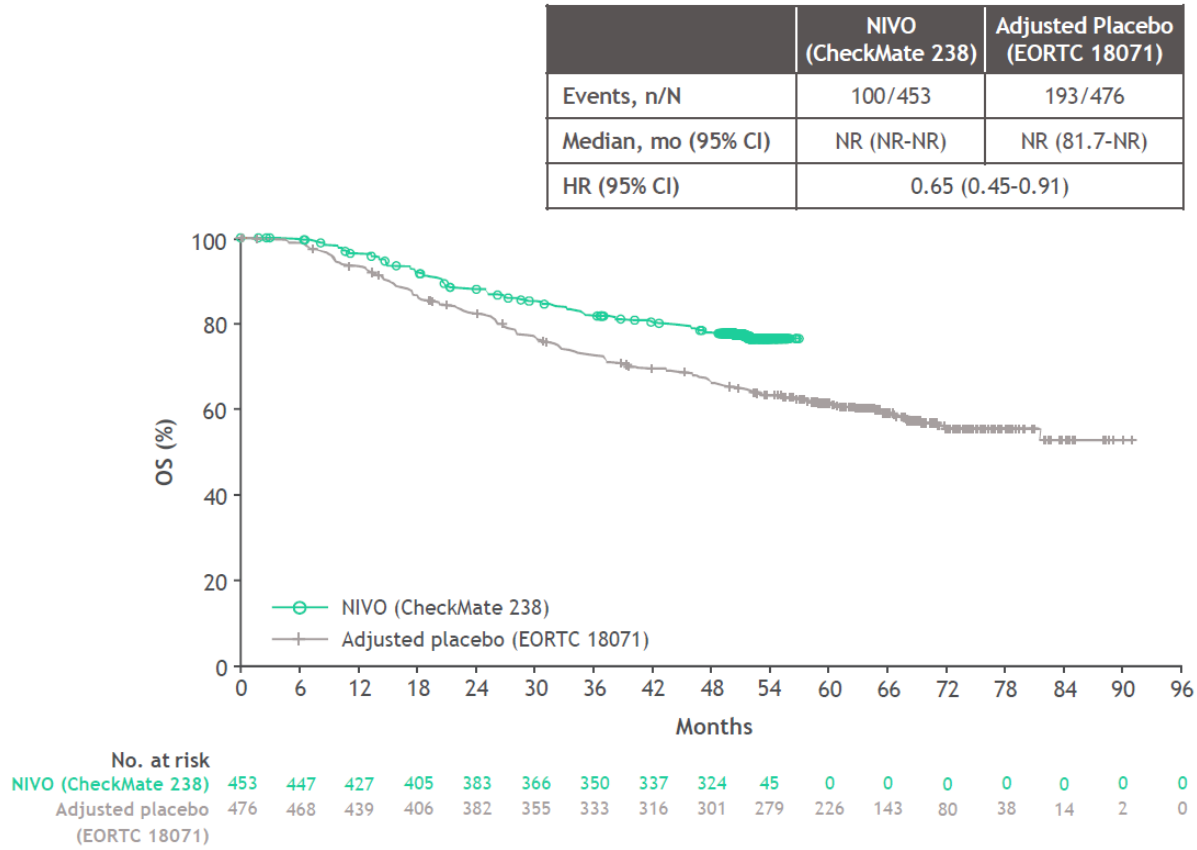
Additionally, as part of the validation process of the submission, BMS compared the results of the routine surveillance arm from the model with the placebo arm from KEYNOTE-054 and COMBI-AD after adjusting the patient population to reflect the trial populations. In both instances, the routine surveillance arm matched the placebo arms, for both RFS and OS (from COMBI-AD), which validates the predictions of routine surveillance from the company model with observed data (see company submission, Section A.15.18, Page 112).

Indirect treatment comparisons

The key uncertainty with OS, as discussed at the committee meeting, was the use of CA184-029 trial to estimate routine surveillance OS given the advances in subsequent treatments since the trial started (ACD, Section 3.7, Page 11). As stated throughout the submission process in this appraisal and in TA558, the inclusion of a fixed effect trial covariate in the ITC PLD meta-regression is analogous to performing a traditional ITC on summary data using ipilimumab as a common comparator because the trial effect will account for all unobserved differences between trials (including age of trials, subsequent treatments, etc.), thus maintaining randomisation. As such, the routine surveillance arm projected in the cost-effectiveness model, reflects a placebo treatment arm from the CheckMate 238 trial using this covariate.

Furthermore, a recent analysis was published where OS was adjusted to account for subsequent therapies specifically in the placebo arm of the CA184-029 trial and compared to nivolumab in CheckMate 238.[9] To account for subsequent therapies on survival, the analysis determined an average increase in post-recurrence survival in the ipilimumab arm in CheckMate 238 versus CA184-029, which was then applied to the ITC. Even with an assumed adjustment of 63% to account for improvements in subsequent therapies, median OS is not predicted to be reached within nearly 7 years for the placebo arm (median OS: N.R. [95% CI: 81.7, N.R.]) – see Figure 6. Furthermore, in this analysis, if adjusting post-recurrence survival of the placebo arm by an 83% increase, an indirect comparison of nivolumab vs. placebo is still in favour of nivolumab (OS HR: 0.69 [95% CI: 0.49, 0.98]).

Figure 6: OS in the nivolumab arm in CheckMate 238 (48-month minimum follow-up) and the adjusted placebo arm in CA184-029 (EORTC 18071), assuming a 63% post-recurrence survival increase (Weber et al. 2020)[9]



Key: CI, confidence interval; HR, hazard ratio; NR, not reported; OS, overall survival

The analysis from both ITC's demonstrates that nivolumab is predicted to have significant OS benefit versus routine surveillance both reporting similar outcomes (HR from ITC PLD meta-regression using Bucher method [redacted]

Overlaying the model's projected OS from the ITC PLD meta-regression and changing the model population to CheckMate 238 shows that the two ITC's show similar estimates of OS for routine surveillance (Figure 7). Adding this analysis into the cost-effectiveness model, using the HR from the adjusted ITC analysis and applying it to the modelled nivolumab arm to produce the routine surveillance arm shows ICERs all well under the £30,000 willingness to pay threshold (Table 1).

Figure 7: OS in nivolumab arm in CheckMate 238 (48-month minimum follow-up) and the adjusted placebo arm in CA184-029 (Weber et al. 2020)[9] versus model projected OS from ITC PLD meta-regression

Key: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; NR, not reported; OS, overall survival; PLD, patient-level data

Table 1: CE model results using the ITC adjusted for post-recurrence survival[9]

Adjusted post-recurrence survival increase in CA184-029		OS HR (96% CI), nivolumab versus placebo	ICER using the uncensored OS ITC for nivolumab	ICER using the censored OS ITC for nivolumab
Ipilimumab	Placebo			
+63%	+53%	0.63 (0.44-0.89)	£12,300	£12,231
+63%	+63%	0.65 (0.45-0.91)	£13,087	£13,013
+63%	+73%	0.66 (0.47-0.94)	£13,508	£13,431
+63%	+83%	0.69 (0.49-0.98)	£14,894	£14,808

Key: CE, cost-effectiveness; CI, confidence interval; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison.
Light green represents ICERs under £20,000

BMS reiterate that, for an active treatment in the adjuvant setting, it is reasonable to expect that median OS may not be reached for some time; therefore, the demonstrated benefits of nivolumab as an adjuvant therapy in melanoma should not be disregarded in absence of median OS. Evidence from observed data from adjuvant melanoma trials and comprehensive and robust analysis demonstrates that nivolumab has a significant benefit of overall survival versus routine surveillance.

2. ERG approach to modelling overall survival

Given the uncertainty around overall survival projections, the ERG explored assumptions about improvements in the OS for routine surveillance to reflect the improved treatments available for patients who have a recurrence. Two overarching assumptions were applied in the ERG's scenarios, assuming an equal hazard of death at 2 years between nivolumab and placebo ("*the hazard of death for routine surveillance and adjuvant nivolumab was set to be the same after 2 years [for example, that survival for routine surveillance is the same as survival for nivolumab after 2 years].*") and fully amending subsequent treatments after routine surveillance to assess a scenario that is not reflective of clinical practice. BMS would like to emphasize to the committee that these two assumptions, in isolation and in combination, lack clinical plausibility, are not resulting from clinical expert opinion in this assessment, and are not based on published evidence for nivolumab or routine surveillance in adjuvant melanoma.

The committee acknowledged that the ERG's scenarios are likely to be conservative and bias against nivolumab, but due to the uncertainty surrounding OS, the committee preferred the ERG's more conservative approach. BMS understand the committee's preference for conservative outcomes based on the uncertainty, however, these assumptions should be based on **clinically plausible** conservative assumptions and not a completely unfounded, clinically unsubstantiated worst-case scenario. These two clinically implausible scenarios were used to generate an 'upper bound' ICER, and following application of these combined assumptions, a negative decision was reached by the committee, on the basis that "*all the ICERs are higher than what NICE considers a cost-effective use of NHS resources*". BMS reinforce that this decision was made on clinically implausible ICERs, which, per NICE graft methods guidance, are not appropriate for decision making.

In NICE's new draft methods guide[10], it explicitly states that *"When exploring uncertainty in an economic model, it is important to take into account the plausibility of the parameters and assumptions that are being used.* ***It is perhaps self-evident that committee decisions must be based on plausible inputs and assumptions that are consistent with the evidence.*** *Nevertheless, there is sometimes value in exploring implausible values to test the function of the model or show relevant features of an analysis…There is a case for change to ensure that the methods have sufficient flexibility to allow such analyses, but also to clearly label such analyses with their purpose and* ***emphasise that they are not suitable for decision making****."*

The ERG assumptions were not explicitly discussed at the committee meeting to truly understand from the ERG why these would reflect a reasonable upper bound on the ICER, and, as such, BMS would like to highlight the issues surrounding these and present more plausible assumptions to consider, which have been based on various analyses exploring available evidence for nivolumab and placebo in adjuvant melanoma patients.

BMS also kindly request, that in light of the statement within the new draft methods guide, that the committee consider only plausible assumptions and to acknowledge the ERG scenarios as necessary only to demonstrate the impact of these assumptions but not suitable for decision making.

Equal hazard time point

In the ERG report, the ERG presented scenarios assuming that nivolumab and routine surveillance have an equal hazard of death at 2-years and 3-years, which were chosen to reflect possible re-challenge of immunotherapies and so after this time point, the same

subsequent treatments were assumed in both treatment arms and hence the same hazard of death. During technical engagement, BMS responded to these assumptions (see company response to technical engagement Issues 5 and 6, Page 10) outlining a number of arguments, by;

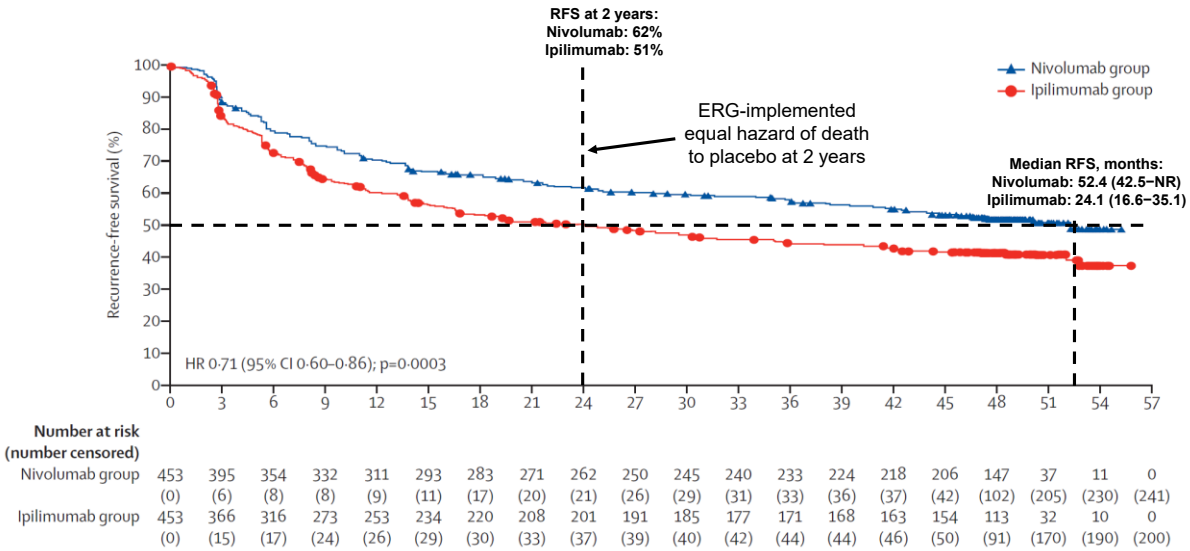
- Highlighting the relevance of the alternative model structure which allows these kinds of scenarios to be explored explicitly
- Explaining how the ITC meta-regression already captures the differences between trials (including time and subsequent therapies) with a trial covariate
- Presenting additional analysis, which adjusts the post-recurrence survival of the placebo arm of CA184-029 to reflect the subsequent treatments used in CheckMate 238 (showing similar outcomes to the current OS ITC)
- Underlining the importance of considering the proportion of patients who are recurrence-free in the nivolumab arm compared to the routine surveillance arm which will have an impact on overall survival. BMS suggested that using the median RFS for nivolumab was a more reasonable time point (52.4 months [4.36 years]).[3]

In response to technical engagement, the ERG rejected the state-transition model based on differing life-years to the partitioned survival model, and overlooked the new additional analysis suggesting not enough information was provided. Further information of this adjusted analysis has been presented in Section 1 above, and this is now also published.[9] Whilst we disagree with the rationale to reject the state-transition model, we are happy for the Committee to consider the partitioned survival model using actual trial data as the primary analysis. We would request, however, that the full extent of the trial data is considered in decision making.

The ERG did however consider the revised time point of [redacted] years suggested as plausible, but instead preferred to use the median RFS from the routine surveillance arm (1.61 years rounded to two years) because by “using the nivolumab median RFS, there is a delay in improved overall survival for routine surveillance patients”. By using the median RFS for routine surveillance, this ignores the fact that more patients in the nivolumab arm are recurrence-free (at 2-years, the model shows that [redacted] are recurrence-free in the nivolumab arm versus [redacted] in the routine surveillance arm) which is not confounded by subsequent treatments. By considering the time point suggested by the ERG will include the additional RFS benefit seen by nivolumab after the 2-year time point into the routine surveillance arm and hence suggesting that these will have an equal hazard of death to patients in the nivolumab arm is improbable.

Figure 8 shows the Kaplan-Meier RFS curves from CheckMate 238 and the time point assumed by the ERG in which equal OS hazard is assumed. The plot clearly shows the continued separation after 2 years compared to ipilimumab, suggesting that an even bigger increased separation versus routine surveillance would be seen. This increased separation and increased benefit for RFS is at odds with the supposed immediate equal OS from this point onwards.

Figure 8: Kaplan–Meier curve for recurrence-free survival by treatment arm – CheckMate 238 (48-month minimum follow-up) (Ascierto et al, 2020)[3]



Key: Ipi, ipilimumab; Nivo, nivolumab.

Unfortunately, these time points were not discussed with clinicians at the committee meeting and therefore, clinical commentary was not available to the Committee to understand the clinically implausible nature of this assumption. We would request the Committee take clinical advice on this assumption, considering the bold clinical nature and influence on the incremental QALY assessment, and reconsider inclusion of an equal hazard of death at two years in the final decision.

Evidence from CheckMate 238

In addition to the precedent of accepted treatment waning time points being later than that suggested by the ERG, the data from CheckMate 238 itself doesn't support the 2-year time point.

The smoothed hazard plots for OS (presented in company response to technical engagement Issue 2 and Figure 9 below) show [redacted]

As such, it is not appropriate to consider the hazard of death between nivolumab and ipilimumab the same until at least [redacted], and subsequently, not plausible to therefore consider equal hazard of death between nivolumab and routine surveillance for at least [redacted]

Figure 9 shows OS hazards from CheckMate 238 over laid with the model predicted OS hazards after adjusting the patient characteristics in the model to reflect CheckMate 238 patients. This demonstrates that firstly, the OS hazard from the model actually overestimates that hazard of nivolumab compared with the actual trial data from 2-years. Secondly, applying the ERG assumption of equal OS at 2-years to routine surveillance shows that routine surveillance is then predicted to have lower hazard of death than ipilimumab after 2-years. This is contradictory to the OS hazards from the actual trial data in CA184-029

(Figure 10) [redacted] (where the smoothed hazard incorporates data from the end of the Kaplan-Meier curve).

Figure 9: Smoothed hazard plots – OS – CheckMate 238

[redacted]

[redacted]

Figure 10: Smoothed hazard plots – OS – CA184-029

[redacted]

In addition to the trial data contradicting the 2-year assumption of equal hazards, the ITC adjusting the placebo arm for subsequent treatments[9] (see Section 1) also shows that after adjustment, the OS hazard of placebo doesn't meet or cross nivolumab's hazard for at least 4 years (up until max trial data for CheckMate 238 - though appears extremely likely to continue for at least up to 6.5 years)– see Figure 11. There is [redacted]

[redacted] seen between nivolumab and placebo arm adjusted for subsequent therapies hazard ratio of [redacted].

Figure 11: Smoothed hazard plots – OS nivolumab from CheckMate 238 and adjusted placebo from CA184-029

Key: OS, overall survival; PBO, placebo; NIV, nivolumab

Figure 12: Smoothed hazard plots – OS ipilimumab from CheckMate 238 and adjusted ipilimumab from CA184-029

The adjustments for subsequent therapy to CA184-029 appropriately capture the estimated subsequent therapy effect on post-recurrence survival as seen in Figure 12 where there are [redacted] and there is [redacted] between the ipilimumab arm from CheckMate 238 and the adjusted ipilimumab arm of CA184-029 [redacted]).
To further investigate the effect of the change of subsequent therapies between the CheckMate 238 and CA184-029 studies, an additional analysis was performed to understand at what point parametric hazards rates cross, which would correspond to an equal hazard of death time point.

The range of standard parametric survival models noted in NICE DSU TSD 14 (exponential, gamma, Gompertz, log-normal, log-logistic, Weibull, generalised gamma and generalised F) were tested. In addition, Royston–Palmer spline models were fitted to explore the merits of more flexible models. The goodness of fit of different parametric models to the observed data was assessed by visual assessment of model curves versus KM data and objectively using Akaike information criterion (AIC). These statistics, across the standard and the various Royston–Palmer spline models tested, are shown in Figure 2.

Table 2: AIC statistics for survival model first to nivolumab from CheckMate 238 and adjusted placebo from CA184-029

Model	**Nivolumab**	**Placebo**
	AIC	**AIC**
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Generalised F	[redacted]	[redacted]
1-knot hazard	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]
2-knot hazard	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]
Key: AIC, Akaike information criterion		

The goodness of fit statistics indicate that the 1-knot normal and 1-knot odds model provides the best statistical fit to nivolumab and adjusted placebo, respectively as it has the lowest AIC value. The fitted curves are presented in Figure 13 and Figure 14 for the nivolumab (CheckMate 238) and adjusted placebo (CA184-029) arms respectively.

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Figure 13: CheckMate 238 OS - 1-knot normal survival extrapolation - nivolumab

Figure 14: CA184-029 adjusted for subsequent therapies OS - 1-knot odds survival extrapolation - placebo

From the parametric curves selected, hazard rate estimates were obtained for nivolumab relative to placebo from time points 1 to 1000 months. The parameter estimates for each arm, along with their variance-covariance matrices were then used to generate parametric bootstrap estimates of the hazard rates for each treatment arm, with 50,000 bootstrap samples being obtained. These bootstrapped hazard rates were then log-transformed and their standard deviation obtained at each time point to obtain an estimate of the standard error for the log hazard rate estimates. These standard errors for the independent models for each treatment arm were then used to derive the standard error for the difference in log hazard rates. An estimated 95% confidence interval for the log hazard ratio (as the difference in the log hazard rates) was calculated by assuming an approximate normal distribution for the log hazard ratio estimate. Finally, this confidence interval was exponentiated to obtain a confidence interval for the hazard ratio.

This process was applied for all pairwise combinations of parametric models fit to each treatment arm. In the best fitting case (1-knot normal for nivolumab and 1-knot odds for placebo) we obtain the following hazard ratio plot over time as seen in Figure 15.
We can see in this figure that the hazard ratio increases from randomization until around [redacted] years after which it reduces again. The hazard ratio is seen to [redacted] however, the confidence interval does not finally cross the hazard ratio of 1, corresponding to equal hazard in both treatment arms, until [redacted] post-randomisation. Although the estimated hazard ratio remains below 1, the confidence interval includes unity from this point onwards. At two years post-randomisation the log hazard ratio is estimated to be [redacted], and its standard error is estimated to be [redacted]. From this we estimate that the probability the log hazard ratio is positive (i.e. the hazard ratio exceeds 1) at this time point is less than [redacted].

When considering the flexible models and those which include 3 or more parameters (best fitting according to the AIC criteria), and the first such point at which the difference in hazard became non-significant in nearly 90% of cases. It can be seen that the minimum point at which the difference in hazard rates became non-significant was [redacted]), and the median was [redacted].

Figure 15: Estimated hazard ratio and 95% CI - Nivolumab from CheckMate238 vs adjusted placebo from CA184-029

[redacted]

In conclusion, BMS consider the ERG's timepoint of 2-years to be unreasonable in light of the evidence available, implausible and without sufficient justification. Based on precedent in other immune checkpoint inhibitor appraisals (NOTE: In the adjuvant pembrolizumab submission (TA553), treatment waning scenarios were explored by the ERG using 3-years as the minimum.[6]), and actual trial data, an absolute minimum timepoint to consider should be 3-years. However, using the evidence from CheckMate 238, [redacted] ITC data suggests that the equal hazard assumption is [redacted]). In addition, the arguments outlined earlier considering the proportion of patients who are recurrence-free in the nivolumab arm, and hence are expected to have a survival advantage, gives a more reasonable conservative time point of 4.36 years based on median RFS. Extrapolation of the placebo arm after adjustment for subsequent treatments show that the hazards are not equal until at least [redacted] where the end of the upper 95% confidence interval crosses 1. As such, 3-years is a highly conservative assumption.

Treatment waning time points previously accepted by committees

Treatment waning adjustments, where the treatment arm and comparator are assumed to have the same hazard of death at certain timepoints, are often incorporated into economic models to explore the impact on treatment effect and how long this is anticipated to last. Mostly, the time points used are based on clinical opinion, though it is often difficult to estimate and demonstrate using trial data what the correct timepoint should be. These adjustments are consistent with the ERG's adjustment to OS, which assumes that after a certain time point, the treatment effect on OS diminishes and the hazard is assumed the same.

A targeted literature review of 10 completed previous nivolumab submissions to NICE was conducted to identify key themes around treatment waning assumptions.[11] This review found that of the 10 appraisals across various indications, if a stopping rule was accepted by the committee, the treatment waning time point was accepted at 3 and 5 years.[12-14]

A follow-on targeted literature review of other immune-checkpoint inhibitors (nivolumab, pembrolizumab, atezolizumab and avelumab) submitted to NICE before May 2020, looked at the treatment waning assumptions used by the companies and accepted by committees in various indications. A summary of findings are presented in the Appendix. In melanoma (adjuvant, metastatic treatment naïve and previously treated), none of the submitting companies presented treatment waning in their analysis and no treatment waning was incorporated into the committee's accepted base case assuming a continued treatment effect.[6, 15-19] In the adjuvant pembrolizumab submission (TA553), treatment waning scenarios were explored by the ERG using 3-years as the minimum.[6] In non-small cell lung cancer (NSCLC), most of the companies included a treatment waning in their base case or provided as scenarios.[12, 13, 20-23] In the majority of the appraisals, the committees accepted a 3-5 year treatment waning time point but did accept a lifetime treatment assumption in two appraisals.[12, 13, 20, 23, 24] Lifetime treatment effect was rejected by committees for the appraisals in urothelial carcinoma[25-29], though only one provided a time point of 3-years to consider.[29] In renal cell carcinoma (RCC), the committee accepted a treatment waning time point of 3-years after discontinuation as plausible for one appraisal.[30] In other indications, 5-years was accepted by committees if treatment waning was deemed appropriate.[14, 31, 32]

In a more recent appraisal for trastuzumab emtansine for the adjuvant treatment of breast cancer, the ERG assumed that treatment effect was maintained for 3 years then gradually decreases to no treatment effect at 8 years.[33] The committee concluded that the ERG's approach was suitable for decision making. This was based on a trial with a 3-years data cut-off and is more immature than CheckMate 238 (7% of patients with an event in the trastuzumab trial versus [redacted] in CheckMate 238). It is inconsistent that a much more conservative assumption is used in this appraisal than in any other appraisal with similar/more immature data.

Treatment waning was historically considered inappropriate for melanoma due to the precedent set by the ipilimumab melanoma data which showed that long-term treatment effect was plausible for immunotherapies in this disease. In the original submission TA558, the committee incorrectly noted that a lifetime treatment benefit was assumed (in fact 10 years was assumed as long-term data was applied to both arms at this point), however, "the Cancer Drugs Fund clinical lead noted that this might be optimistic because in CA184-029, the treatment effect of ipilimumab on recurrence-free survival started to wane after about 3 years".[19] Therefore, it seems inconsistent that a more conservative assumption around treatment effect has been accepted than the original submission with less data.

For other indications, a time point of 3-5 years was considered appropriate and most of these were based on shorter follow-ups than is available for this indication (see Table 4). Based on precedent of accepted treatment waning time points, the ERG suggested time appears highly implausible. In addition, treatment waning is applied immediately, with no gradual waning making it even more conservative.

Subsequent treatment post routine surveillance

In the appraisal committee document, Section 3.8, Page 13, it states "The committee noted there was considerable uncertainty around the assumptions of overall survival and subsequent treatments in the model". At the end of the data collection period for the Cancer Drugs Fund, 72% of patients who received treatment through the CDF were still receiving their initial treatment (1 year maximum). With respect to subsequent treatments, BMS would like to firstly highlight that the conclusion of the committee based on clinical opinion was that data from CheckMate 238 reflected clinical practice (Section 3.3, Page 8) which eliminates the uncertainty associated with the trial data subsequent treatment distributions. Furthermore, in BMS' response to the TA558 ACD, data from real-world UK sources were presented (from IPSOS and Wilmington Health Care) which demonstrated what patients received in clinical practice in the metastatic setting before the availability of adjuvant therapies (Section 2, Page 5 – also presented in the appendix). The conclusion was that this data showed similar treatment patterns to the ipilimumab arm from CheckMate 238.

In response to technical engagement, the ERG presented a new scenario which assumes that after the treatment waning time-point, all patients in the routine surveillance arm receive immuno-therapy and that is assumed to be nivolumab. The ERG provided this scenario because *"patients on routine surveillance who experience a recurrence in their disease will receive the benefits and so incur the costs of an immunotherapy. For simplicity, the immunotherapy is assumed to be nivolumab and the hazard of death from this point onward is assumed to be the same as patients receiving adjuvant nivolumab."*

The original rationale for providing the equal hazard scenarios on the routine surveillance arm was to investigate the impact of an improved survival based on improved subsequent treatments compared to those available in CA184-029. Therefore, at the point of equal hazard of death (waning), the costs of the subsequent treatments received by patients on

the nivolumab arm in CheckMate 238 is also applied to the routine surveillance arm, hence the same hazard and the same subsequent treatment costs are applied. For this scenario, this assumption is appropriate given that the committee, ERG and clinical expert all agree that the subsequent treatments in CheckMate 238 are reflective of clinical practice.

In contrast, assuming that all patients after routine surveillance receive immunotherapy, which is assumed to be nivolumab goes against any data showing what patients actually receive in practice. This assumption lacks clinical plausibility, are not resulting from clinical expert opinion in this assessment, and are not based on published evidence for nivolumab or routine surveillance in adjuvant melanoma. It is fundamentally not plausible to assume that all patients receive the same treatment post recurrence, and indeed CheckMate 238 has been accepted as reflective of clinical practice (ACD, Section 3.3, Page 8), so the need for such assumptions is redundant and unjustified. Similar implausible scenarios were explored by the ERG in the original TA558 submission where simplified assumptions on what patients receive when they recur were explored to address the uncertainty associated with subsequent treatment usage in CheckMate 238. The real-world UK sources presented in TA558 BMS' ACD response demonstrated what patients received in clinical practice in the metastatic setting before the availability of adjuvant therapies (Section 2, Page 5). These sources showed a mix of treatments being given to patients and also showed consistency with the data from CheckMate 238. Given the availability of these sources (see Appendix), and the validity of the current CheckMate 238 subsequent treatments, the uncertainty associated with subsequent treatments, and need for drastic scenarios are unnecessary.

In conclusion, BMS would like the committee to disregard this scenario presented by the ERG due to it being implausible and unwarranted. Subsequent treatments in the model use CheckMate 238 distributions which the committee agree are reflective of clinical practice. In the scenarios assuming equal hazard of death, the subsequent treatment mix post routine surveillance is assumed to be the same as the subsequent treatment mix post adjuvant nivolumab. This seems more reasonable given the hazard is assumed to be the same after this time point.

3. Plausible ICER ranges

Based on the above, and the preferences outlined by the committee in the appraisal meeting, BMS would like to present **clinically plausible** ICER ranges for the committee to consider. These ICERs incorporate the following:

- The partitioned survival model has been used based on the committee's preference for this model structure compared to the state-transition model (Section 3.6, Page 10).
- Including ICERs which uses censored OS in the ITC based on the duration of ipilimumab treatment. As discussed by the ERG and committee, the censored ITC OS analysis is biased against nivolumab and is viewed as a conservative scenario (Section 3.5, Page 9).
    - The plausible ICER ranges consider both uncensored and censored analysis to provide a range in which the true ICER would sit.
- Subsequent treatments based on data from CheckMate 238 which was considered by the committee as being reflective of clinical practice (Section 3.3, Page 7).
- Assuming that the hazard of death between nivolumab and routine surveillance is the same at a certain time point.
    - The plausible ICER ranges consider the most reasonable conservative minimum time point of 3-years (as discussed in Section 2) and the maximum time point originally presented in BMS's base case of 10-years, to provide a range in which the true ICER would sit.

Table 3 presents the most plausible ICER ranges where the true ICER would sit. Ranging from £14,301 using the least conservative assumptions to £29,011 using the most conservative assumptions as its absolute upper bound.

Table 3: Plausible ICER ranges

Equal hazard time point		**Least conservative → Most conservative**	
		Uncensored OS	**One-year censoring of ipilimumab OS patients**
Least conservative → Most conservative	**Company base case (10-years)**	£14,301	£17,404
	9- years	£14,640	£17,899
	8-years	£15,088	£18,550
	7-years	£15,679	£19,405
	6-years	£16,486	£20,568
	5-years	£17,647	£22,230
	4.36-years (median RFS)	£18,789	£23,853
	4-years	£19,431	£24,760

Equal hazard time point		Least conservative → Most conservative	
		Uncensored OS	**One-year censoring of ipilimumab OS patients**
	3-years	£22,487	£29,011

Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; RFS, recurrence-free survival Light green represents ICERs under £20,000, dark green represents ICERs between £20,000-£30,000

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5. Appendices

Treatment waning conclusion from targeted literature review

Table 4: Waning of treatment effect in previous NICE submissions for immunotherapies

Disease area	Intervention	TA number	Data availability	Maximum treatment duration	Treatment waning submitted by company	Treatment waning incorporated into committee's accepted base case
Melanoma	Nivolumab	TA384	CheckMate 066 median FU: 8.9 months CheckMate 067 DBL- 18 months CheckMate 037 median FU 8.4 months CheckMate 003 median FU 55 months	As long as clinical benefit is observed.	None	None
	Nivolumab + ipilimumab	TA400	CheckMate 067&069 12 months data cut CheckMate 069 18m FU for OS CheckMate 066 28m OS FU	As long as clinical benefit is observed.	None	None
	Pembrolizumab	TA366	KN006 DBL 12 months OS follow-up	2-years	None	None

Disease area	Intervention	TA number	Data availability	Maximum treatment duration	Treatment waning submitted by company	Treatment waning incorporated into committee's accepted base case
	Pembrolizumab	TA357	KEYNOTE-002 (IA2): 19 months KEYNOTE-001 (Part B2): 6 months KEYNOTE-006 (IA1): >6 months KEYNOTE-006 (IA2): 12 months	Until progression or unacceptable toxicity	None	None
	Nivolumab	TA558	CheckMate 238: 24 months CA184-029: 57 months	1-year	None	None
	Pembrolizumab	TA553	KEYNOTE-054: median FU 16 months	1-year	None	ERG showed scenarios using 3 years. The Committee recognized the uncertainty in the assumption of lifetime treatment benefit with pembrolizumab as adjuvant treatment and concluded that more mature data on overall survival would help decision-making
NSCLC	Nivolumab	TA483	CheckMate 017; 5-year follow up	2 years	Scenarios of waning at 3, 5 and 10 years following end of treatment included	The Committee preferred the scenario waning treatment effect 3 years after finishing treatment
	Pembrolizumab	TA600	KEYNOTE 407; data cut-off date 3 April 2018;	2 years	Assumed a lifetime treatment effect	In line with previous appraisals, the Committee deemed a lifetime treatment effect to be implausible

Disease area	Intervention	TA number	Data availability	Maximum treatment duration	Treatment waning submitted by company	Treatment waning incorporated into committee's accepted base case
			median FU 7.8 months			
	Nivolumab	TA484	CheckMate 057 12-month data cut; 18-month data cut provided post-submission	As long as clinical benefit is observed.	Scenarios of waning at 3, 5 and 10 years following end of treatment included as scenarios	The Committee preferred the scenario waning treatment effect 3 years after finishing treatment
	Pembrolizumab	TA557	KEYNOTE 189, data cut-off date 8 November 2017; median FU 10.5 months	2 years	Assumed a lifetime treatment effect	The Committee used ERG scenarios where treatment effect was assumed to last 3–5 years was used in decision-making
	Atezolizumab	TA584	IMpower150; data cut-off date 22 January 2018; minimum FU 13.5 months; median FU approx. 20 months	2 years	Treatment effect capped to 3 years after treatment discontinuation in line with previous NICE appraisals	The Committee agreed with the company's base case
	Pembrolizumab	TA531	KEYNOTE-024; data cut-off date 10 July 2017; median FU 25.2 months	2 years	Lifetime treatment effect assumed but treatment effect capping scenarios	The Committee concluded that the company's scenarios were plausible and would be taken into account in its decision-making
	Pembrolizumab	TA428	KEYNOTE 010; data cut-off date 30 September 2015; minimum FU 6 months;	2 years	Lifetime treatment effect as company base case, treatment waning for scenarios when	The Committee rejected lifetime treatment effect although did not have a preferred waning point as treatment effect duration is uncertain

Disease area	Intervention	TA number	Data availability	Maximum treatment duration	Treatment waning submitted by company	Treatment waning incorporated into committee's accepted base case
			median FU 13 months KEYNOTE 001; data cut-off date 23 January 2015; minimum FU 6.4 months; median FU 16.2 months		requested by the Committee	
	Atezolizumab	TA520	OAK; data cut-off date 07 July 2016; minimum FU 19 months	As long as clinical benefit is observed.	Waning was included after committee meeting, either decreasing after 3 years off treatment linearly over the time horizon, or capped at several time points	The Committee considered that the treatment effect was unlikely to last more than 5 years after treatment
Urothelial carcinoma	Atezolizumab	TA492	IMvigor 210: Primary analysis data cut (6 month FU for cohort 1 [1L] and for cohort 2 [2L]). Follow-up analysis data cut (15-month FU for cohort 1 and 20-month for cohort 2)	As long as clinical benefit is observed.	Scenarios with waning at 1, 2, 3 and 5 years were included	Modelling of treatment effect was expected to be unreliable, but a lifetime treatment effect was implausible

Disease area	Intervention	TA number	Data availability	Maximum treatment duration	Treatment waning submitted by company	Treatment waning incorporated into committee's accepted base case
	Pembrolizumab	TA522	KEYNOTE-052: median FU 9.5 months	2-years	Waning scenarios at various time points included after committee meeting	Lifetime treatment effect was deemed implausible. No mention of preferred waning timepoint
	Nivolumab	TA530	CheckMate 275: 31 months CheckMate 032: 36 months	2-years (in revised analysis)	Waning after 3 and 5 years explored in scenarios	Rejection of lifetime treatment effect
	Pembrolizumab	TA519 ID1536	KEYNOTE-045: 23 months	2-years	Waning scenarios at various time points included after committee meeting in TA519. In the CDF review, the company submitted a scenario analysis in which 38.5% of people continued to benefit from pembrolizumab for their lifetime	Lifetime treatment effect for any patients was deemed implausible. No mention of preferred waning timepoint
	Atezolizumab	TA525	IMvigor 210: Primary analysis data cut (6 month FU for cohort 1 [1L] and for cohort 2 [2L]). Follow-up analysis data cut	2-years	Waning at 3 and 5 years after stopping treatment included as scenario analysis	The Committee would take account of 3-year treatment effect cap

Disease area	Intervention	TA number	Data availability	Maximum treatment duration	Treatment waning submitted by company	Treatment waning incorporated into committee's accepted base case
			(15-month FU for cohort 1 and 20-month for cohort 2) IMvigor 211: median FU 17.3 months			
RCC	Nivolumab + ipilimumab	TA581	CheckMate 016: Median follow-up in N1I3: 36 months Median follow-up: 37.7 months CheckMate 214: Aug 2017 data cut Median follow-up 25.2 months	5 years	Initial submission did not include treatment waning. Revised model including waning at 3 years	Not accepted as stopping rule was rejected
	Pembrolizumab	ID1426	KEYNOTE-426 2nd interim-analysis: Jan 2019 data cut (median follow-up 17.4 months, maximum follow-up 27 months)	2-year	Treatment effects capped at 1, 3 and 7 years after treatment discontinuation were included as scenarios	Although uncertain a cap on treatment effect at 3 years after treatment discontinuation was deemed plausible

Disease area	Intervention	TA number	Data availability	Maximum treatment duration	Treatment waning submitted by company	Treatment waning incorporated into committee's accepted base case
	Nivolumab	TA417	CheckMate 010: 38 months CheckMate 003: median follow-up was 45.2 months CheckMate 025: 14 months	As long as clinical benefit is observed.	None	None
Head and neck	Pembrolizumab	ID1140	TA10181 - KEYNOTE-048: Final analysis: 25.33 months	2-year	Lifetime treatment effect was assumed. Scenarios with treatment effect capping at 5 and 10 years included	After 5 years accepted
	Nivolumab	TA490	CheckMate 141: Median duration of follow-up was 5.3 months (range, 0.0-16.8)	As long as clinical benefit is observed.	No, treatment effect capping at 5 and 10 years included as scenarios	After 5 years accepted
Hodgkin lymphoma	Nivolumab	TA462	Not relevant due to focus on SCT access			
	Pembrolizumab	TA540				

Disease area	Intervention	TA number	Data availability	Maximum treatment duration	Treatment waning submitted by company	Treatment waning incorporated into committee's accepted base case
SCLC	Atezolizumab	TA638	IMpower133: median follow-up 13.9 months	As long as clinical benefit is observed.	After a NICE request for a treatment effect cap of 5 years was included in the base case, along with alternative scenarios	The Committee accepted the company's altered base case
Breast	Atezolizumab	TA639	IMpassion130 trial: 2nd interim analysis Jan 2019	As long as clinical benefit is observed.	Lifetime treatment effect	The Committee rejected the ERG's proposed 3 year treatment cap as this is normally assumed in conjunction with a stopping rule. In this case, it would lead to patients on treatment receiving no treatment benefit. As a result, lifetime treatment effect was assumed
Merkel cell	Avelumab	TA517	JAVELIN Merkel 200 trial: Part A: 18 months Part B: 3 months follow-up initiated 15th April	5 years	None, time horizon too short to require long-term treatment effects	The Committee agreed with company
Key: FU, follow-up; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; SCT, stem-cell transplant; SCLC, small cell lung cancer; TA, technology appraisal.						

Real-world evidence of subsequent treatments in England and Wales

Real-world (RWD) data was obtained 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 5 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.

Table 5: 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		

Table 6 summarises the data on subsequent treatments post routine surveillance obtained from IPSOS and Wilmington Health Care.

Table 6: Subsequent treatment data in the metastatic setting

Treatment	IPSOS			Wilmington
	1L	2L	All	All
Total immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]
Anti-PD1s	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Other immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]
Interferon	[redacted]	[redacted]	[redacted]	[redacted]
Ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]
Talimogene laherparepvec	[redacted]	[redacted]	[redacted]	[redacted]
Interleukin	[redacted]	[redacted]	[redacted]	[redacted]
BRAF/MEK inhibitors	[redacted]	[redacted]	[redacted]	[redacted]
Vemurafenib	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib + trametinib*	[redacted]	[redacted]	[redacted]	[redacted]
Dabrafenib	[redacted]	[redacted]	[redacted]	[redacted]
Other systemic cancer therapy	[redacted]	[redacted]	[redacted]	[redacted]
Dacarbazine	[redacted]	[redacted]	[redacted]	[redacted]
Temozolomide	[redacted]	[redacted]	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
Other palliative chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]

Key: 1L, first line; 2L, second line; Ipi, ipilimumab.

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1 COMPANY ADDITIONAL EVIDENCE SUBMISSION: ADDITIONAL CENSORED OS ANALYSIS

With new analysis provided at technical engagement (TE) and in the appraisal consultation document (ACD) response, BMS have been granted permission to submit additional evidence to NICE. This report details the methods used to estimate and adjust the post-recurrence survival between CheckMate 238 and CA184-029 and supplies additional analyses exploring the censoring of ipilimumab as well as placebo.

2 INDIRECT-TREATMENT COMPARISON (ITC) METHODS - SUBSEQUENT TREATMENT ADJUSTMENT

As mentioned in the TE response and ACD response, the new analysis aimed to adjust overall survival in CA184-029 such that it reflected the one that would have been observed if the same subsequent therapies received by patients in CheckMate 238 were available which the committee agree reflects clinical practice. This analysis compared the post-recurrence survival between patients treated in the ipilimumab arms of CheckMate 238 and CA184-029, assuming that the time from randomization to recurrence of disease (per investigator) had little impact subsequent therapies. This adjusted analysis has been presented at an international clinical congress (Society for Immunotherapy of Cancer (SITC) Annual Meeting).[1]

The analysis submitted in the TE response is an analysis that adjusted for possible confounders including age, sex, Eastern Cooperative Oncology Group Performance status (ECOG PS), disease stage, time from surgical resection to randomization, time from randomization to recurrence, type of recurrence, and initiation of subsequent systemic/anticancer therapy. After adjusting for possible confounders, the two ipilimumab arms from CheckMate 238 and CA184-029 were then assumed to be balanced from recurrence date and the only difference arising from this comparison being the effect of the different subsequent therapies on post-recurrence survival.[2] Further detail is provided in the technical report supplied with this response; however, the method will be briefly described below.

Parametric survival modelling methods were based on the 2-stage approach as specified in the NICE Decision Support Unit (DSU) Technical Support Document 16 and Watkins et al. publications.[3,4] Rather than estimating the effect of subsequent treatments by comparing post-recurrence survival between subjects with and without subsequent treatments, which required additional assumptions and introduces further uncertainty, post-recurrence survival between the two studies were compared regardless of subsequent treatment initiated. This was done in order to understand the added effect required to CA184-029 patients based on the subsequent treatments received by CheckMate 238 patients.

The average post-recurrence survival from CheckMate 238 was then used to adjust and increase the post-recurrence survival to CA184-029, assuming that the effect of post-recurrence survival does not depend on the treatment received from randomization. An increase in survival due to subsequent treatment for in ipilimumab in CheckMate 238 was compared to the ipilimumab arm from CA184-029, which demonstrated a 63% average increase; this 63% increase was subsequently applied to CA184-029.

For CA184-029 treatment arms, the original survival time from randomization to recurrence was then combined with the adjusted post-recurrence survival and the Bucher method was applied to calculate the hazard ratio (HR) between nivolumab in CheckMate 238 trial and the adjusted overall survival in placebo CA184-029. Since the adjustment in survival time was only applied to subjects who recurred in CA184-029, and recurrence may be related to

prognostic factors, re-censoring was applied in all subjects in CA184-029 in line with the literature in order to remove the possible bias associated with informative censoring.[5,6,7]

An accelerated failure time model assuming a generalized gamma distribution for the error terms was applied in order to compare post-recurrence survival between ipilimumab in CheckMate 238 and ipilimumab CA184-029. This distribution was chosen because this was the one with the lowest Akaike Information Criterion (AIC) compared to models assuming exponential, log-normal and Weibull distribution of error terms. To account for the variability around the acceleration factor used to adjust post-recurrence survival in CA184-029, a 95% confidence interval around the ITC HR was also calculated via bootstrap method using 10,000 samples.

3 CENSORING OF PLACEBO

BMS would like to reiterate that the censoring of the CA184-029 ipilimumab treatment arm introduces informative censoring biases against nivolumab, which both the ERG and committee agree is a conservative scenario. The smooth hazard plots for OS with ipilimumab censored at 12 months showed that between [redacted] This approach should be viewed as clinically implausible given patients treated with ipilimumab had improved RFS and would have similar subsequent therapy options available (see Technical Engagement Response figure 3). BMS reinforce that, in line with the draft NICE methods guide, which states “committee decisions should be based on plausible inputs and assumptions that are consistent with the evidence”, that the censored analyses should be viewed as a conservative scenario rather than the base case.

In the original submission, OS in the placebo group in CA184-029 was “not considered to reflect that of routine surveillance because of advances in subsequent treatments since the trial started.” Therefore, in the TE and response to ACD, we provided analyses where CA184-029 data were adjusted per the analysis by Weber et al.[1] to aim to account for the advances in availability of metastatic therapies.

Following further request, we herein provide additional scenarios that explore the impact of informative censoring. Based on the new analysis provided at the TE and ACD stage, further scenarios considering censoring of both CA184-029 ipilimumab and placebo arms are included in this document. Notably, we provide smoothed hazard plots for OS for nivolumab from CheckMate 238 versus OS for placebo from CA184-029, as based on different combinations of censoring and adjustment for subsequent therapy for the placebo arm:

- Placebo from CA184-029 without censoring and where subsequent treatment has been adjusted (uncensored and adjusted; Figure 1)
- Placebo from CA184-029 where placebo patients are censored after 1 year of treatment and subsequent treatment has been adjusted (censored and adjusted; Figure 2)
- Placebo from CA184-029 (uncensored and unadjusted) with no subsequent treatment adjustment (Figure 7 in appendix)
- Placebo from CA184-029 where placebo patients are censored after 1 year of treatment (censored and unadjusted; Figure 8 in appendix)

Figure 1 and Figure 2 presents the smoothed hazard plots for OS including the subsequent treatment adjusted CA184-029 data with both placebo uncensored and censored at 12 months of treatment, respectively. BMS feel that the scenarios presented in these two figures are more clinically plausible than those in the appendix (Figure 7 and Figure 8) as the analyses without subsequent treatment adjustment are not reflective of UK clinical practice, but have provided those in the appendix for totality.

When looking across the smoothed hazard plots, all scenarios, regardless of censoring or adjustment, show a clear separation in hazards between nivolumab and placebo, whereby a lower hazard of OS is seen for nivolumab for the duration of the CheckMate 238 study with very minor overlap in uncertainty. It is clear from the most conservative scenario, where placebo is not censored but subsequent therapy adjustment is implemented (presented in Figure 1), there is no evidence for proof of an equal hazard for nivolumab and placebo during the duration of the CheckMate 238 study. In fact, the smoothed hazard for the placebo arm does not reduce to the same hazard of the nivolumab arm ( ) for an additional . This scenario further demonstrates the inappropriateness of the equal hazard of death assumption at 2-years in light of the evidence available.

Figure 1 Smoothed hazard plots - OS nivolumab from CheckMate 238 and subsequent treatment adjusted placebo from CA184-029 (uncensored and adjusted)

Figure 2 Smoothed hazard plots - OS nivolumab from CheckMate 238 and subsequent treatment adjusted placebo from CA184-029 where placebo patients are censored after 1 year of treatment (censored and adjusted)

If patients were not informatively censored, then it would be expected that the prognosis of placebo patients would be similar to the ITT (uncensored) population after one year. With both ipilimumab and placebo censored in CA184-029, the subsequent treatment adjusted results of the Bucher comparison show that treatment with nivolumab is associated with a significantly reduced hazard of death compared with treatment with routine surveillance ([redacted]). The drastic change in the uncensored (ITT) and censored population (ipilimumab and placebo arms), suggests that prognosis of the censored patients is different to that seen without censoring. Furthermore, the size of the treatment effect increases when patients are censored, suggesting that the observed change cannot be due to the treatment duration. The results indicate that [redacted]

All analysis to date has shown only the ipilimumab arm data censored at 12 months, which has been openly acknowledged as biased against nivolumab. In addition, this represents a conservative scenario when compared to the inclusion of a placebo censored population, which demonstrates the impact of informative censoring.

It should be noted that the results of the updated Bucher ITC of nivolumab versus placebo, where ipilimumab patients are censored after 1 year of treatment in CA184-029, show that patients treated with nivolumab have a [redacted] lower hazard of death compared with patients treated with placebo ([redacted]) which is same as that in the company response to clarification, Table 3).

4 CENSORING OF IPILIMUMAB

When applying the adjustments for subsequent therapy to CA184-029, it is seen that this appropriately captures the estimated subsequent therapy effect on post-recurrence survival. The [redacted] are shown in Figure 3, where there is [redacted] between the ipilimumab arm from CheckMate 238 and the adjusted ipilimumab arm of CA184-029 [redacted].

If further implementing informative censoring of patients on therapy at 1 year, after adjusting for subsequent therapy, it is clear from Figure 4 that the hazards [redacted] between CA184-029 and CheckMate 238, [redacted]. Figure 4 demonstrates that a scenario including censoring of the ipilimumab arm is inappropriate for use in any indirect comparison versus nivolumab. Therefore, BMS feel the implementation of adjustment for subsequent therapy is more likely to be reflective of the OS hazards seen in clinical practice and avoids the issues introduced by censoring patients at 1 year.

As previously mentioned, it was considered in the original submission that placebo OS in CA184-029 does not reflect routine surveillance OS due to advances in the subsequent treatment pathway. Therefore, both Figure 10 and Figure 10 in the Appendix represent scenarios that are not reflective of clinical practice with the latter being both pessimistic and unlikely, but these scenarios have been provided in the appendix for totality.
It should be noted that the smoothed hazard plot in Figure 10 is the current base case, which shows a poor overlap of hazards for the two ipilimumab arms as the subsequent treatment of CA184-029 is not reflective of current practice.

The impact of informative censoring has a profound effect on the OS hazard, so much so that if censoring is applied to both the CA184-029 placebo and ipilimumab treatment arms for consistency, the 95% confidence intervals no longer overlap at [redacted], see Figure 8 and Figure 2) regardless of subsequent treatment adjustment. The extreme drop off for placebo is likely to be a result removing healthier

patients with a better prognosis as informative censoring eliminates patients that are less likely to experience an event, as these patients are likely to stay on therapy for longer.

Figure 3 Smoothed hazard plots – OS ipilimumab from CheckMate 238 and subsequent treatment adjusted ipilimumab from CA184-029 (Reproduced from company response to ACD figure 12; uncensored and adjusted)

Figure 4 Smoothed hazard plots – OS ipilimumab from CheckMate 238 and subsequent treatment adjusted ipilimumab from CA184-029 where ipilimumab patients are censored after 1 year of treatment (censored and adjusted)

Following on from the previous analysis provided in response to the ACD on the subsequent treatment adjusted CA184-029 data, additional analyses have also been performed for the following scenarios which can be found in the Appendix:

1. Subsequent treatment adjusted 029 data with placebo censored at 12 months
2. Subsequent treatment unadjusted 029 data with placebo censored at 12 months
3. Subsequent treatment unadjusted 029 data with placebo not artificially censored

The analyses fit parametric models to each treatment arm in each trial and used these as the basis for estimating the HR of nivolumab relative to placebo and as such it is not possible to censor the ipilimumab treatment arm. For each scenario, the best fitting parametric models were then selected, independently for each arm, on the basis of having the lowest AIC (See Appendix). Confidence intervals for the hazard ratio were estimated using a parametric bootstrap based on the parameter estimates and their estimated covariance matrix. The point at which the upper 95% confidence limit of the hazard ratio increases to cross the line of unity (equal hazard rates in both arms) is reported, along with the estimated p-value corresponding to a hypothesis that the hazard ratio exceeds 1 at 24 months. All scenarios demonstrate the equal hazard of death assumption at 2-years preferred is clinically implausible and without significant justification in light of the available evidence. Further, based on the scenarios included, the minimum time point where we can plausibly expect an equal hazard is at [redacted] in the uncensored unadjusted population (see Figure 14).

5 ADDITIONAL ANALYSIS - HAZARD RATIO ANALYSIS

The hazard plots and hazard ratio between nivolumab and placebo from the ITC met-regression (after censoring ipilimumab) have been conducted to assess the appropriateness of assuming the same hazard after a certain time point. A mean of covariates approach was used for OS, censoring the CA184-029 ipilimumab treatment arm (after 1 year of treatment) and matching the patient population across both nivolumab and placebo treatment arms. The populations were then fitted with a generalised gamma distribution (as per the company base case – see company submission, Section A.8.1). Covariate values used within the analysis are presented in the company response to clarification table 4.

Figure 5 presents the hazard plot of nivolumab and placebo fitted with a generalised gamma distribution with the 95% confidence intervals (estimated using 5000 bootstrap samples). This shows the hazard of nivolumab is consistently greater than placebo despite there being an overlap between the confidence intervals throughout. There is an initial overlap in hazard between nivolumab and placebo reflecting the lack of events during this time that is also seen in the hazard ratio plot (Figure 6), which shows a hazard greater than 1 (favouring placebo) at the start of the time period with a large confidence interval representing the uncertainty over this period. The initial period of the plot should be disregarded due to the few events occurring in each treatment arm. Consequently, as the number of events increase, the HR begins to decrease to less than 1 (favouring nivolumab) after [redacted], and the upper confidence interval does not cross the hazard ratio of 1 [redacted], corresponding to equal hazard in both treatment arms, until [redacted] post-randomisation suggesting a significant difference in hazard between nivolumab and placebo during this time period (Figure 6). The hazard plots and hazard ratio with 95% confidence intervals for the observed ITT population (i.e. ipilimumab patients not censored after 1 year of treatment in CA-184-029) are presented in the Appendix and show that the upper confidence interval does not cross 1 (favouring nivolumab) for at least 12-years. Given that the ipilimumab censored analysis is considered a conservative scenario, and the plots below show that it is highly unlikely for the hazard ratio to be 1 until at [redacted], BMS consider the time point of 2-years to be a clinically implausible time point and thus inappropriate for decision making.

Figure 5 OS Hazard plot of nivolumab and placebo using matched population with ipilimumab censored at 12 months

Figure 6 Estimated OS hazard ratio and 95% CI - Nivolumab from CheckMate238 vs adjusted placebo from CA184-029 (ipilimumab censored at 12 months)

In conclusion, BMS would like the committee to reconsider the 2-year equal hazard of death time point, as this assumption lacks clinical plausibility given the evidence available, as the ITC data suggests equal hazard assumption is unlikely until at .

These analyses demonstrate that equal hazards are unlikely until at) and makes the 2-year equal hazard of death conclusion untenable. Using the most conservative, clinically plausible, assumptions when equal hazards are assumed at 4 years nivolumab can be considered a cost-effective use of NHS resources (ICER: £19,431 and £24,760, with and without the censoring of ipilimumab OS patients, respectively) and should be recommended for routine commissioning.

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6 APPENDIX

Smoothed Hazard plots - OS nivolumab from CheckMate 238 and subsequent treatment unadjusted placebo from CA184-029 (censored and uncensored)

Figure 7 Smoothed hazard plots - OS nivolumab from CheckMate 238 and placebo from CA184-029 (uncensored and unadjusted)

Figure 8 Smoothed hazard plots - OS nivolumab from CheckMate 238 and placebo from CA184-029 where placebo patients are censored after 1 year of treatment (censored and unadjusted)

Smoothed Hazard plots - OS ipilimumab from CheckMate 238 and subsequent treatment unadjusted ipilimumab from CA184-029 (censored and uncensored)

Figure 9 Smoothed hazard plots – OS ipilimumab from CheckMate 238 and ipilimumab from CA184-029 (uncensored and unadjusted)

Figure 10 Smoothed hazard plots – OS ipilimumab from CheckMate 238 and ipilimumab from CA184-029 where ipilimumab patients are censored after 1 year of treatment (censored and unadjusted)

Subsequent treatment adjusted CA184-029 data with placebo censored at 12 months

Table 1 AIC statistics for survival model first to nivolumab from CheckMate 238 and subsequent treatment adjusted placebo *censored at 12 months* from CA184-029 (censored and adjusted)

Model	AIC	
	Nivolumab	Placebo
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Generalised F	[redacted]	[redacted]
1-knot hazard	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]
2-knot hazard	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]
3-knot hazard	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]

Figure 11 CA184-029 Adjusted for subsequent therapies OS – Generalised F survival extrapolation – placebo censored at 12 months (censored and adjusted)

Figure 12 Estimated hazard ratio and 95% CI - Nivolumab from CheckMate238 vs adjusted placebo (censored at 12 months) from CA184-029 (censored and adjusted)

Subsequent treatment unadjusted CA184-029 data with placebo censored at 12 months

Table 2 AIC statistics for survival model first to nivolumab from CheckMate 238 and placebo censored at 12 months from CA184-029 (censored and unadjusted)

Model	AIC	
	Nivolumab	Placebo
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Generalised F	[redacted]	[redacted]
1-knot hazard	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]
2-knot hazard	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]
3-knot hazard	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]

Figure 13 CA184-029 Unadjusted for subsequent therapies OS – 2-knot hazard survival extrapolation – placebo artificially censored at 12 months (censored and unadjusted)

Figure 14 Estimated hazard ratio and 95% CI - Nivolumab from CheckMate238 vs unadjusted placebo (censored at 12 months) from CA184-029 (censored and unadjusted)

Subsequent treatment unadjusted 029 data with placebo uncensored

Table 3 AIC statistics for survival model first to nivolumab from CheckMate 238 and placebo from CA184-029 (uncensored and unadjusted)

Model	AIC	
	Nivolumab	Placebo
Exponential	[redacted]	[redacted]
Gamma	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Generalised F	[redacted]	[redacted]
1-knot hazard	[redacted]	[redacted]
1-knot odds	[redacted]	[redacted]
1-knot normal	[redacted]	[redacted]
2-knot hazard	[redacted]	[redacted]
2-knot odds	[redacted]	[redacted]
2-knot normal	[redacted]	[redacted]
3-knot hazard	[redacted]	[redacted]
3-knot odds	[redacted]	[redacted]
3-knot normal	[redacted]	[redacted]

Figure 15 CA184-029 Unadjusted for subsequent therapies OS – 1-knot odds survival extrapolation – placebo (uncensored and unadjusted)

Figure 16 Estimated hazard ratio and 95% CI - Nivolumab from CheckMate238 vs unadjusted placebo from CA184-029 (uncensored and unadjusted)

NICE National Institute for Health and Care Excellence

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 25 November 2020 **email:** 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 UK**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**N/A**]
Name of commentator person completing form:	[redacted]

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NICE National Institute for Health and Care Excellence

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

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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.
1	Melanoma U.K. is a patient support organisation working with melanoma patients and families who are suffering melanoma - from early stage, right up to late stages. We fully appreciate that NICE has a very difficult role when it comes to technology appraisal. We are aware that over the last few years, the lives of many patients and families have been helped enormously by decisions made. However, we feel that in this case, the decision really is not in the best interest of the patient community. Adjuvant treatment in melanoma is extremely important for patients. There is a very clear unmet medical need for stage four patients and this treatment is the only approved and reimbursed treatment for this section of patients. We are concerned that this recommendation would be extremely traumatic for the patient community and a backward step in the treatment of melanoma. Some of the feedback we have received includes: • "Utter devastation" • "Please don't take away the hope" • "This decision is breaking my heart" • "This could be the difference between life & death" • "This is now another worry – what about my children?" • "Just reading this news is having a huge psychological impact on me" • "I am sick to my stomach" • "This will remove a lifeline for so many patients" • "This drug is currently keeping me alive" We must not take any backward steps in the treatment of this brutal disease. Melanoma U.K., along with the patients it represents, urge the committee to review this decision and listen to the views of not only clinicians, but the patient community as a whole.
2	**Patient quote:** *It breaks my heart to think newly diagnosed patients in my position would not be given the same chance I had. It gave me hope.* *I was given the statistics and of course jumped at the chance to have adjuvant therapy no matter the risks. Anything to prolong my life.*
3	**Patient quote:** *I am horrified to learn that this decision of this magnitude has been made on the strength of just two years data. As a patient who was turned down for a trial of adjuvant therapy at an early stage of the disease and then progressed to stage IV fewer than twelve months later, I have spent many sleepless nights wondering whether my current incurable diagnosis could in fact have been prevented. There are so few treatment options for metastatic melanoma as it stands why must we take away a potentially powerful adjuvant immunotherapy option without allowing adequate time for the data to mature?*
4	**Patient quote:** *It's devastating news. I'm stage 4 braf mutant with metastatic melanoma, could be the difference*

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Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

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	between life and death literally.
5	**Patient quote:** *I'm a stage 3 patient currently on adjuvant treatment for 12 months. I have been so grateful to have this treatment to improve the chances of my cancer not coming back. Since diagnosis I have been acutely aware that just a few years ago this would not have been an option for me, I would have just had to watch and wait. Adjuvant treatment gives hope for a return to some normality and is such a recent improvement to the overall treatment options in melanoma. The thought that this could be taken away again would devastate those with this awful disease, myself included. Please don't take away the hope.*
6	**Patient quote***:* *Probably means that in a few months there will be no treatment possible for my condition and so my life expectancy will be less than 1 year*
7	**Carer quote**: *I am the wife of a melanoma patient. Without NICE approved treatment for my husband last year, I would now be a widow.*
8	The above patient testimonials are just a few to show their reaction to this devastating news. Melanoma UK represent the patient voice, but we urge the committee to read the rest of what the melanoma community have to say (see attached supporting patient comments).

Insert extra rows as needed

	FULL NAME	WHAT WILL THIS DECISION MEAN TO YOU AS A MELANOMA PATIENT?	HAS BEING ON TREATMENT GIVEN YOU A GOOD QUALITY OF LIFE THAT YOU MIGHT NOT OTHERWISE ANTICIPATED?	PLEASE USE THIS SPACE TO PROVIDE ANY EXTRA INFORMATION THAT YOU WOULD LIKE TO MAKE THE NICE COMMITTEE AWARE OF - PLEASE PROVIDE
1	[name redacted]	I had adjuvant nivolumab and am grateful.	Absolutely	
2	[name redacted]	I'm a stage 3 patient currently on adjuvant treatment for 12 months. I have been so grateful to have this treatment to improve the chances of my cancer not coming back. Since diagnosis I have been acutely aware that just a few years ago this would not have been an option for me, I would have just had to watch and wait. Adjuvant treatment gives hope for a return to some normality and is such a recent improvement to the overall treatment options in melanoma. The thought that this could be taken away again would devastate those with this awful disease, myself included. Please don't take away the hope.	My side effects have been mild, I'm halfway through my 12 months of treatment and I am living my life with hope that my cancer doesn't return.	A diagnosis with melanoma is something you cannot understand until it happens to you. A whirlwind of treatment and hospital care begins, the terror you feel is overwhelming, then you are told it's stage 3 and you need to meet with an oncologist, the terror increases. Then the oncologist explains there is a treatment option that will improve the odds in your favour, who wouldn't grab that chance with both hands. Please don't take this option away. From a financial perspective, adjuvant treatment to prevent stage 3 cancer returning has to be a cheaper option than treatment of stage 4 and all the coats that incurs.
3	[name redacted]	That my life expectancy could be reduced enormously	Most definitely ,I have had had minimal side effects tumours are shrinking and I can live my life as normal	This treatment has given me and my family hope for the future. I have been well and able to support my children and husband through lockdown which without treatment would of not been able to. Melanoma patients need the same treatment opportunities as other cancer patients and if we can stop reoccurrences at earlier stages the we should be offered the treatments. Lets be proactive rather than reactive. It costs less if we can prevent reoccurrence. This treatment had given hope when years ago there was none. Patients can live normal productive lives, go back to work and contribute to society . Melanoma treatment cannot be a lottery.
4	[name redacted]	This is a hugely disappointing decision. Patients at stage 4 are desperate, frightened and struggle with increasingly diminishing options to help them fight melanoma. Removal of this vital treatment at such an early stage is unexpected. It seems without doubt driven by cost rather than proof of a lack of benefit. This decision makes me question the value of the patient voice in the decision process at NICE. It would cause hugely damaging emotional, psychological and well being issued, not to mention treatment concerns and potentially death for patients across the country.	N/a	
5	[name redacted]	Personally it has no immediate impact physically but I can understand that the loss of what is perceived as an effective treatment that marginally fails to meet cost effectiveness criteria could be psychologically devastating	Not able to comment but certainly having the option helped psychologically	As a former GP I have become aware of how the outlook and consequential hope and ability to enjoy good quality life for melanoma patients has improved significantly in the ten years since I retired. To restrict access to hope is every bit, if not even more, as devastating as the outlook used to be when a diagnosis of melanoma meant an introduction to the terminal care team!
6	[name redacted]	Will add uncertainty and stress to my life. If my cancer comes back then what? Palliative care?	Yes, when I was originally diagnosed this treatment was not available and the outcomes for stage 4 patients was not good. At Ipswich hospital I was only the 11th patient to be given this treatment. Despite some serious side effects and not having any treatment since December 2018, I am nearly a year clear.	
7	[name redacted]	I am now stage 4 as adjuvant Nivolumab wasn't licensed when I was diagnosed stage 3. If it had been there is a high chance I wouldn't be stage 4 now and my stage 4 has responded well to Nivolumab.	It has given me life. I would have died quickly without it. I have had very few side effects apart from fatigue which is manageable.	

8	[name redacted]	It wont affect me personally as I'm already stage four, but will mean that others may be able to avoid to immense challenges that a stage four diagnosis brings.	Absolutely, without a doubt.	When I was diagnosed at stage four in 2013, after successful surgery to remove the melanoma, there were no options other than to watch and wait and see what happened. This was incredibly challenging and left me feeling that I had little control over my future health. With the right information, patients should be given the choice and the chance to reduce their likelihood of progressing to stage four. I have experienced side effects from Nivolumab, but none of them has stopped me continuing to lead a meaningful, happy life.
9	[name redacted]	I'm currently waiting on an appointment with the oncologist to discuss adjuvant therapy as I have had a lymph node dissection in my neck as my senile node was positive for melanoma plus one more node has been found positive. This would obviously be a concern to me not being given the chance to have adjuvant therapy and to reduce my chances of it returning .		
10	[name redacted]	I am horrified to learn that this decision of this magnitude has been made on the strength of just two years data. As a patient who was turned down for a trial of adjuvant therapy at an early stage of the disease and then progressed to stage IV fewer than twelve months later, I have spent many sleepless nights wondering whether my current incurable diagnosis could in fact have been prevented. There are so few treatment options for metastatic melanoma as it stands why must we take away a potentially powerful adjuvant immunotherapy option without allowing adequate time for the data to mature?	My quality of life has been excellent, and I certainly couldn't have anticipated looking and feeling as well as I did during treatment with ipilimumab/nivolumab, and now on my current clinical trial. I experienced limited side effects from immunotherapy and was able to work full time during treatment, helping me to retain a sense of normality as a young adult at an incredibly distressing time. Thanks to my current targeted treatment, I have had No Evidence of Disease for almost one year.	
11	[name redacted]	It's devastating news. I'm stage 4 braf mutant with metastatic melanoma, could be the difference between life and death literally	Yes	
12	[name redacted]	Devastation	Wasn't available to me	I am so grateful for my observations , ct scans etc This medication wasn't available to me
13	[name redacted]	This would have been my treatment option if I was BRAF negative! So where would that have left me now? This is awful news	Yes . It changes the prognosis from If it recurs to WHEN	
14	[name redacted]	As Im passed the date for receiving treatment Im not directly affected by this decision. HOWEVER I would have jumped at the chance of taking treatment to prevent stage 4		The cost of treatment at stage 3 must be considerably less than treating stage 4
15	[name redacted]	It breaks my heart to think newly diagnosed patients in my position would not be given the same chance I had. It gave me hope. I was given the statistics and of course jumped at the chance to have adjuvant therapy no matter the risks. Anything to prolong my life.	I didn't suffer with many symptoms from pembro. I did suffer with extreme fatigue at the beginning but this got better as I had more doses and learned to manage it. I also had muscle stiffness. I felt this was nothing if it meant it keeps the cancer at bay and gives me more time.	I am so grateful to have had the opportunity of having pembro and just wish I could have had the whole course. My body tolerated it well and the statistics show it is worth having the treatment. Please give others the same chance as me in what is a truly horrible diagnosis to be given.
16	[name redacted]	I've always felt I have been given the highest level of expertise and care in the NHS for my melanoma. This step back would certainly be hugely worrying and disappointing, as suddenly the UK isn't the safest place to be with a melanoma diagnosis.	I now take a thyroxine tablet (low thyroid), fostair inhaler (asthma), anti histamine (dust allergy we think) and a nasal spray all because of immunotherapy, but I would take this and any other side effect thrown at me if this disease never returns. Simply put, I'd hands down do it again, and again, and again. If life long side effects means I have hugely better odds for a long life sign me up!	I understand that all drugs have to make financial sense, but surely for the 25% of people you are saving, and who would then not have to go through multiple more treatments, higher toxicity risk and the hugely underestimated psychological impact, it's worth it. In my case, if I progress at the moment I have the potential options of ipi/nivo, 2 lots of targeted therapies, radiotherapy, gamma knife, chemo, further surgery. This along with all the blood tests, scans, supportive medicine to keep side effects at bay, hospital appts and more than likely hospitalisation at times how is this cheaper in the long term. I understand this is only the fiscal impact, but hey if we were looking at what was best for the patient there would be no discussion.
17	[name redacted]	Utter devastation for all diagnosed with this dreadful disease	Yes	This decision must be reconsidered and overturned
18	[name redacted]	devastated	yes	
19	[name redacted]	Life or death.I am currently having treatment but if am luckily enough to become Ned what would happen in the future.I was first diagnosed in 2013 then 2020.	Yes definitely my life changed for the better as soon as I started immunotherapy.before I felt I was slowly dying and very fatigued but the treatment changed that.	
20	[name redacted]	If I get a recurrence the treatment might not be available	N/A	I want all Melanoma patients to have this treatment if needed
21	[name redacted]	It's a worrying development that narrows treatment options.	Yes	
22	[name redacted]	For too long melanoma has taken a backseat and had no treatments available, never seeing the investment other cancers have received. Finally we get a glimmer of hope but it's locked away. These treatments and studies will benefit our today and our future, allowing developments to be made that will help other cancers too. The rate of melanoma incidence is growing and cannot be ignored any longer. As in countries like Australia, it should now be at the forefront of treatment development and trials.	I tried dab/tram 3 times but unfortunately experienced too many side effects to continue beyond 9 days. Other options are very much needed. Not every treatment suits or works for every patient.	

23	[name redacted]	As a melanoma patient, we need easy access to all treatments.	Yes it's definitely given me hope	I actually had a 'mole' cut off my arm in 2013 and I was misdiagnosed as benign because of a human error. They only found out that I had melanoma stage 4 when I was rushed into hospital on May 27th 2029. The NHS let me down so badly. You certainly are not my hero. You are my killer because of human error. I am a wife, mother, grandmother, aunt, great aunt, sister, sister in law and my family will grieve for me forever ever. I have worked all my life as a teacher and business owner before this. I have paid my taxes and this is how you treat me. Shame on you all.
24	[name redacted]	This could potentially be an issue for me in the future. I have just finished 1 year or adjuvent pembrolizumab. Which I have been doing very well on. And Ive been given the all clear... this drug may have saved my life!	Absolutely!!	
25	[name redacted]	This decision would mean that I could miss out on treatment that could give me a chance as at the moment I am on watch and wait which is the cruelest thing ever. Even though you try to put it to the back of your mind you are constantly wondering what if. For patients this is a lifeline sadly I missed out by a few months and never got offered it when my melanoma reoccurred.	N/a	You will take away people's hope if you don oh substitute it with something else.! If you do that I will guarantee your mental health h cases will go through the roof. Watch and wait is cruel. Imagine just sitting there thinking ok well my cancer made it to my lymph nodes so did it make it past this and then knowing the only time you will find out if it has may be too late I".!! At least with this treatment you gave people hope.
26	[name redacted]	I have literally just had the results from my WLE and SLNB this morning... and reading this news yesterday made me feel sick. Luckily for me my cancer hasn't spread and I'm currently NED. However I'm acutely aware this could change at any given time and it is devastating to think you may possibly not have access to a drug they could halt the progression and/or regress stage 3 melanoma	nA	Please consider the patients and their families, we can spend so much on things such as obesity, and other conditions that may be largely preventable. But regardless, people shouldn't be discriminated against. Please don't discriminate us and deny a drug that could make such a difference to a life.
27	[name redacted]	I hope to have access to Nivolumab if needed in the future. Currently withdrawn along with ipilimumab as I experienced an immune response adverse reaction after two cycles of ipi and nivo. I wont be having more ipi, but potentially might have nivo depending on imminent scan results. Nivo was being considered by my consultant as I tolerated adjuvant Pembrolizumab well for 1 year.	Definitely. The surgery and adjuvant Pembrolizumab during my first 15 months after diagnosis enabled me to continue to work as a secondary school D&T teacher & Head of Year in Sixth Form and enjoy all aspects of working and family life normally until I needed to shield. Although I have had recurrence and progression, I feel the treatment potentially delayed this. I am / was hopeful that a return to treatment when appropriate would extend my life. Nivo is the treatment my consultant says will be most suitable in my current circumstances (if needed should my scans show residue, or given that I tend not to go very long without recurrence). This would continue to allow me to have a longer period of good quality life with my family and plan my retirement from work so that I can spend good quality time with my husband and the families of my 4 sons. Adjuvant treatment gives hope at stage 3 that cure is possible and delays stage 4 progression. Hope there will be a future and days to look forward to for as long as possible are essential when you or a family member has a cancer diagnosis.	My treatment and care has been at UNHM Royal Stoke and County Hospital Stafford. The care I received pre and during the COVID pandemic has been exemplary and continues to be so. I have had prompt appointments for recurrence concerns and surgery arranged very quickly when needed. Appointments brought forward for results when it was apparent there was a new problem. Treatment on ipilimumab and nivolumab was actioned very quickly from scan results mid Aug and started 3rd Sept. The Cancer unit seems very well run and safe during the pandemic. The high quality care they provide gives me confidence that I have the best team around me to help me survive for as long as possible. Patients will always want access to medication that has been proven to extend life expectancy. When my 2 year old granddaugher and older grandsons have key milestones in the future graduation, marriage etc, immunotherapy has been such a huge advance in treatment and enhancing life expectancy, I hope to see those milestones!
28	[name redacted]	This decision is quite frightening as Im new on my journey and awaiting SLNB.	N/A	Being recently diagnosed and awaiting further biopsies, my mind is thinking up all potential scenarios. This decision could be devastating for so many families. Im scared that, if I become directly affected by this, I could end up leaving my 2 children behind. My youngest is only 3 years old. Please reconsider, these are peoples lives!
29	[name redacted]	It outs mean my melanoma will take over my body with no means of stopping it. Melanoma is one of THE most deadly cancers & can reoccur at any time	Somewhat. There have been side effects but nothing I wouldn't rather deal with than the prospect of nothing	Please please reconsider the impact on patients abs their families before withdrawing this treatment. When told you have cancer, your whole being just crumbles before your eyes. When you are told there is treatment it gives us all hope. What more can we ask for but longer with our family and hope?

30	[name redacted]	As newly diagnosed and researching treatments and options this would have a devastating effect .Its people lives that will be at risk .Melanoma is not one of the cancers being talked about enough so any treatment gives us HOPE and now you are trying to take that away .This cant happen ..as usual mo ey is more important than peoples lives...	N/A see above.	Having been recently diagnosed I am researching next steps all the time.Due to covid so many trials have been stopped so options limited.This is one of our options so WHY try and take it away from us ....Due to covid my initial appointment was cancelled and my melanoma had advanced. I want as many options as possible to survive .Thank you.
31	[name redacted]	It will limit patients treatment options and put them at greater risk of recurrence.		
32	[name redacted]	It removes hope. There aren't many treatments out there as it is.		Because of Covid I've not met the Professor assigned to me. I've only had phone consultations. The NHS is mismanaged. It is not underfunded. And NICE are a disgrace. The NICE a misnomer.
33	[name redacted]	Being a stage 3 patient who is BRAF negative this will take away one of the few options I have, this is very worrying as MM does have a high reoccurrence rate. I have also reacted badly to pembro so will only have one option if stopped.	Mine was adjuvant so didn't	Please don't stop this, you are putting people who are desperate in a bad place. Listen to the oncologist around the country who support the drug.
34	[name redacted]	Removing adjuvant treatment would effectively mean that my disease would have to progress to stage 4 before there were any options apart from surgery.	Before the Nivo my family and I had endured months of uncertainty. They had watched as I had multiple surgeries and my children had to care for me as I recovered, all whilst revising for, and the sitting their exams. Nivolumab didn't just improve the quality of my life, it improved the quality of life for my whole family.	Here is a rundown of the progression of my disease. At the start of this journey I was 44years old and my children were 7, 14 and 15. · Mole misdiagnosed by GP December 2017. January 2018 initial mole removed from my upper left back 0.97mm and cancer diagnosis given - stage 1b, followed by wider surgical excision in April 2018. Recurrence through my scar 0.5mm and spread to mid back 1.5mm, both removed in September 2018 (both missed during examinations). My moles do not initially appear to be dangerous. Mole on right hip appeared the evening after a plastic surgery check up appointment, removed 0.5mm October 2018. By now New moles were literally appearing overnight. Following all of these I had surgery at Glasgow Royal Infirmary in November 2018 for triple Wider excisions , nuclear tracing and positive SLNB. Having had 4 moles on my skin within 9 months and spread to my lymph nodes there is no question in my mind that this disease would have continued to progress. From January to June 2019 I attended the Beatson every week and received fortnightly intravenous adjuvant Nivolumab. This took its toll on me and caused numerous side effects. I developed hypothyroidism, fatigue and constipation. My treatment had to be stopped as it caused inflammation in my lungs, so from July until November I was on Prednisolone to try and alleviate this and am now on hydrocortisone for adrenal insufficiency. Obviously the thyroid and adrenal damage are negative and lifelong side effects however, given the choice I would absolutely choose Nivo again. Going through the treatment was not an easy option, but waiting to get sick or waiting to die was a mental health nightmare. It consumed my thoughts. I rewrote my will. I made sure my children were as independent as possible and tried to prepare them for the possibility that I may not be there for the important events in their lives.Before Nivo I
35	[name redacted]	Probably means that in a few months there will be no treatment possible for my condition and so my life expectancy will be less than 1 year	The Ipilimumap/Nivolumab treatment was proving very effective and could have been life saving if I had not had severe side-effects. The addition of Nivolumab to that combination treatment had been established as increasing effectiveness in terms of 5 year survival from 35% to 55%. Nivolumab alone was 25%	The Ipilimumap/Nivolumab immunotherapy treatment has now been established as the stand-out treatment for metastatic malignant melanoma and for 55% of people given 5 year survival which is continuing to increase, even after treatment is discontinued. This must be one of the most effective drugs for high risk cancer situations

36	[name redacted]	It is devastating news. When I was diagnosed 10years ago, there was very little in the way of treatment other than surgery and chemo which was accepted not to work, but still had to be given. Treatment such as Nivolumab were like being thrown a life line, a safety net. Removing funding means you are limiting once again the already sparse treatments available for this hideous disease.	I have been NED for nearly 10 years, for which I am truly grateful. But I know of many who havent been so fortunate. I know it can raise its ugly head at any time. As advised, I still do monthly checks, always alert, never becoming complacent. That takes its toll mentally, but knowing there are treatments out there to access, should the unthinkable happen, makes it bearable. Please dont pull one of the few rugs Melanoma patients have.	I was Stage 3a on diagnosis, after my initial surgery, WLE and groin dissection, I was offered a trial, but it had to start within 12 weeks of surgery. Unfortunately it was discovered I had a tumour on my ovary and had to have further surgery and a complete hysterectomy. It turned out to be benign, but by the time it had healed I had passed the deadline of 12 weeks. It was a very scary time, at that point the only thing available to me was 3 monthly checks. I was very fortunate that to have no progression, but the relief when the new treatments started to come online was like a weight being lifted, as though I had been holding my breathe and now I could let it out. There are people who are still in that position, in those first few years, needing to know if the worst happens there are options for them, the more there are, the more peace of mind.
37	[name redacted]	This decision will massively disappoint me as it withdraws hope for many people I know who are seeing the benefit of being treated with this adjuvant therapy.	Very much so.	
38	[name redacted]	It will mean less treatment options if and when they are desperately needed.	Fingers crossed it will	
39	[name redacted]	I am currently stage 3c and given the chance of immunotherapy I would grab it with both hands. Anything that gives hope of regression or stability of this awful disease has to be a good thing. By taking this away from stage 3 patients you are probably creating a larger percent of stage 4 patients.		
40	[name redacted]	It will be devastating for me.	Yes, definitely.	I don't want to die through lack of the ability to access treatment.
41	[name redacted]	As a stage 2C patient the concern that if Nice go a head and discontinue the fund of cancer drug , adjuvant nivolumab it will have a devastating effect on a me as a future options and for the melanoma patients as this has been shown to have been a step forward in combating melanoma .		
42	[name redacted]	I will be very upset if this treatment is withdrawn, I am currently having Nivolumab for inoperable stage 3/4.It wasn't available to me as adjuvant at the time of diagnosis but I wish it had been as I may not have advanced to Stage 4 !	Yes I have had nearly two years of good health with very little side effects which has meant I have been able to continue a near normal lifestyle which is so precious	Melanoma patients unlike other more common cancer patients have waited years for systemic treatments to be available. How can NICE even consider taking away funding it would be a travesty!
43	[name redacted]	It will be devastating, a life line taken away from many patients!	Not began treatment as yet, had two major surgeries and radiotherapy	It is far too early for results to be evidenced, so this decision is being made too rapidly! Almost expected to fail if that makes sense.
44	[name redacted]	Speaking as a Stage 4 melanoma patient this negative decision to discontinue funding of nivolumab is extremely worrying for myself and for so so many of my fellow melanoma patients. At a time when I unfortunately have numerous mets and am acutely aware of the extremely fast rate that this cancer spreads around my own body I would urge with everything I have that this decision is swiftly reconsidered. I currently have 6 tumours (1 in each breast , left lung, adrenal gland , neck and right shoulder blade)	Most definitely. I have managed to keep working 32 hours a week as well as running a home and enjoying a wonderful life .	I do hope that speaking as a patient you could say that I'm an expert when it comes to melanoma treatment. And I am only one of many thousands who have received this and are still alive. Yes it's a very blunt statement but I'm fully aware that I'd have died 5 years ago when I had my first brain tumour were it not for immunotherapy and hope that you are fully aware of the devastating decision on us all . I implore that this decision be overturned before this decision causes loss of life. Thank you for your time,
45	[name redacted]	The thought that I may not be able to have Nivolumab if required in the future and for all the patients who may be excluded.	Absolutely	It appears to be a very short time since it was agreed to use this drug. I feel it does not give enough time for a worthwhile research to be carried out. It feels that it was the intent to consider not using Nivolumab in the prescribed setting as soon as it was agreed to start it.
46	[name redacted]	I am worried that my nivolumab treatment might be stopped prematurely.	Yes. I have virtually no side effects so have a good quality of life which I can spend with my children.	If I had had nivolumab as an adjuvant treatment once melanoma had been found in my sentinel lymph node, it might have prevented stage 4 occuring therefore i might have lived a long life. I am 57 now and will probably only have a very short time left. This could have been different if Id had nivolumab earlier. It could therefore save the lives of many people.
47	[name redacted]	Extreme anxiety and mental health issues surrounding the recurrence of MM	Yes, my mm has not recurred and mental health is fine. Knowing I had adjuvant therapy helped me focus and plan	My professor advised me adjuvant therapy would half my chance of the statistical recurrence. I had zero side effects and still have no recurrence. My original MM was a significant breslow which had travelled to the sentinel lymph node. My mm is a rare mm therefore there is not as much information for this unlike cutaneous, therefore, because I had this treatment reduced my risk and enable me to carry on with life as normal without the feeling there is more chance of a recurrence than not.
48	[name redacted]	It would be devastating	Its given me hope	

49	[name redacted]	It means that a patient that needs this special treatment cannot get it and may die. At present, I am not on immunotherapy but, as I get older, my immune system weakens and I may need it at some point in the future.		Life saving treatment should not be withheld. It is bad enough having cancer as it is let alone knowing that there is something that could treat your cancer, or prolong your life, and not being able to receive such treatment because of cost. How much is a life worth?
50	[name redacted]	The decision will be crucial because it will have an effect on my future and how hopeful that might look	At the moment I'm lucky in that my melanoma has not progressed but I know that if it does then it may not be a death sentence.	Treatments like this are a game changer in the fight against melanoma. We shouldn't have to fight or worry about funding to enable us to live and spend more time with our families
51	[name redacted]	It will be devastating as although in remission at the moment (due to immunotherapy)I would certainly need it again if I have more recurrences	I had some side effects which were managed well and yes I have had much better than ever expected life	Immunotherapy has made such a difference in the treatment of melanoma and given thousands of people hope and life.please never take that away from us
52	[name redacted]	Whether people live or die	Yes, quality of life is now the same prior to diagnosis	
53	[name redacted]	I am fortunate to have had a years worth of nivolumab treatment (09/18 - 09/19) but I am devastated for newly and future diagnosed stage 3 patients who may lose their access to adjuvant treatment.	Yes it has. Without nivo, I would have been compelled to undergo neck dissection (which would have actually missed another node that was only identified after I chose a different treatment path where it was picked up on a pet scan). Aside from the accepted risks of a long surgical procedure the risk of reduced shoulder mobility (I was told I would not be able to shrug afterwards!) meant that I would have had to end my career as a surf school operator and surf coach, and would have been no longer able to surf (my main pursuit since the mid 90s) or indeed swim, play tennis, throw an overarm bowl... As a fit 40 something this reduction in sport options open to me would surely have advanced the aging process and led who knows where in terms of physical and mental health decline, and I would still be no better off regarding the primary aim behind all of this: reducing my risk of melanoma progression. I had zero side effects with nivolumab.	In 2018 I did my own research into nivo which NICE had yet to approve and lobbied my oncologist. I was gifted treatment thanks to his open mindedness and up-to-date grasp of the mm treatment landscape, and of course Bristol Myers-Squib in an expanded access trial outside of the normal clinical trial setting. Immuno was an emerging treatment for mm and the node dissection was still gold standard despite all the current at the time international mm conferences showing data upon data that dissection has no curative benefit. Still in early 2018 the thinking was dissection is better than nothing - but when side effects and surgery risks are accounted for, no it isnt. Thanks to various patient groups from other countries I obtained data from the big German d-cog trial on monotherapy for stage 3 patients presented at the recent 2018 European mm symposium. My onc had just returned from this meeting, we had a chat about my wish to take nivo and forget the neck dissection. He agreed and consulted with ten of his peers around the UK saying that we should expect ten different answers... In our next meeting he said that every one of his peers agreed that a course of nivo and cancelling the neck dissection would be the right way to go. Unfortunately NICE had yet to approve nivo for stage 3 mm, it was expected to happen early 2019 but was we were into June 2018 by this point that did not help me. Happily, intervention came as I have explained in my opening paragraph. It looked liked the treatment landscape in the UK for high risk mm was at last changing away from the dissections and it s complications and catching up with Australia and the USA. It was baffling to hear stories of surgeons and teams in some countries including the UK still pressing to
54	[name redacted]	new melanoma can be cruel and spread anywhere on our bodies. new moles, lumps etc. are normally dealt with promptly and subsequent treatment given. The worry of this is immense, especially if NICE dont support the cancer drugs in the future. Death warrants come to mind.	defo	
55	[name redacted]	It has removed a significant proactive strategy that would help to prevent a further spread of my melanoma . I'm currently 3 C with statistical a 67% chance of further spread and without this option I feel extremely vulnerable .	Can't say but I do know it that it makes me feel extremely vulnerable being so at risk of a further spread which will mean more surgery , which nearly killed me last time (PE's, infections , pneumonia) and has reduced my quality of life .	I would like as many options available to me as possible to prevent a further spread as once I get to stage 4... I enjoy my life despite physical limitations due to surgery to remove the cancer and I now feel that I have to rely on luck without any help from science / treatment to prevent a spread
56	[name redacted]	It is devastating as I am stage 3 and without this adjuvant treatment the effects mentally would have been far worse for me.	Mentally I can not put into words to do justice as to how this adjuvant treatment has helped. Even though physically I am suffering effects of treatment I am extremely grateful to be recieving this for my long term future and preventative reoccurrence hopefully of melanoma.	
57	[name redacted]	More fear. Altho I only managed four treatments and had to stop due to side effects I really would have felt safer having completed the course I feel fearful if I relapse again that adjuvant treatment won't be available. I'm Braf wild type so cannot have targetted therapy	Quite possibly Certainly from the mental health side of things. Actively having a choice of adjuvant treatment was very important to my physical and mental health	

58	[name redacted]	As a stage 4 melanoma patient it was very encouraging to see that immunotherapy and targeted therapy were being made available for stage 3 patients. When I was a stage 3 patient in 2017 there was no adjuvant treatment available and I progressed to stage 4 of the disease. Trials have shown that providing treatment at stage 3 of the disease prevents recurrence in 70% of cases and will act to prevent patients moving to stage 4 melanoma. The decision by NICE to refuse access to patients with stage 3 melanoma to life saving immunotherapy which has been proven to be effective and place more patients on watch and wait will result in the higher risk of moving to stage 4 plus the anxiety that causes to the patient and their family. In the long run there will also be a higher cost to the health service as treating stage 4 patients comes with significantly higher cost and time to the NHS and their already stretched teams.	Yes I have been able to live an almost normal life for the last 3.5 years. I have travelled the world and been able to complete a number of fundraising challenges including climbing Kilimanjaro and climbing 15 mountains over 3000 ft in one weekend in Wales. Without this life saving treatment and the care of the fantastic team at the Royal Marsden I would not still be here to spend more quality time with my loved ones.	I would like to ask that you reverse this decision to provide life saving adjuvant preventative immunotherapy nivolumab to stage 3 patients. The long term benefits to patients with stage 3 melanoma are significant especially with the trials showing it to be 70% effective in preventing recurrence. With watch and wait and no treatment it is 50% so the reduction is highly significant.
59	[name redacted]	It will put my life at risk.	Absolutely yes.	Please dont do this, if its a matter of financial cut-backs, Nivo is saving lives. Surely you can tighten up cash elsewhere?
60	[name redacted]	I was fortunate that I have the option of other therapies as Im BRAF. Ive still found the waiting very challenging. If I hadt been BRAF and had no options, the wait and see would have been unbearable.	Being on treatment means my mental health is better than waiting to see.	
61	[name redacted]	Less choices as far as treatment goes	Definitely	
62	[name redacted]	I lived with Advanced Stage 3c Melanoma &constant invasive treatments, scars & disability, Immunotherapy saved my life & put an end surgery. Clearly this therapy improves quality of life for melanoma patients, whilst I am lucky to survive I wouldn't wish what I went through on anyone.	Yes	
63	[name redacted]	Not being able to have this treatment if required in the future	Yes	
64	[name redacted]	I'm not sure but it could affect me a great deal	When I was told 15 months ago that it had metastasised, I never expected that the treatment would work as well as it has. Treatment must continue!	I would like the NICE committee to realise that from a personal perspective, I am an otherwise very fit person with lots in life to look forward to. A great family , a great life. The question is, Without this treatment what would happen to me?
65	[name redacted]	That I have less options for a disease that already has a poor enough prognosis.	N/A	That this decision takes away the already limited options that this cohort of patients have. It's unethical. There has not been enough time elapsed to allow robust research to take place.
66	[name redacted]	I would be grateful if any drug issues that could help me in the future. Melanoma uk do a great job getting medication licensed.		
67	[name redacted]	As someone who received nivolumab for Stage 3 Melanoma for the entire 2019, I believe that this drug has saved my life. To discontinue a drug that appears to be a super drug has left me speechless and very emotional and upset.	Absolutely. I was diagnosed 2 weeks before my little boy came along and I didnt think I would still be here but so far all CTs since have been clear.	Please just think this through! This is literally life or death. What options are these patients going to be left with?!
68	[name redacted]	A shocking loss of choice to treatment that could save my life	Yes definitely I was given 6 months 15 months ago	We have suffered enough with having cancer ..then Covid stopped our treatments... Please dont take this away it can save lives from this cruel cancer
69	[name redacted]	The drug is currently keeping me alive	Yes I wouldn't be here without it	Stopping this drug will kill people
70	[name redacted]	It means others in same situation as me may not ultimately be melanoma free 2 years post treatment	Definitely	
71	[name redacted]	When I had my surgery Nov 2018 I was fortunate to be offered a year of fortnightly Nivo which my oncologist informed me would be used as "a mop up" to deal with any rogue cells that could still be there. This was a choice I had and accepted as I was grateful for the chance to choose this path as opposed to watch and wait. I think it is horrendous that this choice could not be there in the future should I or any other melanoma patient require it. Why does money have to come first when we are supposed to protect our great NHS, where is OUR PROTECTION going forward?	Given ANY chance of a life without cancer following adjuvant not only reduced my chances of the cancer returning but reduced my anxiety whilst having to endure living with the diagnosis	I was led to believe that Nivo as an adjuvant treatment only became available on the NHS in late 2018, so many people until this time had to "watch and wait" only 2 years on now they are considering the cost over the effects how is this fair and reasonable?
72	[name redacted]	Nivolumab is holding my cancer a bay. Prolonging my life.	I am living with side effects that have ment my quality of life is not what it was when I was healthy. But I have been alive 2 years longer than originally given.	
73	[name redacted]	This is an option for me if my first line of treatment fails me.	Not started yet but am hoping for good things 🤞	
74	[name redacted]	As a recently diagnosed melanoma patient this recommendation to discontinue CDF funding of adjuvant nivolumab appears frightening. I'm signing in support of the melanoma patient community for NICE to reconsider and overturn.		
75	[name redacted]	It will mean that my treatment cannot go ahead and I am relying on this drug to help to reduce my cancer.	At the moment no as I reacted badly to the first treatment. Hoping to restart the treatment but one drug at a time rather than both together.	
76	[name redacted]	It would be devastating to see more patients get to stage 4 because adjuvant therapy wasn't given to prevent it! Surely it's more cost effective to prevent them from getting to this stage too!	My treatment begins next Wednesday	

77	[name redacted]	This news is devastating at such an already worrying time for Melanoma patients.	N/A	
78	[name redacted]	It reduces that amount of treatments that are available and could mean the difference between life and death	100% without treatment I wouldn't be here today	So many people have lost their lives we need more treatments available to save lives
79	[name redacted]	I've just received adjuvant therapy and if it wasn't for the adjuvant therapy I feel I wouldn't be dealing with things as well as I am, and would be extremely anxious about recurrence. I think it's important there are many options of treatment for melanoma patients because melanoma is so aggressive and sneaky so we need to be aswell to save more lives!	I have managed to keep working and doing all the things I usually do and has helped with my anxiety a lot allowing me to continue living a normal life	
80	[name redacted]	I am due to have adjuvant therapy for stage 3b		I was misdiagnosed for a year with an acral melanoma on my heel. I want to try everything to stop it coming back
81	[name redacted]	I am due to go on to nivolumab for stage 4 melanoma. What happens if this is withdrawn? What next? My children have to watch me die?? This is disgraceful and involves people's lives!	It's given me hope that I may be able to live with this disease!	
82	[name redacted]	Im stage 4 now but was very pleased to have been able to access adjuvant nivo at stage 3 for a brief time. There arent any other options available to try to prevent reoccurrance or slow down progression, particularly for people like me who have Braf negative status. The emotional and mental strain is appalling when one has had surgery at stage 3 to clear melanoma, only then to just have to wait for it to regrow in order to achieve stage 4 and be able to access immunotherapy.	As above, its unlikely that I would be alive now without access to the ipilimumab/nivolumab combination then mono nivolumab. Immunotherapy comes with side effects, but I can say yes, I DO have a good quality of life.	
83	[name redacted]	If my cancer returns this treatment will no longer be available to ensure that my melanoma can be beaten.	It was tough being on the treatment as the side effects were quite severe but I would put up with anything to ensure life quality and longevity. It gives you hope and a feeling of being able to do something to help yourself rather than wait and see!	
84	[name redacted]	I was a trial IPI stage IV patient in 2006 which saved my life. I have many friends in a melanoma support group who will be adversely affected by this decision.	Definitely	.
85	[name redacted]	It will mean that treatment for melanoma will have jumped back a decade, and that potentially means you have a choice of surgery OR drug treatment. This is not a choice that anyone should be asked to make.... Other cancers receive effective drug treatments from stage 1. You already have to be on deaths door to receive treatments for melanoma, and there are no treatments for early stages of the disease except surgery, which does not prove curative in many cases. To then not allow a drug treatment that has proven itself to be effective from stage 3 onwards is heartbreaking on a disease that claims the lives of all ages of the population. I am writing this, not for myself, as I have already benefited from this incredible drug, but for the thousands of young parents that will leave this life and their young children behind, if this drug is restricted or withdrawn. These patients are our countrymen and women and they should not be failed by those that haven't had to walk in our shoes	Yes. I would be dead without nivolumab It is as simple as that	
86	[name redacted]	A choice in treatment and as to if I live or die	Yes	
87	[name redacted]	May not get the treatment I require to continue living my life.Sept	Yes	Without immunotherapy I would not be alive today as this is continuing to fight my malignant melanoma and it would be reassuring to know that further immunotherapy would be available if required to prolong my life.
88	[name redacted]	I had melanoma at 24 years and there was a 5% chance it could return, 10 years later it returned. I was very unlucky to be within that 5%. So anymore treatment suitable to help me actually be cancer free will be amazing. Im now a mum to a 22 month old and any treatment that can help me live longer and see him grow up is all I ask you.	Unable to answer this at the moment.	Melanoma is a very deadly cancer and giving patients like me extra treatment to help save a life or improve their life quality means the world to anyone. Me being able to spend time with my son and watch him grow up would mean everything to me. Knowing I had a recurrence 10 years later is heartbreaking.
89	[name redacted]	It fills me with dread for my future and other melanoma patients too	If treatment hadn't worked, I wouldn't be here now! I have enjoyed an extra year of life of a good quality thanks to treatment and hope and pray this will continue.	
90	[name redacted]	As a melanoma patient, this decision is devastating. It would be putting lives as risk and taking away vital treatment for those ego desperately need it.		
91	[name redacted]	Knowing there is a way to try to prevent the disease from coming back is a huge relief and I've been lucky enough to benefit but if this hasn't been available I'm not sure how mentally I could have coped being in constant worry of when it would return. I worry that if later in life I need to have treatment again it's not available and I wouldn't have much chance of survival	Treatment was tough but had I not had it then quality of life could have been very bad had the cancer returned	
92	[name redacted]	Greater risk of recurrence and worry so quality of life affected	Yes	Although I have had some quite serious side effects, notably adrenal insufficiency, it can be managed and is better to have than constant worry about recurrence and the risk and subsequent cost of any future treatment
93	[name redacted]	It's devastating news, and definitely needs to be reconsidered.		
94	[name redacted]	Better quality of life	Yes	

95	[name redacted]	This decision will have a detrimental impact on any patient diagnosed with a malignant melanoma. Adjuvant treatment can provide a lifeline, extension of remaining clear of future incidents which in the long term would relieve funding at a later stage of care which involve greater expense. Prevention and reduction is extremely important to a melanoma patient. Further consideration of this decision is required.	Yes, despite side effects. It is worth the impact and knowledge can be used to improve care for future patients.	Please don't make a decision in haste. Take a longer term view in light of increased costs at later stages of life care.
96	[name redacted]	I was diagnosed with Stage 3 melanoma before this treatment was made available. However, should I have a recurrence, this is the treatment I would then be offered. To have this withdrawn would seriously affect my future health and the thought of this is very distressing.	N/A	Over the years that I have had melanoma I have seen the mental and physical health of my fellow patients improve due to the treatments that have become available. 11 years ago there was nothing - now there is hope and it would be injurious to the future of all melanoma patients if the funding for this treatment was withdrawn.
97	[name redacted]	I was diagnosed as stage 3 melanoma in July 2020. I am currently on Nivolumab. This treatment may allow me to live for another few years so I get to spend more time with my family. That cost is absolutely priceless to me and many more like me.	Yes	
98	[name redacted]	Not good		
99	[name redacted]	Difference between an active life, and death	Too soon to tell	
100	[name redacted]	The worry of not having this treatment available if I, or other cancer patients, needed it in the future.	Yes	The need to offer the widest range of immune therapy options to help melanoma patients, this is a last chance for us.
101	[name redacted]	Having had melanoma recently i would be devastated if i had a reoccurence & could not have this treatment to save my life.		
102	[name redacted]	I am the wife of a melanoma patient. Without NICE approved treatment for my husband last year, I would now be a widow.	He enjoys a good quality of life which we hope will continue for many years	
103	[name redacted]	Maybe no treatment	Most definitely	We need as many options as possible to try get rid of the cancer
104	[name redacted]	It will mean a great deal knowing that there is a safety net available if we ever need this treatment. Its essential to those with further progression of this nasty disease.		Melanoma is something to be understood by only those going though it. Listen to the community who are asking for this treatment.
105	[name redacted]	This decision limits the opportunity for myself and others to receive a treatment that could potentially have a positive impact on the prognosis of our illness. As someone who is in their early adulthood, this could have a significant impact on my lifespan, if my illness progressed in the future.		
106	[name redacted]	I won't get the treatment needed for me to stay stable	Yes	
107	[name redacted]	Is saddens me to think that my options are further limited should my disease progress and that of the wider melanoma community.		
108	[name redacted]	My current treatment plan is that I will go onto Nivo for up to two years once my current cancer treatments stop working.	The treatments have prevented me from dying. I had 2 infusions of ipi nivo. Nivo is also in my treatment plan for in the future. I am 43 years young.	
109	[name redacted]	This is devastating. I have been treated for melanoma and my daughter recently diagnosed too. I urge NICE to reconsider in support of myself, daughter and fellow melanoma patient community.		
110	[name redacted]	It is devastating to think that there could be no adjuvant treatment for a Stage 3 melanoma diagnosis. Being proactive and having preventative treatment reduces so much of the risk of spread and further treatments once stage 4	Yes the prognosis would be very different if I didn't have treatment	I greatly support the use of adjuvant immunotherapy treatment in the setting of melanoma. It can be an aggressive cancer once it progresses without treatment. Therefore reducing the risk of distant metastatic spread is paramount in extending the lives of many patients.
111	[name redacted]	That I will not have access to life saving drugs at a point before I come 'incurable'		
112	[name redacted]	I did receive adjuvant treatment for high risk respected malignant melanoma in late 2017 under a trial. Today I no evidence of disease. My prognosis had been very poor. I am alive today because of that treatment. Talking to my consultant he has said this treatment has made an incredible difference. Instead of saying to patience sorry there is nothing we can do for you they can now say we have this new drug. It is working for 50% of patients. Some scientists are say we might even be able to say we have a cure. Time will tell. This is making a massive difference to those who have MM and those who work for patients with MM	Definitely. The thought of just waiting for more rumours to appear. The stress of wait and see would have been intolerable. A person who is sick needs to be treated not left to die. It is a great lift to your spirits and mental well being that something is being down that might help you and has helped others. To take that away from patients would be devastating	
113	[name redacted]	I am stage 4 so I am personally unaffected but I am seriously concerned at NICE's decision	Yes	

114	[name redacted]	Removal of treatment options when the full survival or progression free data is yet to be realised is fundamentally poor science. The variations between treatments give hope, removal of an option reduces hope in the event of progression....and potentially removes a lifeline.	N/a	We cannot have a situation where people's lives are under threat and used as pawns in a price negotiation. This is ethically unsound and immoral. We also cannot pull life saving options when we've not got the data to support that decision. Immunotherapy is still new and we need the long term data in a variety of situations to inform future decisions. We know a change from one therapy to another can see better outcomes and all options need to be kept open. We can't let the UK become a third world vacuum for melanoma treatment options and dissuade pharmaceutical companies to provide further trials and treatment options here.
115	[name redacted]	Devastating and extremely disappointed for all sufferers of this dreadful disease.	Absolutely as well as helping my mental health, worrying and anxiety.	Our country is a world leader in this field and we are incredibly lucky and grateful to have such fantastic scientists, doctors, nurses and oncologists. To withdraw this treatment would be a significant step backwards in the advances that have been made in recent years.
116	[name redacted]	Removes possible options for future treatment	Yes it has given me a life when I would have died	This proposal will deny new patients similar treatments to those which saved my life.
117	[name redacted]	None at present	Yes , no problems , even have driving licence returned	Not sure if I was eligible to fill this in as my treatment. has finished but without it I would not be here
118	[name redacted]	Lack of options and hope for the future. Frightening and like we dont matter	absolutely - as above	This would cause devastation and worry for so many people . Potential reducing outcomes for people to live!!!!
119	[name redacted]	A lot as knowing how fast this cancer spreads	Yes	
120	[name redacted]	A lot as knowing how fast this cancer spreads	Yes	
121	[name redacted]	This is a potential death sentence for me as a current young women with an early diagnoses who's cancer has the potential to progress, this adjacent treatment option is an advanced leap forward to stop melanoma spreading.		
122	[name redacted]	It's vital	N/a	
123	[name redacted]	We need as many options available to treat advanced melanoma, as it keeps us alive. The evidence is clear that it is advantageous, and I might not be here if I did not have adjuvant immunotherapy.	Yes I have been able to continue life as normal since recovering from my operation to remove the melanoma	Keep our options open. Those of use, especially BRAF wild type have very limited options available to us, and as my Clinical Nurse Specialist said, without the new treatments (Immunotherapy) Melanoma diagnosis used to be a Death Sentence. Keep this treatment, so that that melanoma diagnosis does not come back to being a death sentence.
124	[name redacted]	A drug I could require in the future.		
125	[name redacted]	I will not have access to treatment which could potentially stop me from progressing to Stage 4.		By removing this treatment you are removing the potential for a stage 3 patient to not progress to stage 4, therefore resulting in more surgery and treatment to save lives.
126	[name redacted]	At present, it doesnt affect me personally(Brad positive) but it may in the future and will definitely effect more people in the future. Thankfully I received adjuvant Dab / tram treatment and have since had no further spread because I was given that option. Others will no doubt have melonoma spread because they were not offered nivolumab initially and this will cause needless suffering, anxiety and further operations, exisions etc	Yes definitely	
127	[name redacted]	Why should I not be worthy enough to receive it, if and when it is required?	N/a	
128	[name redacted]	It will give me huge piece of mind going forward. My melanoma was Stage 2 when removed, but I was offered nivolumab as an option when a tumour was then discovered on my lung. Surgery revealed it was primary lung cancer, but to have nivolumab as a treatment should I need it in the future would be amazing.	N/a	
129	[name redacted]	I will not get a chance to fight and stay alive for longer should / when I progress.	Not received yet	Your taking away the chance of life over money and preventing progression. It's wrong to put a value on someone's life
130	[name redacted]	Awful decision. We live each day in hope that this cancer will go away		
131	[name redacted]	Possible option in case of relapse	Yes	
132	[name redacted]	This will mean my treatment will be stopped and my cancer would grow. This gives me immense anxiety as i did not know this was happening until now when i saw it on social media. If this drug was not funded then i fear for my life.	My life has improved drastically since receiving immunotherapy. I used to suffer from a pleural effusion and was fitted with a drain where were draining 550ml of fluid daily. I now do not drain anything and have had to drain removed thanks for immunotherapy. My tumours used to cause me lots of pain and i no longer experience this which has improved my quality of life. I feel exceptionally well at the moment albeit a few side effects.	I am only 33 years old and surgery was never discussed as an option for me. If this is removed i would be devastated and fear i will die.

133	[name redacted]	This decision would put accessibility to treatment back towards sit and wait, risking further reoccurring mm. The impact on home countries who have little treatment options and referral to larger cancer specialist hospitals. I feel the impact would damage the objectives set out to tackle mm and provide suitable treatment for those at stage 3, would impact the mental health and wellbeing of a diagnosis further.	I would not be here today without treatment at stage 3.	Nice has a duty of care towards its patients, the removal of a necessary treatment that went on to aid the treatments of other cancers is a downgrading of care for those at stage 3. The risks associated both mentally and physically are not in the best interests of the patients should this go ahead. The doctors who provide and want to help their patients will be limited, and home countries that have difficulty getting access to treatments would see increases in referrals to specialist cancer hospitals. It is cutting off one hand in the fight against this terrible illness at a critical staging.
134	[name redacted]	Everything! It has given so much hope and given more time. Please do not let those drop	Absolutely. No doubt about that	Please dong take this life enhancing option away from us all.
135	[name redacted]	I think it's awful as we have the right to these good treatments to help as live	definitely	Please let people to have these treatments it's peoples lives at risk here we need these to carry on normal lives
136	[name redacted]	The potential of livening a full and happy life.	Yes	
137	[name redacted]	It is very worrying that treatment may be taken away from people who needs it. This could be the difference to whether someone lives or die. It is awful to think that that someone's life comes down to funding. Surely if something is working and helping to save lives then this should still be readily available.	N/A	
138	[name redacted]	Less options in my future treatments	Yes, most definitely.	
139	[name redacted]	Its a devastating decision to have a lifeline taken away from those whose survival rely on it.	I went from having 80 tumours on my leg that surgery couldnt fix, to being NED because of nivolumab and ipililumab. The treatments not only gave me quality of life, they saved my life. I am still on treatment and am working 50 hours a week through lockdown in my job as a Childrens TV producer at the BBC. I also exercise 7-8 hours a week, run a small business, coordinate animal rescues, love travel and am planning my second book!	
140	[name redacted]	Would like to think if needed it woukd be available!		
141	[name redacted]	As a stage 3c patient this decision reduces options available and therefore may impact on life expectancy	Unknown	
142	[name redacted]	I means if my cancer returns (Im stage 4) I cannot retry it.	Yes! Ive had to magically retire but I have lived my life as full as possible with my loved ones.	This is taking away options, life and hope from people. This is putting a price on peoples lives and well being when theyre at their most fragile. What if it was your relative?
143	[name redacted]	Now the melanoma cancer show signs of becoming resistant to the current treatment (dabrafenib and trametinib) Nivolumab will be my next treatment. This would most likely give me a better chance to survive this cruel disease which is extremely aggressive and has wreaked my life and health. By being denied this treatment is the same as sentecing me to certain and early death.	It has reduced considerably the constant pain, nausea, inability to eat, inability to get off the bed, inability to work and do the basiscs. It enabled me to have a normal life that is so precious to everyone of us. And for this I am forever grateful to the NHS and everyone involved in the research to find the treatments so needed.	We dont choose to have cancer, nobody does. The cancer diagnosis is like a death sentence, it brings despair to patients and our families. It steals the dreams and family plans and leaves a hollow space inside, we feel lost and devastated. Life is never the same, all we have is a ticking clock ready to stop at anytime. The only thing that is left to us is a thread of hope that the treatment available under NHS can give us a second chance to life. Please do not take that away ..
144	[name redacted]	If the treatment I'm on now stops working that's my next step	Yes	
145	[name redacted]	The difference between everything being done to help me and this being taken from me.	Not on it but the fact it is there is reassuring	This is a very scary diagnosis but the thought of treatment being available if needed helps with feelings of anxiety

NICE National Institute for Health and Care Excellence

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 25 November 2020 **email:** 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):	NCRI-ACP-RCP-RCR
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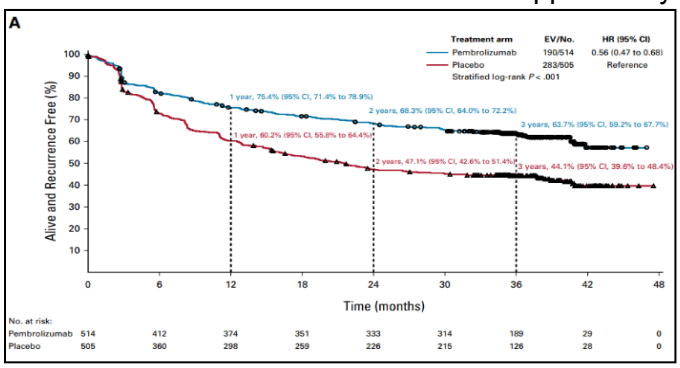
Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease [ID1681]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 25 November 2020 **email:** NICE DOCS

	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.
General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.
	Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (CDF review of TA558) [ID1681] As a group of consultant oncologists from across the UK who lead on the treatment of patients with advanced malignant melanoma, we are writing to express our objection to the NICE recommendation to not support the NICE TA558 guidance and hence discontinue CDF funding of adjuvant nivolumab in high risk resected malignant melanoma. Treatment of patients with resected melanoma at high risk of relapse (resected stage III & IV) has been an area of significant unmet need for many years, since approximately 40-60% of patients with resected stage III and 80-90 % of stage IV melanoma will die from their melanoma within 5 years of their surgery. The demonstration of significant improvement in relapse-free survival with adjuvant therapy has been a milestone in melanoma treatment and has led to adjuvant therapy being the standard of care for resected high-risk melanoma in all developed countries. The adjuvant melanoma Checkmate 238 trial comparing nivolumab with ipilimumab demonstrated a significant improvement in recurrence-free survival, with an acceptable toxicity profile. Based on these results, nivolumab was licenced as adjuvant treatment and is recommended as standard of care in all evidence-based international melanoma patient management guidelines. Across the UK, virtually all patients with resected stage III or stage IV melanoma will have the risks and benefits of adjuvant therapy discussed with them routinely. The revaluation of NICE guidance and a reversal of the recommendation for CDF funding of adjuvant nivolumab (TA558) appears to be based on: • review of updated data on the 906 patients in the Checkmate 238 study data & on new real-world SACT data from PHE/CDF comprising 284 patients prescribed adjuvant nivolumab • an appraisal of overall survival and cost of patients receiving adjuvant treatment • appraisal of how survival and cost without adjuvant treatment might be affected by use of subsequent treatments for advanced melanoma and hence the magnitude of beneficial effect of nivolumab being given as an adjuvant. **Nivolumab clearly reduces the risk of recurrence.** The new updated data on Checkmate 238 (Ascierto, Lancet Oncology, Nov2020) show that the recurrence-free survival (RFS) data remains robust with a 4 year RFS of 51.1 months following adjuvant treatment with nivolumab and an overall 4 year survival of 77.9%. There is no direct comparison with a placebo/no treatment arm in this study. However, indirect comparisons have been made with the outcomes of the placebo arm in other adjuvant studies and real-world data. These

comparisons of RFS are still valid, as there is no indication that the rate of recurrence has changed significantly over time in non-treated patients.

Therefore, the magnitude of beneficial effect of effect of nivolumab in preventing recurrence is still robust. The hazard ratio is in the region of 0.5-0.6, which is among the best for any systemic adjuvant therapy in cancer reported to date. This beneficial effect is supported by the updated 3 year follow results of the EORTC 1325/Keynote054 trial of 1019 patients comparing adjuvant pembrolizumab to placebo (Eggermont ,J Clin Onc Nov 2020). Pembrolizumab is another anti-PD1 antibody, equivalent to nivolumab. The 3 year results of EORTC 1325/Keynote 054 confirm a large benefit of adjuvant pembrolizumab in preventing recurrence in resected high risk stage III disease. RFS at 3 years is 63.7% in the pembrolizumab group vs 44.6% in the placebo group with a hazard ratio of 0.56. The data on overall survival are too premature to be able to assess effect on overall survival.



Currently, the additional, real-world data from PHE/CDF are too immature to be helpful for making decisions on efficacy. The cohort of treated patients is very small, 72% of patients are still on treatment and there is no robust overall survival data available.

The recommendation of the NICE committee with steer from the Evidence Review Group appears to be driven by the potential effects on survival of (the new) systemic treatments in recurrent advanced disease, and the premise that this is so great that it negates the benefit of adjuvant therapy to prevent recurrence.

This is based on selection of a model that uses a pessimistic projection resulting in an unfavourable incremental cost effective ratio (ICER). it appears that the uncertainty on OS has been addressed by giving weight to the most pessimistic models and/or assumptions largely on the basis that they are more conservative. Using these to define the QALY cost as too high becomes essentially a self-fulfilling argument. NICE's guide of course require the ERG and committee to 'take into account the degree of certainty'. However, we feel they have inappropriately interpreted this and have taken most conservative rather than most likely scenario. There are clearly other models that are equally valid that show a very different and more favourable ICER.

Essentially, uncertainty arises because the models are based on data that are immature, and without sufficient follow-up. **We would like to assert that it is premature and inappropriate to reverse a decision to fund adjuvant nivolumab at this stage; this would lead to significant potential harm to patients with high risk melanoma**. **We therefore request that funding continue until more robust data are available.**

We recognise the need to revaluate the efficacy of drugs as more information comes to hand, but for this setting, ie the adjuvant therapy for melanoma, it is clearly too early, at this stage, to come to such conclusions. The data will be forthcoming with further follow-up in ongoing studies and as real-world data mature.

The harm to patients of stopping funding of adjuvant therapy is the significantly increased risk of recurrence of melanoma and the consequences of this, which includes high chance of death, despite access to treatment options for advanced melanoma. In the absence of adjuvant therapy, the majority of patients with resected stage

NICE National Institute for Health and Care Excellence

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	III/IV melanoma will experience disease recurrence. Treatment of advanced disease offers only median survivals of around 3 years, so most will die from metastatic melanoma and experience the increased morbidity of living with and dying from cancer. The physical and psychological burden of developing metastatic disease for patients and carers is significantly worse following recurrence, even if patients are fortunate enough to have a very good long-term survival with subsequent treatments. Of particular concern is the withdrawal of adjuvant nivolumab funding for the resected stage IV patients. These patients, although relatively small in number, are the ones at highest risk of recurrence. Nivolumab is the only adjuvant treatment currently licenced for this indication with 4 year recurrence free survival of 48.6% in the Checkmate 238 study. Support of this benefit in resected stage IV melanoma is seen in the IMMUNED randomised phase II study showing a 2 year RFS of 42% with adjuvant nivolumab vs only 14% in a placebo group (Zimmer et al Lancet May 2020) Withdrawal of funding for adjuvant nivolumab will cause significant harm to this patient group. **In summary** • **The recommendation to discontinue adjuvant nivolumab funding is based on uncertainty of the resulting QALYs generated by immature treatment outcome data.** • **More data will be forthcoming,** • **Withdrawal of funding will cause significant harm to patients.** **Therefore, we urge the committee to reconsider and to commend continued CDF funding of nivolumab in resected high risk melanoma.** This statement has been reviewed and endorsed by 55 consultant melanoma specialists working across the UK.

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

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- 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.

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

Name	[redacted]
Role	
Other role	
Organisation	Melanoma Focus
Location	
Conflict	
Notes	
Comments on the ACD:	

Are the recommendations sound and a suitable basis for guidance to the NHS?

I have stage III melanoma and have recently completed a year of adjuvant treatment. Prior to treatment, I had a proactive discussion with my oncologist where we discussed the evidence of the approved treatment options. I can continue to lead my very active life knowing I have had treatment to reduce the likelihood of my melanoma returning. It is really important for people living with melanoma to have access to adjuvant treatments with the potential to prevent the development of metastatic disease.

I understand that nivolumab went into the Cancer Drugs Fund so that further patient information could be observed and that patients in the original trial would have also been followed up for a longer period. 284 people had nivolumab treatment via the Cancer Drugs Fund and 72% patients were still having treatment when the data was reviewed which indicates a short follow-up, particularly in the adjuvant setting. It greatly concerns me as someone fortunate to have adjuvant treatment that patients will be refused this option. It seems that on this basis both adjuvant immunotherapies could suffer the same fate and so only patients with a BRAF mutation could have adjuvant treatment offered to them. After citing an unmet need in TA558, it is difficult to understand the process.

We are also in the predicament that the licences for the various adjuvant treatments vary and nivolumab is the only treatment available for resected stage IV patients so this subset will no longer be eligible for treatment in England. In Scotland, the treatment will still be permitted causing inequity between the devolved nations which will be an appalling situation.

As a patron for melanoma charities (Melanoma Focus and Melanoma UK), I feel duty bound to express my deepest concern with the NICE recommendation to not approve nivolumab for adjuvant treatment. Adjuvant treatments are a critical choice for melanoma patients and I urge you to reconsider the outcome.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

As a Melanoma stage 3 patient receiving adjuvant Nivolumab this consultation shocks me to the core.

I was diagnosed in April. During lockdown. I'm lucky enough to be have private healthcare or I worry that covid would have delayed my diagnosis and treatment.

I would hate to thing that having had the cancer and lymph nodes removed, that I was reliant on scans alone. By the time a scan would have found a tumour, it's already establised and therefore much harder to try and shrink. Microscopic cells are targeted with Nivolumab and this is much more reassuring.

I am 38. I don't have cancer because I went on sun beds. I hate the sun. I am just very unlucky. I have two children aged 7 and 4. I wake up everyday and think thank god I am still alive and receiving Nivolumab as I hope beyond hope that this means I will be able to live, see my children grow up and enjoy a long life with my husband.

There are more younger people being diagnosed with Melanoma. These people and myself deserve a chance. This is not an old persons disease. You're not talking about giving a person a few more years. At 38, I hope that I would live a lot longer.

Please reconsider. Give time for evidence to show that it does work to reduce recurrence.

Name	[redacted]
Role	East Midlands Skin Cancer Expert Clinical Advisory Group (ECAG)
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

I am commenting as Chair of the East Midlands Skin Cancer Expert Clinical Advisory Group (ECAG). As a group of clinicians we are deeply troubled by this plan to end access to adjuvant Nivolumab based on a small cohort of patients in SACT data who have not yet completed their follow up. You comment yourselves that you only have estimates on cost effectiveness. You also comment that recurrence free survival is improved but it is "uncertain" if overall survival is improved.

My colleagues and I are very concerned that you appear in this uncertainty to presume that it is not cost effective despite not having all the necessary data yet, and are assuming it does not significantly improve overall survival but do not know yet whether it does? Where the clinicians in the field feel strongly that this drug is of great benefit, and there is evidence of significant benefit in recurrence free survival, it would surely be better to continue to allow access to the drug until greater clarity is achieved? If we were to discover in a few years time when the data has matured and more patients have completed follow up, that actually it was cost effective and did improve overall survival it would be a bitter pill to swallow for the families who missed out during the period of your uncertainty.
We are deeply concerned about this approach to change what in many units is the standard of care, on small amounts of uncertain data. We would request that you reconsider your recommendation until you have stronger evidence to suggest changing course.
Yours sincerely,
Mr Jonathan Pollock
Consultant Plastic & Reconstructive Surgeon
Chair East Midlands Skin Cancer Network

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

I am a consultant medical oncologist with 20 years of experience managing melanoma patients and have been involved in the clinical trials of immunotherapy both in metastatic disease as well as in the adjuvant setting. I chaired the NCRI skin cancer group between 2012 and 2017. I am a trustee of the national melanoma charity, MelanomaFocus and I am the clinical lead for melanoma in our region.

I am also a member of the CCIG, which oversees the SACT dataset. Working with PHE colleagues, I co-led and published a project to evaluate the introduction of immune checkpoint inhibitors as treatment for metastatic melanoma by analysing the SACT dataset (Board et al, Int J Cancer 2020).

I am therefore very familiar with the strengths and weaknesses of the SACT data.

I am deeply concerned with this proposed recommendation. It appears to be based on analysis of a small dataset of 284 treated patients, 72% of whom remain on treatment at the time of analysis. Not surprisingly as this is an adjuvant cohort, there is no survival data available.

The SACT real world dataset has many flaws particularly when it comes to data accuracy . It comes into its own when analysing large numbers preferably in their thousands and there is a hard end point such as survival available. Neither of these are available for this analysis. It is not surprising that the outcome is a wide variation in ICERs generated by different models and therefore widely varying QALYs. The response to this uncertainty must be to allow access to continue while more data is collated. Not as is the case here, to remove access.

The recommendation to remove access flies in the face of all that we know about now a series of RCTs evaluating adjuvant immunotherapy in resected stage III/IV melanoma, which have generated one of the biggest hazard ratios favouring treatment every recorded for any funded adjuvant therapy. How can it be that we will soon be telling our patients that a treatment that literally halves their chance of recurrence will no longer be available to them, but instead they can only be treated when their cancer returns?

How can it be that we will be telling our patients in England that if they lived in Scotland they could have this potentially life-saving treatment.

The committee must reconsider this unreasonable recommendation that flies in the face of everything we know about prevention being better than palliation.

Dr Pippa Corrie

Consultant and Associate Lecturer in medical oncology, Cambridge University Hospitals NHS Foundation Trust

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

No, they are not. They demonstrate uncertainty because the dataset is so small with limited follow-up and the interpretation of this should therefore be to allow access to continue to build a bigger dataset and longer follow-up.

Has all of the relevant evidence been taken into account?

It's difficult to imagine that the committee has truly taken into account all the adjuvant randomised clinical trial data because they consistently show a halving of risk of recurrence with treatment. The only conclusion taking this data into account would be to recommend continuation of access.

Are the recommendations sound and a suitable basis for guidance to the NHS?

No, they are completely unsound (see comments above and below).

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

The outcome of the proposed recommendation will generate completely unacceptable discrimination against patients with melanoma living in England, since treatment will be available in other devolved nations.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?

Please see joint submission from 55 Consultant Melanoma Oncologists from across the UK

Has all of the relevant evidence been taken into account?

As a group of consultant oncologists from across the UK who lead on the treatment of patients with advanced malignant melanoma, we are writing to express our objection to the NICE recommendation to not support the NICE TA558 guidance and hence discontinue CDF funding of adjuvant nivolumab in high risk resected malignant melanoma.

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The revaluation of NICE guidance and a reversal of the recommendation for CDF funding of adjuvant nivolumab (TA558) appears to be based on:

- review of updated data on the 906 patients in the Checkmate 238 study data & on new real-world SACT data from PHE/CDF comprising 284 patients prescribed adjuvant nivolumab
- an appraisal of overall survival and cost of patients receiving adjuvant treatment
- appraisal of how survival and cost without adjuvant treatment might be affected by use of subsequent treatments for advanced melanoma and hence the magnitude of beneficial effect of nivolumab being given as an adjuvant.

Nivolumab clearly reduces the risk of recurrence. The new updated data on Checkmate 238 (Ascierto, Lancet Oncology, Nov2020) show that the recurrence-free survival (RFS) data remains robust with a 4 year RFS of 51.1 months following adjuvant treatment with nivolumab and an overall 4 year survival of 77.9%. There

is no direct comparison with a placebo/no treatment arm in this study. However, indirect comparisons have been made with the outcomes of the placebo arm in other adjuvant studies and real-world data. These comparisons of RFS are still valid, as there is no indication that the rate of recurrence has changed significantly over time in non-treated patients.

Therefore, the magnitude of beneficial effect of effect of nivolumab in preventing recurrence is still robust. The hazard ratio is in the region of 0.5-0.6, which is among the best for any systemic adjuvant therapy in cancer reported to date. This beneficial effect is supported by the updated 3 year follow results of the EORTC 1325/Keynote054 trial of 1019 patients comparing adjuvant pembrolizumab to placebo (Eggermont ,J Clin Onc Nov 2020). Pembrolizumab is another anti-PD1 antibody, equivalent to nivolumab. The 3 year results of EORTC 1325/Keynote 054 confirm a large benefit of adjuvant pembrolizumab in preventing recurrence in resected high risk stage III disease. RFS at 3 years is 63.7% in the pembrolizumab group vs 44.6% in the placebo group with a hazard ratio of 0.56. The data on overall survival are too premature to be able to assess effect on overall survival.

Currently, the additional, real-world data from PHE/CDF are too immature to be helpful for making decisions on efficacy. The cohort of treated patients is very small, 72% of patients are still on treatment and there is no robust overall survival data available.

The recommendation of the NICE committee with steer from the Evidence Review Group appears to be driven by the potential effects on survival of (the new) systemic treatments in recurrent advanced disease, and the premise that this is so great that it negates the benefit of adjuvant therapy to prevent recurrence.

This is based on selection of a model that uses a pessimistic projection resulting in an unfavourable incremental cost effective ratio (ICER). it appears that the uncertainty on OS has been addressed by giving weight to the most pessimistic models and/or assumptions largely on the basis that they are more conservative. Using these to define the QALY cost as too high becomes essentially a self-fulfilling argument. NICE's guide of course require the ERG and committee to 'take into account the degree of certainty'. However, we feel they have inappropriately interpreted this and have taken most conservative rather than most likely scenario. There are clearly other models that are equally valid that show a very different and more favourable ICER.

Essentially, uncertainty arises because the models are based on data that are immature, and without sufficient follow-up. We would like to assert that it is premature and inappropriate to reverse a decision to fund adjuvant nivolumab at this stage; this would lead to significant potential harm to patients with high risk melanoma. We therefore request that funding continue until more robust data are available.

We recognise the need to revaluate the efficacy of drugs as more information comes to hand, but for this setting, ie the adjuvant therapy for melanoma, it is clearly too early, at this stage, to come to such conclusions. The data will be forthcoming with further follow-up in ongoing studies and as real-world data mature.

The harm to patients of stopping funding of adjuvant therapy is the significantly increased risk of recurrence of melanoma and the consequences of this, which includes high chance of death, despite access to treatment options for advanced melanoma. In the absence of adjuvant therapy, the majority of patients with resected stage III/IV melanoma will experience disease recurrence. Treatment of advanced disease offers only median survivals of around 3 years, so most will die from metastatic melanoma and experience the increased morbidity of living with and dying from cancer. The physical and psychological burden of developing metastatic disease for patients and carers is significantly worse following

recurrence, even if patients are fortunate enough to have a very good long-term survival with subsequent treatments.
Of particular concern is the withdrawal of adjuvant nivolumab funding for the resected stage IV patients. These patients, although relatively small in number, are the ones at highest risk of recurrence. Nivolumab is the only adjuvant treatment currently licenced for this indication with 4 year recurrence free survival of 48.6% in the Checkmate 238 study. Support of this benefit in resected stage IV melanoma is seen in the IMMUNED randomised phase II study showing a 2 year RFS of 42% with adjuvant nivolumab vs only 14% in a placebo group (Zimmer et al Lancet May 2020) Withdrawal of funding for adjuvant nivolumab will cause significant harm to this patient group
In summary

- The recommendation to discontinue adjuvant nivolumab funding is based on uncertainty of the resulting QALYs generated by immature treatment outcome data.
- More data will be forthcoming,
- Withdrawal of funding will cause significant harm to patients.

Therefore, we urge the committee to reconsider and to commend continued CDF funding of nivolumab in resected high risk melanoma.
This statement has been reviewed and endorsed by 55 consultant melanoma specialists working across the UK. The full list of consultants is supplied below.

Signatories to Joint statement objecting to potential withdrawal from the Cancer Drug Fund of adjuvant Nivolumab for resected high risk malignant melanoma – Nov 2020

Dr Mazhar Ajaz PhD FRCP FRCR
Consultant Clinical Oncologist
Royal Surrey Hospital NHS Foundation Trust, Guildford

Dr Clare Barlow PhD FRCP
Consultant Medical Oncologist
Somerset NHS Foundation Trust

Dr Ruth Board
Consultant Medical Oncologist and Lead Cancer Clinician.
Rosemere Cancer Centre
Lancashire Teaching Hospitals NHS Trust

Dr Pippa Corrie PhD FRCP
Consultant medical oncologist
Cambridge University Hospitals NHS Foundation Trust

Dr Nicola Cresti,
Consultant Medical Oncologist
Newcastle upon Tyne

Dr Shanthini Crusz MRCP PhD
Consultant Medical Oncologist
Barts Health NHS Trust, London

Dr Elaine Dunwoodie

Consultant Medical Oncologist
Leeds Teaching Hospitals NHS Trust

Prof Sarah Danson
Professor of Medical Oncology/Honorary Consultant Medical Oncologist
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Dr Benjamin P Fairfax, PhD MRCP
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Dr Guy Faust
Consultant Medical Oncologist
University Hospitals of Leicester NHS Trust

Dr Alberto Fusi
Senior Lecturer in Medical Oncology/Honorary Consultant Medical Oncologist
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The Christie NHS Foundation Trust, Manchester
Dr Mark Harries MA FRCP PhD
Guy's Cancer Centre.
Guy's Hospital, London

Dr Chris Herbert
Consultant Clinical Oncologist
University Hospitals Bristol NHS Foundation Trust

Dr Martin Highley
Consultant Medical Oncologist
Plymouth Oncology Centre
Derriford Hospital, Plymouth

Dr Ioannis Karydis MA MB BCh DPhil MRCP
Consultant and Honorary Associate Professor in Oncology
Southampton University Hospitals and University of Southampton

Dr Leila Khoja MBchB PhD
Clinical Senior Lecturer/ Honorary Consultant Medical Oncologist
University of Birmingham/ Birmingham University Hospitals NHS Trust

Prof James Larkin PhD FRCP F Med Sci
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Royal Marsden NHS Foundation Trust, London

Dr Jim Lester
Consultant Clinical Oncologist
Sheffield Teaching Hospital NHS Foundation Trust

Prof Paul Lorigan
Professor of Medical Oncology/ Honorary Consultant Medical Oncologist
University of Manchester/ The Christie NHS Foundation Trust

Dr Najibah Mahtab
Consultant Clinical Oncologist
Northern Centre for Cancer Care
Freeman Hospital, Newcastle upon Tyne

Dr Lavanya Mariappan
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Northern Centre for Cancer Care
Newcastle Hospitals NHS Foundation Trust

Prof Mark Middleton
Professor of Experimental Cancer Medicine/Honorary Consultant Medical Oncologist
University of Oxford/Oxford Cancer & Haematology Centre

Dr Mukesh Mukesh
Consultant Clinical Oncologist
Colchester Hospital

Dr Paul Nathan
Consultant Medical Oncologist
Mount Vernon Cancer Centre

Dr Steve Nicholson
Consultant in Medical Oncology
Mid & South Essex NHS Trust

Dr Jenny Nobes
Consultant Clinical Oncologist
Norfolk and Norwich University Hospital NHS Trust

Christian Ottensmeier MD PhD FRCP
Professor of Immuno-Oncology
University of Liverpool/The Clatterbridge Cancer Centre NHS Foundation Trust
Adjunct Professor-La Jolla Institute for Immunology

Dr Lalit Pallan
Consultant Medical Oncologist
Queen Elizabeth Hospital Birmingham

Dr Sophie Papa FRCP PhD
Clinical Reader/Honorary Consultant Medical Oncologist
King's College London /Guy's and St Thomas' NHS Foundation Trust, London

Prof Poulam Patel PhD FRCP
Professor of Clinical Oncology/Honorary Consultant Medical Oncologist
University of Nottingham/Nottingham University Hospitals NHS Trust

Dr Christine Parkinson PhD MRCP
Consultant Medical oncologist
Cambridge University Hospitals NHS Foundation Trust

Dr Miranda Payne DPhil FRCP
Consultant Medical Oncologist

Oxford University Hospitals NHS Foundation Trust

Prof Ruth Plummer FRCP FMedSci
Professor of Experimental Cancer Medicine/Consultant Medical Oncologist
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Dr Anki Rao PhD MRCP
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Nottingham University Hospitals NHS Trust

Dr Sukaina Rashid, PhD, MRCP
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Dr Gihan Ratnayake, MBBS MRCP(MedOnc)
Medical Oncology Consultant
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Dr Catherine Shankland
Consultant Medical Oncologist
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Dr Heather Shaw
Consultant Medical Oncologist
University College London Hospital and Mount Vernon Cancer Centre Hospital

Dr Shobha Silva
Consultant Medical Oncologist
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Dr Neil Steven MB BS PhD FRCP
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University of Birmingham/ Birmingham University Hospitals NHS Trust

Prof. Peter Szlosarek
Medical Oncology
St Bartholomew's Hospital, London

Dr Yun Yi Tan MBChB MRCP
Consultant Medical Oncologist
Beatson West of Scotland Cancer Centre, Glasgow

Dr Hannah Taylor
Consultant Medical Oncologist
University Hospitals Bristol NHS Foundation Trust
Dr Tania Tillett
Consultant Medical Oncologist
Royal United Hospitals Bath NHS Foundation Trust
Dr Samra Turajlic MD PhD
Consultant Medical Oncologist, The Royal Marsden NHS Foundation Trust
Group Leader, The Francis Crick Institute. Reader, The Institute of Cancer Research
Prof. John Wagstaff MD FRCP

South West Wales Cancer Institute
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Dr Ashita Waterston PhD FRCPSG
Consultant Medical Oncologist
Beatson West of Scotland Cancer Centre, Glasgow
Dr Steven Watkins
Consultant Clinical Oncologist
University Hospitals Birmingham NHS Foundation Trust
Dr Sarah Welsh PhD MRCP
Consultant Medical oncologist
Cambridge University Hospitals NHS Foundation Trust
Dr Sarah Westwell
Consultant Clinical Oncologist and Clinical Director for Cancer Services
Brighton and Sussex University Hospital Trust
Dr Matthew Wheater PhD FRCP
Consultant Medical Oncologist
University Hospital Southampton
Dr Pam Woodings
Consultant Clinical Oncologist
Royal Derby Hospital, Derby
Dr Helen Winter
Consultant Medical Oncologist
University Hospitals Bristol NHS Foundation Trust
Dr Kate Young MBBS MA MRCP MD(Res.)
Consultant Medical Oncologist
The Royal Marsden NHS Foundation Trust, London

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

I write on behalf of the Skin Cancer Special Interest Group BAPRAS (British Association Plastic Reconstructive Surgeons) as our Chair.
in essence this proposed recommendation is wrong for our melanoma patients. The advent of adjuvant therapy for these patients has been a game changing moment for all of us involved in the care of highly vulnerable patients. With recurrence rates approaching 50% , being able to make significant in roads with a highly favourable side effect profile has been profound.
This recommendation appears to be based on a 'worse case scenario' set of data' rather than something akin to real world data and risks depriving patients from an overall small cohort in current trials with immature data receiving treatment that on balance clearly improves their survival.
As a committed oncological surgeon and academic it worries me profoundly that biased date are being presented that will impact the lives of our patients without due full sight of the facts.
At the very leat we anticipate a pause to consider all available data before looking to answer these essential questions on behalf of both patients and their care givers.

Sincerely
Prof Rowan Pritchard Jones FRCS Plast) MD(Bris) MRCS(Eng)
St Helens & Knowsley NHS Trust

Has all of the relevant evidence been taken into account?

The evidence is both immature in time and low on overall patient numbers to make a decision on withdrawing care that is currently available.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No
These seem unreasonable pessimistic and would NOT have my professional support.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Not discriminatory in law, but of concerning academic quality.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Are the recommendations sound and a suitable basis for guidance to the NHS?

Melanoma Focus is a national charity that supports both professionals, patients and carers by commissioning and funding innovative research, while providing support and information on all stages of melanoma. We wholeheartedly support the professional body -coordinated by the NCRI melanoma CSG - who are collectively objecting to the recommendations. We agree that the assessment does appear flawed. The approach to base a decision on the ERG's flawed modelling is unfair and unreasonable. If there are two modelling approaches, neither of which is fit for purpose, perhaps there should be a recommission of this work?

The criticism of Checkmate 238 as not having an NHS standard of care control arm is unreasonable. The control arm in the study, ipilimumab, has already been shown to be superior to observation alone in a large EORTC study (Eggermont et al. November 10, 2016
N Engl J Med 2016; 375:1845-1855). Furthermore, given the Keynote-054 and COMBI-AD data showing superior outcomes for pembrolizumab and targeted therapies compared to placebo, we strongly believe that observation is no longer the UK standard of care. In addition, all recent trials now include this as the control arm (Checkmate 915 which has completed accrual of nearly 2000 patients compared combination immunotherapy with nivolumab, and the EORTC proposal for sequential treatment in Stage III also had a PD-1 inhibitor as standard of care. The fact that BMS did not use competitor data in their model prevented the Committee from adequately considering these clinically highly relevant datasets.

Whilst we support further data collection via the CDF; such data for adjuvant treatments require significant follow up, and therefore with 72% patients on treatment at the time of the data review, a negative recommendation at this juncture is not justified.

We feel that this negative outcome sets a precedent as there will likely be a similar result for pembrolizumab when this is later reviewed and therefore, we could be in the dreadful position where no immunotherapies are available for patients with stage III and resected stage IV disease. These are the only adjuvant treatment options for the 60% of patients with BRAF wildtype melanoma.

Melanoma is the 5th most common cancer and its incidence is related to age, however, there is a large increase in incidence (7-8 fold) in the 15-24 year age group and it is the second most common form of cancer in the 15-34 age group. There is therefore a growing population of melanoma patients who are younger in

age with the majority of their life ahead of them: they want to increase the possibility of seeing their children grow up and reaching important milestones.

We canvassed the opinions of patients at a Patient Workshop and they informed us that their biggest fear is stage IV disease. Being told that the melanoma has spread scares patients more than the risk of having treatment. Patients have informed us that they would rather have treatment when they are fit and healthy and have single agent immunotherapy rather than combination immunotherapy if they were diagnosed with metastatic disease. Given a diagnosis of high-risk melanoma we believe that the vast majority of the committee would want this treatment available for themselves or their loved ones.

Melanoma Focus would be delighted to work with NICE to provide real world data drawing together clinicians and patients in a common purpose.

BMJ TAG

Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (CDF review of TA558)

ERG response to BMS ACD comments

December 2020

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1 Introduction

This document provides the Evidence Review Group's (ERG's) critique of the company's response to the appraisal committee document (ACD). The company's response addressed the following issues raised in the ACD:

1. Immature overall survival data;
2. ERG's approach to modelling overall survival; and
3. Plausible ICER range.

The ERG's critique of the company's response to each of these issues is discussed in Section 2.

In their ACD response, the company accepted the committee's preference for partitioned survival model. The company's base case for the partitioned survival model remains unchanged from that presented in the ERG report and results are given in Table 1.

Table 1. Company's deterministic cost effectiveness results – partitioned survival model

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine surveillance	[redacted]	18.65	[redacted]	-	-	-	-
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	14,301

Abbreviations: ICER, incremental cost effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

2 ERG response to issues

2.1 Immature overall survival data

The ERG notes that the clinical data presented by the company in their response to the appraisal consultation document (ACD) originate from the 24- and 48-month data-cuts of CheckMate 238 that have been previously presented and discussed by the ERG. However, the company also reported that CheckMate 238 observed a slower than anticipated rate of death and that when nivolumab entered into the Cancer Drugs Fund (CDF) in November 2018, the estimated study completion date was November 2020 which coincided with all subjects having a minimum follow up of 48 months.[1] The company reports in their response to the ACD that the CheckMate 238 study completion date has now been amended and that the next planned data cut will comprise a [redacted]

The trial level results from CheckMate 238 demonstrated no statistical difference in overall survival (OS) between nivolumab and ipilimumab at the 48 month data-cut (HR 0.87, 95% CI: 0.66 to 1.14). However, nivolumab demonstrated a statistically significant benefit in recurrence-free survival (RFS) compared to ipilimumab (HR 0.71, 95% CI: 0.60 to 0.86). In addition, the ERG notes that the company highlights the benefits of nivolumab in stage III patients for distant-metastasis free survival (DMFS), where the HR for nivolumab versus ipilimumab was 0.79 (95% CI: 0.63 to 0.99). The ERG notes that the comparison of interest for this appraisal is nivolumab versus routine surveillance and the evidence for this comparison is derived from an indirect treatment comparison using the CA184-029 trial.

The CA184-029 trial demonstrated a benefit in OS for ipilimumab versus placebo (HR 0.73, 95% CI: 0.60 to 0.89) although, as discussed in the ERG report, the ERG has concerns regarding the use of ipilimumab for up to three years in CA184-029 and differences in the patient population due to the exclusion of stage IV patients from CA184-029. The results of the ITC of nivolumab versus placebo using the Bucher method and applying censoring at 1 year of ipilimumab treatment to patients in CA184-029 showed that patients treated with nivolumab have a lower hazard of death compared to patients treated with placebo [redacted] although the hazard is [redacted] compared to when the observed ITT ipilimumab data from CA184-029 are used in the analysis [redacted] The company also highlighted that the benefit of active adjuvant treatment over routine surveillance has been widely acknowledged by clinical experts in other adjuvant melanoma

assessments (TA544 and TA553)[2, 3] although the ERG notes that TA544 is in a different population (resected stage III BRAF V600 mutation-positive melanoma) and pembrolizumab (the drug of interest from TA553) is currently being funded via the CDF.

The company conducted a patient level data (PLD) meta-regression to inform RFS and OS in the economic model and the meta-regression included covariate adjustment to account for observed and unobserved differences between CA184-029 and CheckMate 238. In addition, the company compared extrapolated RFS and OS curves for routine surveillance against KM data for placebo from KEYNOTE-054[4] (RFS only) and COMBI-AD[5] (RFS and OS) as part of their validation process for the results of the routine surveillance arm from the model. The ERG agrees that these steps taken by the company are beneficial but due to time constraints the ERG is unable to fully critique the company's extrapolated curve validation.

The company also reported in their ACD response that nivolumab has demonstrated [redacted] of progression on next-line therapy (PFS2) compared with ipilimumab [redacted] In addition, they reported that nivolumab [redacted] of time to next line systemic therapy [redacted](first-line metastatic therapy) and time to second next systemic therapy [redacted] (second-line metastatic therapy) compared with ipilimumab (HR for time to next line systemic therapy: [redacted] and HR for time to second next line systemic therapy: [redacted]). The company cited a paper that suggests that PFS2 has a positive correlation with OS in solid tumours, although they also acknowledged that there is limited data in melanoma to confirm a similar relationship.[6]

Finally, the company discuss the analysis of OS that was presented in their response to technical engagement, where OS was adjusted in CA184-029 to reflect the OS that might have been observed if the same subsequent therapies received in CheckMate 238 were available to patients in CA184-029. As discussed in the ERG response to technical engagement, the analysis estimated that there was an average increase of 63% in post-recurrence survival for ipilimumab in CheckMate 238 compared with ipilimumab in CA184-029. Further detail on the methods used by the company to estimate the 63% increase in survival were requested by NICE and the ERG and were supplied by the company in an additional evidence submission. The company explained that the analysis comparing the ipilimumab arms in CheckMate 238 and CA184-029 was adjusted for possible confounders including age, sex, Eastern Cooperative Oncology Group Performance status (ECOG PS), disease stage, time from surgical resection to randomization, time from randomisation to recurrence, type

of recurrence, and initiation of subsequent systemic/anticancer therapy in order to isolate the impact of subsequent treatments on post-recurrence survival. The company then used a two-stage approach (as described in the Decision Support Unit Technical Support Document 16[7] [DSU TSD 16]), typically used to adjust analyses in the presence of treatment switching to compare post-recurrence survival between the two studies irrespective of subsequent treatments initiated. The estimated average increase to post-recurrence survival was then applied to the ipilimumab and placebo arms in CA184-029 and utilised in an ITC which resulted in a HR of 0.65 (95% CI: 0.45 to 0.91). The company explored the impact of varying the average increase by -10%, 10% and 20% for only the placebo arm and the resulting HRs ranged from 0.63 (95% CI: 0.44 to 0.89) to 0.69 (95% CI: 0.49 to 0.98).

The ERG has been unable to thoroughly critique the company's methods for the adjustment for subsequent treatments as the ERG still remains unclear as to the exact methods used by the company. Nevertheless, the ERG considers that any analyses which include the company's subsequent treatment adjustment should be interpreted with caution as the methods employed are typically used to account for treatment switching and are based on the uncensored ipilimumab CA184-029 data. However, the ERG also notes that the various adjustments to post-recurrence survival [redacted] and the company has not used the subsequent treatment adjustment to update or inform their base case analysis.

2.2 Modelling of overall survival and plausible ICER range

One of the company's primary concerns presented in its response to the ACD was with the ERG's two-year time point chosen for the assumption of equal hazard of death for nivolumab and routine surveillance. The aim of the hazard of death scenarios was to explore improvements in OS for routine surveillance in line with expectations of survival due to advancements in treatments for patients who have a recurrence in their disease. The ERG's choice of the two-year time point was based on median RFS for the routine surveillance arm, as that is the point at which 50% of patients would have relapsed and started their next line of treatment, thus would have improved post-relapse survival, in line with receiving immunotherapies.

The company argue that the two-year time point is not clinically plausible based on a comparison of median RFS for nivolumab and routine surveillance. Median RFS for nivolumab is 4.36 years compared with 1.61 years for routine surveillance. The company state that by setting the equal hazard of death time point to two years means that routine surveillance patients gain the mortality

benefit of nivolumab patients who have recurrence-free disease rather than nivolumab patients who have post-recurrence disease, which they deem is implausible. At two years, the company states that [redacted] of nivolumab patients are recurrence-free and informing OS. However, the ERG considers that as nivolumab is part of the subsequent treatments received by routine surveillance patients, it's not unreasonable albeit potentially optimistic to assume that the mortality benefit should reflect RFS for nivolumab, though it is recognised that it would be more appropriate to use RFS for nivolumab in the metastatic setting.

The company also presents a more in-depth analysis of the hazard plots presented during technical engagement and state that modelled hazards for nivolumab are overestimated compared with hazards obtained from CheckMate 238 and that equal hazard of death at two years results in predicted hazards for routine surveillance being lower than for ipilimumab. However, the ERG reiterates its response to the company during technical engagement, that it is concerned about [redacted]. The ERG considers that the Kaplan–Meier OS curves for nivolumab and ipilimumab overlap until approximately 52 months, and, as expected given the data cut, there is heavy censoring from 48 months onwards (Figure 1 of the company's response to the ACD). As such, the ERG considers the OS data beyond 48 months are likely to be unreliable. The HR for the minimum 48-month follow-up data suggests no statistically significant difference in OS for patients treated with nivolumab compared with those treated with ipilimumab (HR 0.87, 95% confidence interval [CI]: 0.66 to 1.14).

To further investigate an appropriate timepoint for the equal hazard of death assumption, the company performed several new analyses to investigate the point at which parametric hazard rates for OS cross applying different combinations of assumptions for censoring of placebo data in CA184-029 and using the subsequent treatments adjustment, discussed in Section 2.1. In addition to the standard parametric curves (exponential, Weibull, Gompertz, log-normal, log-logistic, generalised gamma and generalised F), the company explored Royston-Palmer spline models, though these analyses were not included with the economic model submitted with the company's response to the ACD. The company used the model with the best fit according to Akaike information criterion (AIC) statistics to obtain hazard rate estimates for nivolumab relative to routine surveillance, for time points one to 1,000 months. For the company's primary analysis, based on uncensored CA184-029 data and using the subsequent treatment adjustment, the 1-knot normal model for nivolumab and

the 1-knot odds model for routine surveillance was selected to produce a plot of the estimate hazard ratio over time (Figure 1). The ERG notes that for the company's base case, the generalised gamma was selected as the best-fit distribution to extrapolate OS for both nivolumab and routine surveillance, though a plot of the estimated hazard ratio over time for this distribution has not been presented by the company.

Based on Figure 1, the company infers that after [redacted] years the hazard ratio is decreasing and only starts to [redacted] and states that the confidence interval around the hazard ratio does not cross one until [redacted]. Furthermore, the company investigated that the timepoint by which the difference in the hazard ratio became non-significant in 90% of cases using the flexible models and the models which include three or more parameters and estimated this to be [redacted] months (~[redacted]) and the median was [redacted] months (~[redacted]).

Figure 1. Estimated hazard ratio and 95% confidence interval – nivolumab versus routine surveillance (Figure 15 of the company's response to the ACD)

Figure 1 highlights that between year 2 and 3, the confidence intervals around the hazard ratio are the smallest as a result of OS data that is not heavily censored being available from CheckMate 238 and demonstrate that the hazard ratio is decreasing during this time frame. Between year 3 and 4,

the hazard ratio reaches its lowest point before increasing, which the ERG assumes could relate to the impact of subsequent treatments improving OS for routine surveillance patients.

NICE and the ERG requested additional analysis from the company which included 1-year censoring of ipilimumab patients in CA184-029 and removing the subsequent treatment adjustment. The company supplied the requested analysis, along with additional analyses exploring the hazards over time when placebo patients in CA184-029 are censored at one year and including the subsequent treatment adjustment. The ERG considers that any analysis which includes censoring of placebo patients in CA184-029 is inappropriate as treatment would not discontinue if patients are progression-free. Whereas for ipilimumab patients, in CheckMate 238 treatment was restricted to one year compared with a maximum of three years treatment in CA184-029.

Figure 2 presents the hazards over time for nivolumab versus routine surveillance, based on the company's indirect treatment comparison including one-year censoring of ipilimumab patients and excluding the company's subsequent treatment adjustment. Figure 3 presents the hazards over time for nivolumab versus routine surveillance, based on a naïve comparison of uncensored placebo data from CA184-029 and excluding the company's subsequent treatment adjustment. Figure 2 and Figure 3 demonstrate that the timepoint for which the hazard of death is likely to be significantly different between nivolumab and routine surveillance is [redacted] or less.

Figure 2. Estimated OS hazard ratio and 95% CI - Nivolumab from CheckMate238 vs ITC adjusted placebo from CA184-029 (ipilimumab censored at 12 months) (Figure 6 of the company's addition evidence submission)

Figure 3. Estimated hazard ratio and 95% CI - Nivolumab from CheckMate238 vs unadjusted placebo from CA184-029 (uncensored and unadjusted) (Figure 16 of the company's addition evidence submission)

The ERG considers that based on all of the evidence supplied by the company for modelled hazards, the two-year time point for assuming equal hazard of death between nivolumab and routine surveillance may be overly conservative, and that the company's preferred minimum time point of three years is relevant for consideration. However, the ERG notes that in the additional evidence submission presented after the company submitted their response to the ACD, the company state that [redacted] is the minimum timepoint for while the hazards of death should be equal between nivolumab and routine surveillance. In its response to the ACD, the company presented what it considered a plausible ICER range, exploring the equal hazard of death assumption for the timepoints of 3 to 10 years, with and without one-year censoring of OS ipilimumab patients. The company's ICER range is presented in Table 2.

As mentioned previously, the ERG considers that the maximum time point for the equal hazard of death assumption should be five years as [redacted]. In addition, in Figure 10 of the company's response to the ACD, hazards for ipilimumab and placebo based on CA184-029 cross just after five years. The ERG considers that the plausible range of ICERs reduces

down to the scenarios for time points of 3 to 5 years, which covers the most recent data cut for CheckMate 238. Furthermore, as the committee has stated a preference for the one-year censored analysis of ipilimumab OS patients, the relevant ICER range is between £22,230 to £29,011.

Table 2. Company's preferred ICER range (Table 3 of the company's response to ACD)

Time point for equal hazard of death	Uncensored OS	One-year censoring of ipilimumab OS patients
Company base case (10 years)	£14,301	£17,404
9 years	£14,640	£17,899
8 years	£15,088	£18,550
7 years	£15,679	£19,405
6 years	£16,486	£20,568
5 years	£17,647	£22,230
4.36 years (median nivolumab RFS)	£18,789	£23,853
4 years	£19,431	£24,760
3 years	£22,487	£29,011

Abbreviations: ACD, appraisal committee document; ICER, incremental cost-effectiveness ratio; OS, overall survival; RFS, recurrence-free survival.

Note: Green shading indicates the ICERs the ERG considers are relevant for committee consideration.

As mentioned previously, OS data beyond 48 months from CheckMate 238 are potentially unreliable and as such the ICER estimate for the five-year time point is subject to increased uncertainty compared with the estimate at the three-year time point. Thus, the ERG considers the relevant timepoint for the equal hazard of death scenario that limits the uncertainty with cost-effectiveness analysis (though does not eliminate the uncertainty) is three years.

The ERG notes that the ICERs presented in Table 2 include the assumption that subsequent treatments for patients from the point at which equal hazard of death is assumed reflects the nivolumab arm of CheckMate 238. The ERG considers that using nivolumab subsequent treatment costs after the equal hazard of death time point is methodologically correct, as costs are aligned with the associated survival benefit. Nonetheless, in clinical practice, use of subsequent immunotherapies for patients who have relapsed on routine surveillance is likely to be higher than for patients who have relapsed on nivolumab. The ERG previously assumed that from the point at which equal

hazards of death is assumed, routine surveillance patients will incur subsequent treatment costs based on subsequent nivolumab, which was implemented as a simplification. In the ACD, the committee stated that, "*subsequent treatments in CheckMate 238 are consistent with what would be expected to be used in the clinical practice*". Furthermore, the committee did not state a preference for the ERG's assumption of subsequent treatment costs based entirely on nivolumab for routine surveillance patients from the timepoint at which the hazard of death is equal for both arms of the model. As such, the ERG considers the company scenario with equal hazards of death at three years, one-year censoring of ipilimumab OS (consistent with RFS), and subsequent treatments based on CheckMate 238 to meet the requirements of committee.

However, the ERG considers that it is still useful to explore two illustrative scenarios around the timepoint of three years for equal hazard of death, which reflects increased immunotherapy use (specifically subsequent nivolumab). The first scenario implements the subsequent treatment distribution from the ipilimumab arm of CheckMate 238, where nivolumab use was approximately [redacted] for both local/ regional and distant recurrences. The second scenario employs an assumption of 50% usage of subsequent nivolumab, with all other subsequent treatments in the ipilimumab arm of CheckMate 238 redistributed to the remaining 50%. Table 3 presents the company's ICER for the three-year time point for equal hazards and the ERG's two illustrative scenarios for subsequent treatment costs, with all scenarios using the committee's preferred assumption of one-year OS censoring for ipilimumab patients.

Table 3. ERG illustrative cost-effectiveness scenarios

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company scenario - equal hazard of death after three years & one-year censoring of ipilimumab OS patients	25,721	0.89	29,011
ERG scenario 1 - equal hazard of death after three years, subsequent treatment costs based on the ipilimumab arm of CheckMate 238 & one-year censoring of ipilimumab OS patients	25,823	0.89	29,126
ERG scenario 2 - equal hazard of death after three years, subsequent treatment costs based 50% nivolumab usage (ipilimumab CheckMate 238 data redistributed) & one-year censoring of ipilimumab OS patients	27,482	0.89	30,997

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

As mentioned in the ERG report, the true benefit of an immunotherapy compared to routine surveillance is only likely to only be established once the ongoing KEYNOTE-054 study for pembrolizumab compared with placebo reports and mature data are available to be used in a robust indirect treatment comparison. However, the scenarios presented in Table 3, using conservative assumptions, are a step closer to reducing the uncertainty around the cost-effectiveness of nivolumab.

3 References

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