NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma [ID1465]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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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.

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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	BMS is disappointed with the Committee's draft recommendation, particularly given the conclusion that an ICER of £49,840 (which comes in below the threshold of £50,000 per QALY gained) should be used in decision making. In response to the ACD2, this response addresses the key areas of uncertainty outlined by the Appraisal Committee: that it is unclear how long people lived beyond the CheckMate 649 trial period and the duration of nivolumab's treatment benefit. Additionally, further clarification of the modelling approach used in the BMS base case is provided.	Thank you for your comment. The consideration of the further clarification on the modelling approach is described in section 3.9 of the Final Appraisal Document. The company's updated commercial arrangement reduced the ICER comfortably below £50,00 so recommendation 1.1 in the Final Appraisal Document has been amended and the technology is now recommended.
2	Consultee	Bristol-Myers Squibb	In the ACD2 the committee agrees that NIVO+CHEMO addresses an unmet clinical need. While pembrolizumab has recently been recommended by NICE, this recommendation includes only adults with oesophageal cancer and gastro-oesophageal junction cancer whose tumours express PD-L1 with a combined positive score (CPS) of 10 or more,1 and excludes patients with either gastric cancer or PD-L1 CPS scores <10. In this document, BMS has provided the following evidence: • Additional detail describing the approach to survival modelling and the rationale for this approach (Section 1) • Overall survival estimates at 5 years, 10 years, and 20 years, respectively (Table 12) • Cost-effectiveness analyses including treatment waning scenarios, deterministic and probabilistic ICERs (Table 10 and Table 11)	Thank you for your comment. Sections 3.8-3.11 in the Final Appraisal Document includes information specifically about survival modelling, overall survival estimates and treatment waning. Furthermore, section 3.13 refers to the committee's conclusion on the cost-effectiveness analysis that include treatment waning scenarios.
3	Consultee	Bristol-Myers	Of note, survival estimates in Table 12 are similar to the ERG's, with	Thank you for your comment. Section 3.11 in

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
		Squibb	only minor differences between scenarios. That estimates are similar goes some way to reducing uncertainty around the duration of survival anticipated for patients in this population. Based on clinical evidence, BMS' preferred treatment waning scenario of 6.5 years was applied resulting in a deterministic ICER of £48,847 whereas the ICER in the BMS base case with no treatment waning was £45,383. This assumption aligns with a similar precedent used in TA737 where waning ended at 7 years. Further, all scenarios other than the most conservative treatment-waning scenario (waning at 5 years) resulted in deterministic ICERs below the £50,000/QALY willingness-to-pay threshold. It is intended that these new analyses allay the remaining uncertainty around cost-effectiveness. **The technical detail provided by the company in response to consultation describing the survival modelling, overall survival estimates, and cost effectiveness estimates have not been reproduced here. The company response in full is available within the Committee papers**.	the Final Appraisal Document refers to the company's and ERG's approaches to overall survival estimates. Furthermore, section 3.13 refers to the committee's conclusion on ICERs using a treatment waning assumption.
4	Clinical expert		The UK patients will be significantly disadvantaged as nivolumab + chemotherapy is now the standard of care chemotherapy globally for her-2 negative non resectable gastric and gastro-oesophageal adenocarcinoma patients. There is an acknowledgment that the end of life criteria are met which implies a survival advantage would be lost if UK patients were denied this treatment. This would result in a significant inequity in care in the UK compared to the rest of the world	Thank you for your comment. Section 3.2 in the Final Appraisal Document refers to the unmet need people with this condition face in the UK. Additionally, section 3.14 states that the end-of-life criteria is met. The committee considered these factors in its decision making.
5	Clinical expert		UK R+D will fall behind: UK will struggle to attract multi-national studies that use chemotherapy + nivolumab as the standard arm in their design.	Comment noted.
6	Clinical expert		Concerns this decision has been made based on less than robust overall survival modelling and waning effect estimates There have been difficulties reconciling differences in opinion regarding the overall survival modelling and the waning effect between the company and the ARG.	Thank you for your comment. In section 3.9 and 3.10 in the Final Appraisal Document the committee concluded that that although the company and the ERG had different ways to model overall survival and waning effect both were reasonable.

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			However, there is an absence of actual long term data on survival and waning effect of chemotherapy + nivolumab which, in my opinion, limits the conclusions that can be drawn. Nivolumab is an agent which utilises a patient's immune system to mount an anti-cancer effect. In doing so, it also employs memory T cells which continue to provide immune protection against the cancer beyond the last dose of nivolumab. Hence, using modelling which is ordinarily used for standard chemotherapies (which does not continue to work beyond its last administration) is dubious – especially when looking at the waning effect).	
7	Clinical expert		**Practicalities in clinic:** The Keynote 590 trial testing pembrolizumab + chemotherapy was similar in design and outcomes compared to the Checkmate 649 trial. If use of Nivolumab is not approved for the gastric cancer patients, there will become a clear divide in clinic where both oesophageal/ gasto-oesophageal patients sit next to (and share notes with) gastric cancer patients. We will have created division in therapy based on anatomy (often dependent on a rough guess by the diagnostic pathway) and factors other than survival outcomes. This will become problematic	Thank you for your comment. The unmet need is described in section 3.2 of the Final Appraisal Document. Following an updated commercial agreement for nivolumab the committee recommended the use of this technology for routine use in the NHS.
8	Clinical expert		**Emphasis on long term benefits (which benefit the few) rather than shorter term benefits (which benefit most)** The natural history of this cancer is associated with a poor prognosis. Even with the introduction of nivolumab, unfortunately the prognosis for the majority of patients will remain poor. However, the cost effectiveness analysis and NICE decision not to fund for this population seems to be heavily influenced by long term survival outcomes (i.e. 5 years or more) which are only relevant to minor cohort of patients. For this specific population of patients, where the prognosis is poor (less than 18 months), should more consideration be made of the benefits of this treatment during the first 18-24 months which is relevant to the majority of patients.	Thank you for your comment. The committee was aware that the differences in modelled long-term survival had a large effect on the cost-effectiveness estimates. For this reason, it was important for the committee to discuss the uncertainty around this, see section 3.11 of the Final Appraisal Document.
9	Web comment	Lancashire Teaching Hospitals NHS foundation trust	I would like to express my dismay for this recommendation on behalf of my patients at Lancashire Teaching Hospitals NHS foundation trust. I am very concerned that this recommendation would mean that the UK falls behind in its ability to participate in global phase 3 trails as we will not be offering what is now the global standard of care. I am also concerned that the survival data used is not reflective of this	Thank you for your comment. Following an updated commercial agreement for nivolumab, this technology was recommended for routine use in the NHS, see recommendation 1.1 of the Final Appraisal Document.

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			patient group where the survival is sadly a lot less and treatment is about improving quality of life. This recommendation would create a lack of equity among oesophageal and gastric cancer patients where one group can access immunotherapy and the other can't when in reality they are similar diseases.	
10	Web comment		**Has all of the relevant evidence been taken into account?** Yes. **Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** Mostly. I was surprised to see survival was so good in the standard arm (19% at 2 years). I wonder if this is a reflection on patient selection. I would think the benefit of 2 year survival would greater than this in real world data **Are the recommendations sound and a suitable basis for guidance to the NHS?** I would like to see nivolumab available for patients with a PDL-1 CPS score of greater than 5. Currently a score of greater than 10 is required for immunotherpay use and I believe patients are missing out on effective therapy as a result.	Comment noted. Thank you for your comment. The committee noted that nivolumab with chemotherapy improved progression-free survival and overall survival compared with chemotherapy. Please see section 3.4 of the Final Appraisal Document. Thank you for your comment. At the third committee meeting, this technology was recommended for routine use in the NHS, see recommendation 1.1 of the Final Appraisal Document.
11	Web comment	Heartburn Cancer UK	**Are the recommendations sound and a suitable basis for guidance to the NHS?** HCUK believe the recommendations are sound and suitable guidance for the NHS because for this specific cohort of patients the options for quality of life and support relating to immunotherapy are very limited and this provides a vitally needed additional option. - There are very limited options for OGJ patients and this provides an additional option _ Pembro is only suitable for patients with a CPS of 10 or above, this solution gives hope to an additional cohort of patients as this Nivolumab treatment cater for a CPS of 5 or above -With such limited solutions available and chemo alone causing significant problems for a patient, this treatment provides greater life	Thank you for your comment. At the third committee meeting, this technology was recommended for routine use in the NHS, see recommendation 1.1 of the Final Appraisal Document.

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
			expectancy and greater life quality - The UK has the largest incidence of adenocarcinoma in the world, we can't exclude patients from a treatment that might work - We don't want disparity between treatment options available in Europe and the UK	
12	Web comment	The Royal College of Radiologists	**Has all of the relevant evidence been taken into account?** Yes checkmate 649 trial is a large phase 3 RCT with demonstrates the benefit of the addition of NIvolumab to chemotherapy in this patient cohort providing level 1A evidence.	Comment noted.
13	Web comment	The Royal College of Radiologists	**Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** We agree that there has been a systematic and balanced assessment of the available evidence; however the findings for cost effectiveness analysis for this population may be overly skewered towards to longer term survival outcomes (i.e. 5 years or more). For this specific population of patients, where the prognosis is poor (less than 18 months) we do not feel that sufficient consideration to the benefits for this treatment in terms outcomes have been fully considered. It would appear that although the committee acknowledged the findings of the checkmate 649 trial was generalisable to the NHS, the outcome to not fund was weighted more heavily on the long term remission / cure which is represents very small proportion of patients. The issue appears to be predicated on the role of maintenance therapy beyond 2 years which is uncommon and further discussion with the commercial company on this would be encouraged to mitigate the ICER threshold. We note and agree with the conclusion of the end of life criteria being met. We recognise the uncertainty and difficulties in modelling beyond this period of time and we note the remit for these decisions as outlined in the technology appraisal. However, as part of this process there would need to be consideration towards the “natural history of the disease”. The population involved with the pre-defined characteristic, as noted by the committee have “a poor prognosis and a large impact on quality of life.” As noted by the committee these patients have a higher burden of care, throughout their treatment journey including, but not restricted to issues relating to poor nutrition due to poor intake as a direct complication of the disease. The improvement in the ORR would invariably lead to improvements in quality of care and reduce the	Thank you for your comment. The committee was aware that the differences in modelled long-term survival had a large effect on the cost-effectiveness estimates. For this reason, it was important for the committee to discuss the uncertainty around this, see section 3.11 of the Final Appraisal Document. The committee noted that nivolumab with chemotherapy improved progression-free survival and overall survival compared with chemotherapy. Please see section 3.4 of the Final Appraisal Document. Finally, this technology was recommended for routine use in the NHS, see recommendation 1.1 of the Final Appraisal Document.

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			burden on the NHS with reduced inpatient care for nutritional support, ongoing nutritional interventions e.g maintenance of feeding tubes / stents etc. the burden of supportive care in this cohort of patients is considerable (and costly) and reflects the natural history of the disease. Furthermore, the improved responses (e.g. 60% vs 45% response rate in PDL- CPS ≥ 5 and 12% vs 7% complete response in PDL- CPS ≥ 5 in the chemo plus Nivo vs. chemo alone group) will facilitate the potential use of alternative and less costly treatments to further improve patient outcomes, for instance increased use of targeted therapies like radiotherapy to reduce the need for further systemic therapies either to the primary disease1,2 or metastasis directed therapies. As outlined by the committee the role of maintenance Nivolumab beyond 2 years in uncertain but it may facilitate more access to alternative options to improve / sustain outcomes. We would also like to highlight that this indication would expand access to the use of effective immunotherapies in this group of patient. Currently, based on the NICE TA 737, patients with HER 2 negative oesophageal and GOJ adenocarcinoma which express PD L1 with a CPS of 10 or more are eligible to receive pembrolizumab with systemic chemotherapy. The approval of the current application will enable and expanded cohort to include the same group of patients, but also those gastric cancer and those who express PD L1 with CPS of 5 or more to access this treatment. From a clinical perspective, this would enable a consistent and more equitable access to an effective treatment for more patients in this cohort which would further improve outcomes. It is unclear if the detail on health burden has been accounted for, but as it may have significant implications on the NHS costs, we think that it should be considered and included in the overall evaluation. It may be a specific area for research / prospective data collection to ascertain the impact on clinical, patient quality of life and health care costs prospectively. In this context, without taking into account the implications of the burden on healthcare it is unclear if the assessment of the benefit of cost effectiveness has been fully addressed and it would be useful for the commercial company's analysis on this area. Ref	

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			1. Hingorani M, Dixit S, Johnson M, et al. Palliative Radiotherapy in the Presence of Well-Controlled Metastatic Disease after Initial Chemotherapy May Prolong Survival in Patients with Metastatic Esophageal and Gastric Cancer. Cancer Res Treat. 2015;47(4):706-717. doi:10.4143/crt.2014.174 2. SP Parikh, R Goody, O Coen, G Radhakrishna, P Hatfield, M Hingorani. Palliative radiotherapy to the oesophagus: Less is just as good. Clin Onc 2019. 31(suppl1)	
14	Web comment	The Royal College of Radiologists	**Are the recommendations sound and a suitable basis for guidance to the NHS?** In this instance, we feel that more detailed analysis on the cost effectiveness in this vulnerable group of patients is required and we would encourage ongoing dialogue and review of the decision. We think that to not approve this drug on the current analysis would significantly disadvantage this patient group and potentially lead to considerable health inequalities and poorer outcomes for our patients compared to others globally. The option, for ongoing prospective analysis on impact on health care costs and outcomes may be mutually useful to both NHS and commercial partners and should be pursued as an active area of research / innovation.	Thank you for your comment. At the third committee meeting, this technology was recommended for routine use in the NHS, see recommendation 1.1 of the Final Appraisal Document.
15	Web comment	The Royal College of Radiologists	**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?** No	Comment noted.
16	Web comment	Srinivasan Madhusudan	**Has all of the relevant evidence been taken into account?** Yes	Comment noted.

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			Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Yes **Are the recommendations sound and a suitable basis for guidance to the NHS?** I have some reservations as stated below: Improvement of survival outcomes for upper GI cancers in an area of unmet need and a priority for GI cancer patients in the UK. In gastric cancer patients, there is currently no chemotherapy plus immuno-oncology options for patients. If Nivolumab is not available for this group of patients, it will seriously limit survival outcomes for these patients. In patients with CPS between 5-10 there is currently no immuno-oncology treatment options. If Nivolumab is not available, it will seriously limit survival outcomes for these patients. Availability of chemotherapy + immuno-oncology treatments for oesophageal and GOJ tumours but not for gastric cancer patients is unfair to patients and denies them a clinically effective treatment for this devastating disease. I have treated gastric cancer patients with Nivolumab in clinical trials and have seen their lives transform for the better whilst on therapy. Nivolumab is a standard of care therapy in Europe and elsewhere. Not having this treatment available for patients in the UK will impact out standards of care. UK is heavily involved in cancer clinical trial research. To not be able to recommend such UK trial generated treatment, will in the long term, also adversely affect UK's ability to attract future cancer clinical trials. **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?** None	Comment noted. Thank you for your comment. Section 3.2 in the Final Appraisal Document refers to the unmet need people with this condition face in the UK. The committee was aware that nivolumab plus chemotherapy improved progression free survival and overall survival. The committee recommended the use of this technology for routine use in the NHS. Please see recommendation 1.1 and section 3.4 of the Final Appraisal Document. Comment noted.

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17	Web comment	Wales Cancer Network, the South Wales OG Cancer MDT and the UK and Ireland Oesophago-gastric Group (registered CIO)	**Has all of the relevant evidence been taken into account?** Yes **Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?** No, the over reliance on long term curability of outcomes following systemic therapy of advanced OG cancer is an unreasonable model **Are the recommendations sound and a suitable basis for guidance to the NHS?** No this will not allow for a very effective treatment for patients with advanced OG cancer and not any immunotherapy for gastric cancer (which pembrolizumab is not licensed for) **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?** Yes one should look at hazard ratios of differential outcomes compared with standard chemotherapy or median survival, not 5, 10, 20 year survival given the uncertainty regarding long term outcomes	Comment noted. Comment noted. Thank you for your comment. The committee recommended the use of this technology for routine use in the NHS. Please see recommendation 1.1 of the Final Appraisal Document. Thank you for your comment. The committee was aware that the differences in modelled long-term survival had a large effect on the cost-effectiveness estimates. For this reason, it was important for the committee to discuss the uncertainty around this, see section 3.11 of the Final Appraisal Document.

Response to the Appraisal Consultation Document 2

Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

ID1465

Bristol-Myers Squibb Pharmaceuticals Ltd

April 2022

Contents

Executive summary

This document provides a response to the Appraisal Consultation Document 2 (ACD2) describing the use of nivolumab in combination with chemotherapy (NIVO+CHEMO) for patients with untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

BMS is disappointed with the Committee's draft recommendation, particularly given the conclusion that an ICER of £49,840 (which comes in below the threshold of £50,000 per QALY gained) should be used in decision making. In response to the ACD2, this response addresses the key areas of uncertainty outlined by the Appraisal Committee: that it is unclear how long people lived beyond the CheckMate 649 trial period and the duration of nivolumab's treatment benefit. Additionally, further clarification of the modelling approach used in the BMS base case is provided.

In the ACD2 the committee agrees that NIVO+CHEMO addresses an unmet clinical need. While pembrolizumab has recently been recommended by NICE, this recommendation includes only adults with oesophageal cancer and gastro-oesophageal junction cancer whose tumours express PD-L1 with a combined positive score (CPS) of 10 or more,[1] and excludes patients with either gastric cancer or PD-L1 CPS scores <10. In this document, BMS has provided the following evidence:

- Additional detail describing the approach to survival modelling and the rationale for this approach (Section 1)
- Overall survival estimates at 5 years, 10 years, and 20 years, respectively (Table 12)
- Cost-effectiveness analyses including treatment waning scenarios, deterministic and probabilistic ICERs (Table 10 and Table 11)

Of note, survival estimates in Table 12 are similar to the ERG's, with only minor differences between scenarios. That estimates are similar goes some way to reducing uncertainty around the duration of survival anticipated for patients in this population.

Based on clinical evidence, BMS' preferred treatment waning scenario of 6.5 years was applied resulting in a deterministic ICER of £48,847 whereas the ICER in the BMS base case with no treatment waning was £45,383. This assumption aligns with a similar precedent used in TA737 where waning ended at 7 years. Further, all scenarios other than the most conservative treatment-waning scenario (waning at 5 years) resulted in deterministic ICERs below the £50,000/QALY willingness-to-pay threshold. It is intended that these new analyses allay the remaining uncertainty around cost-effectiveness.

1 Explanation of modelling approach

BMS used models of overall survival (OS) and progression free survival (PFS) within the economic model to estimate the time spent by patients in the pre- and post-progression model health states until death. These models were fitted following the guidance of the NICE Decision Support Unit (DSU) in Technical Support Document 21 (TSD21) – "Flexible Methods for Survival Analysis."[2] In particular, general recommendation III was implemented to ensure the plausibility of model extrapolations. This recommendation reads in part:

> ***Incorporation of background mortality.*** *Incorporating background mortality into survival models is recommended because it helps avoid extremely implausible projections. This is true for standard parametric models, FPMs, mixture models, landmark models and piecewise models and is* essential *for cure models. Background mortality rates should either be incorporated when making the extrapolation, or used as a sense-check when plotting the marginal survival, and particularly the marginal hazard functions that have been extrapolated.*
>
> **TSD21[2], 7.1 III, pp 89**

BMS incorporated the background rate of mortality in extrapolation models. The baseline hazard was estimated using annual rates of mortality from national lifetables contemporary to the CheckMate 649 (CM649) trial.

1.1 BMS model structure – Relative Survival / Excess Mortality

The model structure chosen by BMS is defined by the following fundamental hazard equation, following the precedence of Nelson et al. (2007).[3] Consider an all-cause (AC) hazard function $\lambda_{AC}(t|\boldsymbol{x_i})$ for an individual with covariates $\boldsymbol{x_i}$. Assume that this hazard is composed of two independently competing hazards, a baseline (BL) hazard $\lambda_{BL}(t|\boldsymbol{x_i})$ and an additional, conditional excess (E) hazard $\lambda_E(t|\boldsymbol{x_i})$. If the excess hazard function is independent of the baseline hazard, then the unconditional marginal excess hazard function $\lambda_E(t)$ may be defined, and the all-cause hazard function is given by:

$$\lambda_{AC}(t|\boldsymbol{x_i}) = \lambda_{BL}(t|\boldsymbol{x_i}) + \lambda_E(t) \qquad (1)$$

The baseline hazard function, obtained from national life tables, is defined. Parameters of a model describing $\lambda_E(t)$ are then fitted in a manner similar to conventional survival modelling, assuming that this hazard can be described by a particular statistical distribution family, such as Gompertz.

When fitted in this manner using these "proper" survival distributions, $\lambda_E(t)$ must be strictly positive or zero for all times after model initiation. This means that the total hazard is constrained to be *at minimum* the baseline hazard. For the time horizon for all models presented by BMS, the excess hazard has been greater than zero, i.e., patients are at greater risk of dying than the matched general population.

In application within the cost effectiveness model, the following formula was used:

$$S_{AC_{Marginal}}(t) = S_E(t) \int S_{BL}(t|\boldsymbol{x})\, dG(\boldsymbol{x}) \quad (2)$$

The all-cause survival curve is the product of the survival function due to the excess hazard and the average survival due to the matched baseline (lifetable) hazard. In the initial models submitted by BMS in February 2021 the trial data was represented directly up to the 6.44-month cut point using the Kaplan-Meier estimator, and this relative survival structure was not implemented until after the cut. At the request of the ERG at the clarifications stage, this initial period of the model was converted to relative survival using the above formula to estimate $S_E(t)$. $S_E(t)$ is estimated by dividing the Kaplan-Meier estimator of $S_{AC_{Marginal}}(t)$ by the matched marginal baseline survival in the CM649 population.

1.2 Rationale for model structure

As detailed in TSD21,[2] the benefit of incorporating background mortality into survival models is to enforce a minimum hazard upon the model so that, as the population ages, the estimated hazard in the treatment group does not dip below that of the general population. This was relevant to the modelling of NIVO+CHEMO for the first-line advanced upper-GI adenocarcinoma population as it was assumed that a fraction of patients would experience long-term survival. As mortality hazard decreased during the trial, it was necessary to incorporate an aging-related rise in hazard, based on external data. If this had not been done, there would have been an intercept between the model-predicted hazards and the mortality hazard of the general population.

Simple parametric models can intercept the general-population mortality hazard, breaking the validity of long-term survival assumption. The post-hoc modification (i.e., identifying the point at which the parametric model intercepts the general-population mortality and setting the model to follow this rate from this point of intercept onwards) has the drawback of underpredicting the hazard. Conversely, models fitted with the relative survival framework will never intercept the general population hazard, thus preserving their face validity and not underpredicting the survival. They also allow for free selection of more complex hazard functions. This was important in this indication, where data from CM649 demonstrated a sharply decreasing hazard profile for both PFS and OS from their peaks within the first year of the trial.

The piecewise Gompertz model fitted particularly well to these data: it had top-ranking internal “goodness-of-fit” statistics (AIC, BIC), which was considered plausible by clinical experts at the second ACM. This survival function was also the committee’s preferred estimate for decision making.[4] In a relative-survival context, the BMS base case cannot intercept the general population mortality.

Further, while the ERG’s model predicted survival hazard to be equal to the general population at 10.3 years, the company model predicts that the hazard for the NIVO+CHEMO arm is double that of the general population at this time point. Table 1 compares the percentage of people alive in both arms at the time the ERG’s survival hazard becomes equal to the general population hazard. As pointed out previously, the hazard from BMS’

base-case model is greater than the general population, therefore, the percentage of the surviving population will be less in the treated vs. general population.

Table 1 Comparison of the percentage survival population from the base case model at the time when the predicted survival hazard from ERG modified scenario becomes equal to the general population

Scenario		Intercepts with general population hazard	Percentage of people alive at the time of intercept (when ERG scenario meets the general population)
BMS base case (no treatment waning)	NIVO+XELOX	N/A	[redacted]
	XELOX	N/A	[redacted]
ERG modified case (treatment waning at 5 years)	NIVO+XELOX	10.3 years	9.1%
	XELOX	12.9 years	1.3%

N/A – not applicable.

1.3 ERG model structure – Curtailment

At the time of the second committee meeting, the ERG expressed uncertainty around how BMS had implemented the relative survival models within the economic model. These issues were addressed in a virtual meeting between BMS and the ERG.

The ERG raised two areas of uncertainty:

- It was not aware that the factorisation of the two survival components (baseline and excess) as in equation *(2*) was a consequence of the assumption of independently additive hazards made in equation *(1*).

- Misunderstanding this first point, the ERG assumed that the relative survival-curves input to the model $S_E(t)$ were the marginal all-cause survival curve $S_{AC_{Marginal}}(t)$.

As a result, in implementing their modification of BMS' base-case model, the ERG used the relative survival curves as all-cause survival curves, systematically under-estimating hazard and over-estimating survival. Without factoring in the baseline hazard of the general population, the model will not be constrained to a hazard that is plausible, i.e., one that is consistently higher than the baseline hazard derived from lifetables. It followed that the intercept with lifetables occurred at the point at which the excess hazard is equal to the baseline hazard (in fact, this is the point at which the BMS model predicts *twice* the baseline hazard). The ERG model then curtails the distribution by setting the hazard to the lifetable hazard, as discussed above. This incorrect intercept led to questioning of the validity of the Gompertz model and alternative scenarios were presented.

Following BMS' provision of further materials to the ERG after the ACM2 and a subsequent virtual meeting, the ERG confirmed that they understood the approach used in BMS' economic model and commented that it would take time to replicate this method. Their feedback was that the OS estimates are plausible and double counting of events is unlikely. This is a correction of the initial assessment at ACM2, where the ERG thought that the approach overestimated the hazard and underestimated overall survival. BMS anticipates that the ERG will conclude that the BMS modelling approach is (1) a robust method and (2) has been implemented as described.

Despite the misunderstanding noted above, results from the ERG model are presented here. This demonstrates that the cost effectiveness results are in fact similar between the two models.

2 Treatment waning

Currently, there is a lack of evidence of treatment waning in relation to immunotherapies, and limited guidance on how treatment waning should be considered for the purpose of health technology assessment. This can increase uncertainty around, and risk of bias of, estimates.

The assumption that the survival benefit of treatment wanes over time may be appropriate for some indications (e.g., where there is extensive long-term survival) and therapies (e.g., standard chemotherapy, where the patient's immune system is not harnessed to achieve tumour control). However, this may not be appropriate for indications with shorter survival outcomes and where a post-treatment survival benefit is plausible.

Nivolumab potentiates immune-mediated tumour destruction, stimulating the patient's own immune system to mediate an anti-tumour response against cancer cells (in the same way that it would any other "foreign" cell), resulting in destruction of the tumour. Hence, it is biologically plausible that patients would experience treatment effect after treatment is stopped.[5]

There is no evidence that a treatment-waning effect occurs instantaneously with NIVO+CHEMO for gastro-oesophageal adenocarcinoma. That is, the hazard in this arm does not immediately return to that of the CHEMO arm after treatment stops. This has been validated with clinical experts. For CM649, data is available for a minimum follow-up of 24 months. Maximum follow-up for the NIVO+CHEMO arm is 49.5 months.[6] For this period of follow-up, no evidence of treatment waning is observed in CM649 (see Figure 1).

[redacted]

Figure 1. CheckMate 649 [redacted] database lock: Overall survival (OS) for patients with PD-L1 CPS ≥5[7]

Exploratory analysis assesses progression-free survival on subsequent therapy: this is defined as the time from randomisation to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever was earlier (PFS2).

PFS2 favoured NIVO+CHEMO vs. CHEMO with a 25% reduction in risk of death or disease progression on subsequent therapy (HR 0.75, 95% CI 0.67-0.84) (Figure 2).[8] In other words, the progression-free survival benefit of NIVO+CHEMO vs. CHEMO appears to endure into patients' subsequent line of treatment.

Figure 2. CheckMate 649 [redacted] database lock: progression-free survival on subsequent therapy (PFS2) for all randomised patients[8]

Along this line, clinical experts in the second ACM explained that a long-term benefit after treatment with nivolumab had stopped was plausible. In the undertaking on TA737 for pembrolizumab (another anti-PD-1 agent) with chemotherapy, one clinical expert stated that, if a patient is alive at 2 years, then it may be that their disease is in remission and may not progress in future.[1]

In summary, there is no evidence to support treatment waning for nivolumab in this indication considering clinical study data, biological plausibility and clinical expert opinion. Therefore, the company's base case did not include treatment waning, but such analyses have been explored in this response as scenarios, in line with the ACD2 request.

While it is acknowledged that implementing treatment waning in the model produces a conservative analysis, put forward to form an upper-bound ICER, it is important that these scenarios are viewed in this light. NICE's new draft methods guide[9] 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."*

2.1 Sustained benefit of Checkpoint Inhibitors

There is increasing evidence of long-term benefit of PD-(L)1 inhibition in advanced solid tumours. While long-term follow-up data is limited in the gastrointestinal space, we might look to data for other tumour types.

In advanced melanoma, nivolumab monotherapy and in combination with ipilimumab was investigated for previously untreated patients in the CheckMate 067 (CM067) trial. Survival outcomes to 6.5 years (78 months) have been published by Wolchock et al.[10]

In this trial, patients were not required to stop nivolumab therapy at a pre-specified time point.[11] However, among patients in the nivolumab-monotherapy arm who were alive at 6.5 years, only 7% (8/122) were receiving study therapy while 25% (n=30) were receiving subsequent systemic therapy, and 69% (n=84) were treatment-free.[10] In this arm, median duration of treatment among those who had (1) discontinued nivolumab and (2) were alive or

had died on subsequent systemic treatment (n=237) was 8.6 months (range 0-79.8 months). The mortality hazard profile (that is, the risk of dying generated from pseudo patient-level data obtained from the OS KM curves of CM067 which are shown in Figure 3, bottom panel) was monotonically decreasing despite the high proportion of patients no longer on study treatment.

There is also long-term follow-up data available for nivolumab monotherapy and in combination with ipilimumab for advanced non-small-cell lung cancer (NSCLC). This may be more applicable to the advanced upper-GI cancer population than melanoma data given that advanced NSCLC and advanced upper-GI cancers are both moderately immune sensitive and have similar survival expectations.

CheckMate 057 (CM057) investigated nivolumab monotherapy vs. docetaxel in previously treated non-squamous NSCLC. Five-year outcomes were presented by Borghaei et al.[12] and are reproduced in **Error! Reference source not found.** which also includes the data for CM067.

Figure 3. Overall Survival and all-cause mortality hazard profiles of CheckMate 057 Nivolumab (Nivo) arm, CheckMate 067 Nivolumab arm, and CheckMate 649 CPS ≥ 5% nivolumab + chemotherapy (NC) subgroup

Top panel: Kaplan-Meier survival estimates, digitised from Borghaei et al. (CM057 – nonsquamous)[12]; Wolchock et al. (CM067)[10], and generated from CM649 patient-level data. Bottom panel: B-spline estimators of hazard for pseudo patient-level data from CM 057 and 067, and patient-level data from CM649. This figure showing the risk of an event at each time point within the respective trials).

Patients in CM057 were not required to discontinue treatment at a pre-specified time point. At 5 years, 50 of 427 patients assigned to nivolumab were still alive, including 18 who remained on treatment.[12]

The overall survival curve for CM057 is more similar to that of CM649 (CPS ≥ 5%) than that of CM067 (**Error! Reference source not found.**). There is deviation at the start, where the effect of the addition of chemotherapy to nivolumab in the CM649 treatment regimen may be preserving patients. After this, patients in CM649 experience an increased hazard versus CM057, until the overall survival rates equalise at approximately 18 months.

After 18 months, the two curves are very similar. The hazard profile of CM057 continues to decrease smoothly to the end of follow-up. This monotonic decline starts at approximately year two and does not show any tendency to increase. The CM057 and CM649 survival curves are similar over the 24-48-month period, therefore, it might be expected that the long-term benefit seen in CM057 beyond 48 months might also be seen in CM649.

Long-term survival benefit has been observed in advanced-melanoma patients treated with pembrolizumab, another anti-PD-1 therapy. The long-term outcome in KEYNOTE-006 (KN006)[14] is generally consistent with the outcomes seen in the melanoma cohort of KN001[11] which, in contrast to KN006, did not include a 2-year stopping rule. This can be seen in the digitised KM data of overall survival as shown in Figure 4.

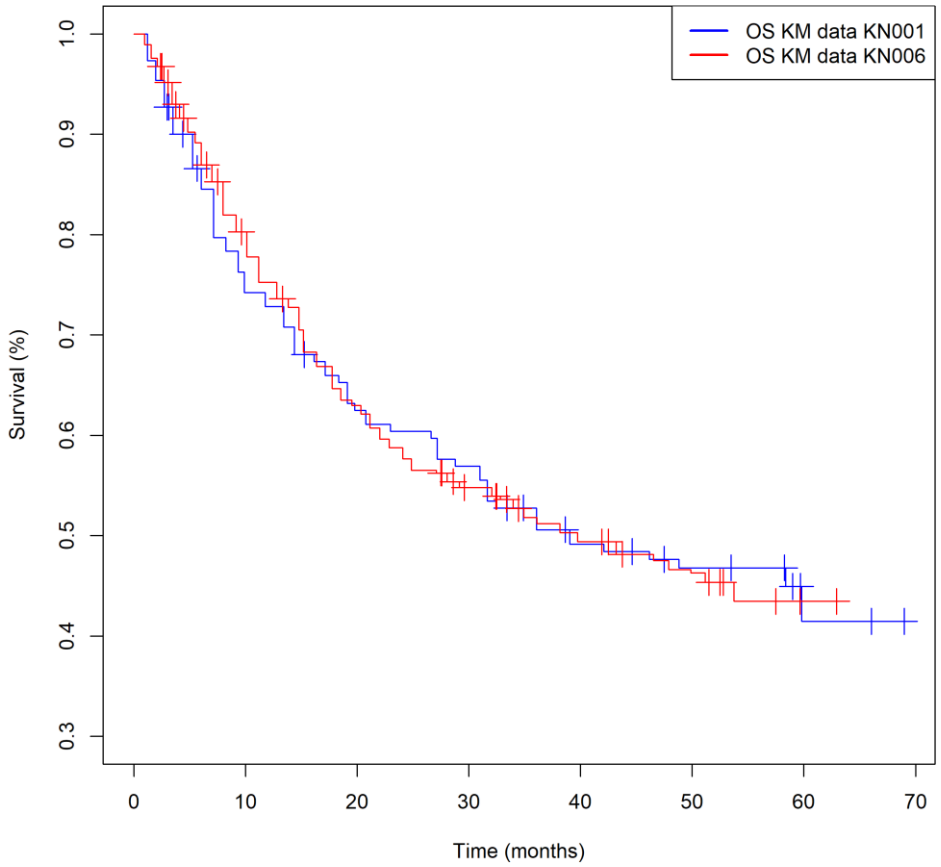

Figure 4. Digitised KM data of overall survival of KEYNOTE-001 (no stopping rule) and KEYNOTE-006 (2-year stopping rule) based on Robert at al.[14] and Hamid et al.[11]

Several conclusions are drawn from this review:

- Long-term (≥5 years) survival with nivolumab treatment is seen in non-GI cancers, such as NSCLC, where there is longer follow-up available, with most survivors having discontinued study therapy.

- In CM067 and CM057, there is no evidence that discontinuation results in a rise in the marginal hazard among long-term survivors. In fact, hazards continue to decrease towards background rates of mortality.

- The KN006 trial included a 2-year stopping rule whereas KN001 did not. However, the long-term benefit seen in the two trials is comparable. Given that pembrolizumab and nivolumab are similar molecules (both anti-PD-1 agents), BMS assumes that applying a stopping rule would not have significantly altered the long-term benefit seen in CM067.

- Given that 6.5 years is the longest available follow-up data for CM067, 6.5 years is the BMS conservative estimate for treatment waning in the first-line upper GI adenocarcinoma indication. Supporting this assumption, the hazard profile from CM649 remains steady and predictable for the follow-up period available (minimum follow-up of 24 months, maximum follow-up for the NIVO+CHEMO arm is over four years)[6].

- This conservative assumption of 6.5 years is in line with TA737 where a treatment waning for pembrolizumab of up to 7 years was applied.

2.2 Long-term hazard profiles

Necessarily, if an economically relevant fraction of the patient population is preserved, models incorporating long-term survival will approach general population mortality, and the absolute difference in hazards between treatments among those surviving at these times would be expected to diminish. If there was a limiting excess hazard applicable to survivors on all treatments, this would be approached asymptotically, and the difference in hazards between treatments would further diminish until negligible. This is a form of "treatment effect waning" independent of the waning supposed due to cessation of treatment.

Mitry et al. (2008)[15] performed a retrospective study of survival in stomach cancer in England and Wales from the 1980s to 2001. In this study, "Ten-year survival for those diagnosed during 1991-1995 was 9-10%, not much less than the 5-year survival rate, suggesting that most of the excess mortality in stomach cancer patients occurs in the first 5 years." Whilst this study included patients diagnosed at any stage, a low rate of mortality must be reflected in any patients with advanced cancer surviving to this time.

Within the company economic model, the hazard of mortality at year 5 upon the chemotherapy arm is predicted to be approximately 23 times that of the general population, and 11 times that of the general population (labelled as lifetable on the plot), upon the NIVO+CHEMO arm (Figure 5).

Figure 5. Survival and hazard profiles in the Company Model when applying the ERG waning rule

Top panel: overall survival from CheckMate 649 CPS ≥ 5% subgroup (Kaplan-Meier estimator - "KM"), predicted by company model without treatment waning (light extrapolations), and predicted by company model when applying a switch of hazard profile on nivolumab + chemotherapy ("NC") to the chemotherapy ("Chemo") hazards at year 5 (dark blue extrapolation). Bottom panel: hazards of mortality by any cause estimated within trial using B-spline estimator ("Bspline") and model predictions as for top panel.

At this point (year 5), extrapolation from maximum follow-up in CM649 is less than one year, and both the absolute and relative magnitude of these mortality hazard estimates are unlikely to be significantly modified with additional follow-up.

With reference to these “fixed” points, and to be consistent with the assumption of similar (low) long-term residual excess mortality, the absolute difference between the two hazards would be expected to reduce over the following period.

In addition, the excess hazard would be expected to reduce in both arms, with that of the chemotherapy arm reducing at a greater absolute rate. i.e., the difference in hazard between the NIVO + CHEMO arm or CHEMO arm vs the general population reduces. This implies that longer a patient is alive the more likely that he/she reaches normal life expectancy. This is the profile demonstrated in the BMS base case (Figure 5) and is strongly violated by the ERG approach to treatment waning, discussed below.

2.3 ERG approach to treatment waning

In the ERG’s revision to the BMS model, treatment waning was implemented in a simplistic manner, by applying a strict switch of the XELOX hazard profile onto the NIVO+CHEMO hazard profile at an arbitrary time, that is 5 years post treatment initiation.

The hazard profile upon NIVO+CHEMO implied by this switch is highly implausible, as demonstrated in Figure 5, which overlays the model predictions output by the model upon estimators of survival and hazard from the CM649 CPS ≥ 5% subgroup.

When applied to the BMS base case relative survival models, the ERG waning scenario results in an instantaneous doubling of the NIVO+CHEMO hazard of mortality from 0.178 / month to 0.372 / month, returning it to a level last predicted approximately 2.5 years post treatment initiation.

This is well within the observed trial period, where hazards were observed to be rapidly declining. There is nothing within the trial data which indicates that such a sudden, sustained increase in hazard at 5 years is likely. The evidence suggests that a scenario where treatment waning is applied at 5 years to NIVO+CHEMO (using the XELOX hazard profile) would not be appropriate or plausible in this patient population

3 Cost-effectiveness modelling results

3.1 Base case analysis

The previously presented base case analysis is a conservative estimate of the cost-effectiveness of NIVO+XELOX versus XELOX in the NHS England setting. After clarification with the ERG, it is anticipated that the remaining uncertainty has been addressed and the company believe that the survival modelling in the company base case analysis has been undertaken according to best practice guidelines and generates plausible outcomes that are in line with the ERG’s estimates.

Further, as outlined in Section 2, any potential effect of treatment waning upon the hazard progression is captured within the trial-specific survival models, as protocol dictated a discontinuation of nivolumab at 2 years, and external evidence suggests that the hazard profile continues to develop smoothly after treatment discontinuation in other nivolumab indications.

In summary, the survival assumptions for the company base case are that:

- PFS modelled by relative survival, using rates from Kaplan-Meier estimator until month 6.44, and a log-normal extrapolation thereafter, informed by the CPS ≥ 5% subgroup of CM649. The NIVO+XELOX and XELOX models are derived independently. The relative survival is multiplied by baseline (lifetable) survival to inform all-cause PFS

- OS modelled by relative survival, using rates from Kaplan-Meier estimator until month 6.44, and a Gompertz extrapolation thereafter, informed by the CPS ≥ 5% subgroup of CM649. The NIVO+XELOX and XELOX models are derived independently. The relative survival is multiplied by baseline (lifetable) survival to inform all-cause OS

- There is no possibility of intercept with general population mortality, as this is added into the models during evaluation using the relative survival approach. This approach incorporates excess as well as background mortality to give an all-cause mortality that at no time is equal to the general population

- There is no modification of the survival curves to equalise hazards (treatment waning).

Total discounted costs associated with NIVO+XELOX (with PAS), accrued over the modelled time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with comparator XELOX were lower ([redacted]). Incremental discounted costs for were predicted to be [redacted], under base case assumptions. The incremental discounted QALYs were predicted to be [redacted]. The resulting ICER estimate was £45,383 per QALY. The results of the base-case analysis (without treatment waning assumption) are summarised in Table 2. The probabilistic analysis (PSA) results of the base case analysis without any treatment waning assumption are shown in Table 3.

Table 2. Results of base case analysis without treatment waning

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,383**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

Table 3. PSA results of base case analysis without treatment waning

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,873**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

3.1.1 Comparison with ERG scenarios

For the purpose of demonstrating the sensitivity of the model to alternative assumptions, the model incorporating ERG modifications was run. The survival assumptions used for this model are that:

- PFS modelled by relative survival, using rates from Kaplan-Meier estimator until month 6.44, and a log-normal extrapolation thereafter, informed by the CPS ≥ 5% subgroup of CM649. The NIVO+XELOX and XELOX models are derived independently. The relative survival is NOT multiplied by baseline (lifetable) survival, the relative survival directly informs all-cause PFS until intercept with the general population mortality hazard

- OS modelled by relative survival, using rates from Kaplan-Meier estimator until month 6.44, and a Gompertz extrapolation thereafter, informed by the CPS ≥ 5% subgroup of CM649. The NIVO+XELOX and XELOX models are derived independently. The relative survival is NOT multiplied by baseline (lifetable) survival, the relative survival directly informs all-cause OS until intercept with the general population mortality hazard

- Intercept with the general population mortality occurs in both arms, and at this point the curves are modified to use the general population mortality hazard

- There is no arbitrary modification of the survival curves to equalise hazards (treatment waning)

With the ERG preferred modifications to the model the total discounted costs associated with NIVO+XELOX (with PAS), accrued over the modelled (lifetime) time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with comparator XELOX were lower ([redacted]). Incremental discounted costs were [redacted]. The incremental discounted QALYs for NIVO+XELOX were predicted to be [redacted]. The resulting ICER estimates for NIVO+XELOX were £41,738 per QALY. The results of the ERG modified scenario without any treatment waning assumption are summarised in Table 4.

Table 4. Results of ERG modified scenario analysis without treatment waning

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]				
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£41,738**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

PSA results of the ERG modified scenario analysis without any treatment waning assumption are shown in Table 5. PSA indicates that NIVO+XELOX has a [redacted]% probability of being cost-effective with a willingness to pay threshold of £50,000.

Table 5. PSA results of ERG modified scenario analysis without treatment waning

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]				
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£42,939**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

3.2 Treatment waning

A scenario incorporating treatment waning was run, as described in Section 2. In brief, the hazard of mortality by any cause upon the NIVO+XELOX arm was assumed to be modified by a time-varying hazard ratio informed by CM649 until intercept with the hazard of the XELOX arm.

As reasoned in Section 2.1, this treatment waning profile started at 6.5 years, the time of greatest follow-up of CM067 as until this time the continued smooth reduction in marginal hazard is known within this external population, and there is no reason to believe that the CM649 hazard profile requires modification to be consistent with these external data. For this this reason, a scenario based on treatment waning at 6.5 years has been applied. In addition, this assumption would align with a similar precedent used in TA737 where waning ended at 7 years for pembrolizumab in a similar patient population.

The effective modelled rise in hazard after this period remains uncertain, and these results should be viewed as a response to the arbitrary and implausible scenario presented by the ERG in which the modelled hazard more than doubles and dramatically rises at 5 years. The company does not take the position that this modelled loss of treatment effect should be expected but wishes to demonstrate the effect of this uncertainty upon the decision problem using the best available evidence.

The total discounted costs associated with NIVO+XELOX (with PAS), accrued over the modelled (lifetime) time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with comparator XELOX were notably lower ([redacted]). Incremental

discounted costs for NIVO+XELOX was reduced to [redacted] (versus XELOX), under base case assumptions. The incremental discounted QALYs for NIVO+XELOX were predicted to be [redacted]. The resulting ICER estimates for NIVO+XELOX were £48,847 per QALY. The results of the base-case analysis with treatment waning assumption are summarised in Table 6.

Table 6. Results of base case analysis with treatment waning at 6.5 years

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£48,847**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

PSA results of the base case analysis with treatment waning assumption are shown in Table 7. The PSA indicates that NIVO+XELOX has a [redacted]% probability of being cost-effective with a WTP of £50,000.

Table 7. PSA results of base case analysis with treatment waning at 6.5 years

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£51,174**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

3.2.1 Comparison with ERG scenarios with treatment waning

The ERG treatment waning scenario was re-run to demonstrate sensitivity to the ERG's assumptions. This scenario consisted of a modification of the ERG Gompertz model with modification of the NIVO+XELOX all-cause mortality hazard, set equal to the XELOX hazard at 5 years until time horizon.

The total discounted costs associated with NIVO+XELOX (with PAS), accrued over the modelled (lifetime) time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with comparators were notably lower ([redacted]). Incremental discounted costs for NIVO+XELOX was [redacted] (versus XELOX). The incremental discounted QALYs for NIVO+XELOX were predicted to be [redacted]. The resulting ICER estimates for NIVO+XELOX were £49,840 per QALY. The results of the ERG modified scenario with treatment waning assumption are summarised in Table 8.

Table 8. Results of ERG modified scenario analysis with treatment waning at 5 years

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,840**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

PSA results of the ERG modified scenario analysis with treatment waning assumption are shown in Table 9. PSA indicates that NIVO+XELOX has a [redacted]% probability of being cost-effective with a WTP of £50,000.

Table 9. PSA results of ERG modified scenario analysis with treatment waning at 5 years

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£51,772**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

Deterministic and probabilistic results (including probability of cost-effectiveness) for various starting points of treatment waning for the company's base case and the modified ERG base case are provided in Table 11 and Table 11.

Table 10. Deterministic results for various starting times of waning – comparison of base case scenario with ERG modified scenario

Scenario	Treatment waning starting at			
	5 years	6.5 years	8 years	9 years
Base case	[redacted]	[redacted]	[redacted]	[redacted]
ERG modified base case	[redacted]	[redacted]	[redacted]	[redacted]

Table 11. PSA results for various starting times of waning – comparison of base case scenario with ERG modified scenario

Scenario	Treatment waning starting at							
	5 years		6.5 years		8 years		9 years	
	ICER	Prob of CE	ICER	Prob of CE	ICER	Prob of CE	ICER	Prob of CE
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG modified base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CE: cost-effective; ICER: incremental cost-effectiveness ratio; Prob: probability;								

3.3 Model predicted survival

Survival at key time points from the above scenarios are given in Table 12. To avoid confusion regarding the reduction of mortality hazards towards the general population, and the survival rates in this population, the general population survival from the model is also presented in Table 12.

It is of note that the survival estimates in Table 12 are relatively similar, with only minor differences between scenarios, providing certainty around the duration of survival anticipated for patients in this population.

Survival at 20 years for NIVO+XELOX ranged from 3.10% (ERG treatment waning at 5 years) to 5.86% (ERG no treatment waning) compared to 54.28% in the general population. The company base case analysis predicts survival of 4.61% (no treatment waning), which lies between the values presented to clinical experts (i.e. 5.9% Gompertz, 3.1% Gompertz with treatment waning, and 0.5% generalised gamma). However, it should be noted that the application of a conservative treatment waning scenario had limited impact on the ICER, which increased by £3,464/QALY (£3,301/QALY in probabilistic ICER) (difference of ICER from base case treatment waning starting at 6.5 years compared to ICER from base case with no treatment waning).

Table 12. Survival at key time points from the base case and ERG modified scenario analysis

Technology	Percent alive at each time point					
	Company Base case			ERG scenario		
	5 years	10 years	20 years	5 years	10 years	20 years
Survival in general population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without waning						
NIVO+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With waning at 5 years						
NIVO+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With waning at 6.5 years						
NIVO+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.4 Discussion

The company believes that the base case analysis presented in Table 13 is the best available estimate of the cost-effectiveness of nivolumab + XELOX versus XELOX in the NHS England setting, presenting a deterministic ICER of £45,383 per QALY and a probabilistic ICER of £47,873 per QALY.

In this response, the company have provided overall survival estimates at 5 years, 10 years and 20 years, which are relatively similar to the ERG's, with only minor differences between scenarios. The similarity between these estimates reduces the uncertainty around the duration of survival anticipated for patients in this population. The predicted survival at 20 years (4.61%) remains above that preferred by clinical experts at the previous appraisal committee meeting. However, this value lies between the values presented to clinical experts (i.e. 5.9% Gompertz, 3.1% Gompertz with treatment waning, and 0.5% generalised gamma). Further, this aligns with previous comments from clinical experts related to the long-lasting impact of immunotherapies, as outlined in Section 2.

BMS' preferred treatment waning scenario of 6.5 years was applied resulting in a deterministic ICER of £48,847 This assumption aligns with a similar precedent used in TA737 where waning ended at 7 years.

Further, it should be noted that all scenarios explored, including those considering treatment waning at different timepoints, provide deterministic ICERs below the £50,000/QALY willingness-to-pay threshold but the most conservative treatment-waning scenario (waning at 5 years). Therefore, these analyses demonstrate that there is relatively little uncertainty around the impact of different modelling assumptions on the cost-effectiveness of nivolumab with XELOX that could inform decision making.

Table 13. Summary of cost-effectiveness analysis results

		Deterministic			Probabilistic		
		Inc. life years	Inc. QALYs	ICER (£/QALY)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Company base case	Without waning	[redacted]	[redacted]	£45,383	[redacted]	[redacted]	£47,873
	With waning at 6.5 years	[redacted]	[redacted]	£48,847	[redacted]	[redacted]	£51,174
ERG scenario	Without waning	[redacted]	[redacted]	£41,738	[redacted]	[redacted]	£42,939
	With waning at 5 years	[redacted]	[redacted]	£49,840	[redacted]	[redacted]	£51,772

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Cost-effectiveness modelling results

Base case analysis

The analyses and hence the document was updated to reflect the change in PAS from [redacted]% to [redacted]%.

The previously presented base case analysis is a conservative estimate of the cost-effectiveness of NIVO+XELOX versus XELOX in the NHS England setting. After clarification with the ERG, it is anticipated that the remaining uncertainty has been addressed and the company believe that the survival modelling in the company base case analysis has been undertaken according to best practice guidelines and generates plausible outcomes that are in line with the ERG's estimates.

Further, as outlined in Section 2, any potential effect of treatment waning upon the hazard progression is captured within the trial-specific survival models, as protocol dictated a discontinuation of nivolumab at 2 years, and external evidence suggests that the hazard profile continues to develop smoothly after treatment discontinuation in other nivolumab indications.

In summary, the survival assumptions for the company base case are that:

- PFS modelled by relative survival, using rates from Kaplan-Meier estimator until month 6.44, and a log-normal extrapolation thereafter, informed by the CPS ≥ 5% subgroup of CM649. The NIVO+XELOX and XELOX models are derived independently. The relative survival is multiplied by baseline (lifetable) survival to inform all-cause PFS

- OS modelled by relative survival, using rates from Kaplan-Meier estimator until month 6.44, and a Gompertz extrapolation thereafter, informed by the CPS ≥ 5% subgroup of CM649. The NIVO+XELOX and XELOX models are derived independently. The relative survival is multiplied by baseline (lifetable) survival to inform all-cause OS

- There is no possibility of intercept with general population mortality, as this is added into the models during evaluation using the relative survival approach. This approach incorporates excess as well as background mortality to give an all-cause mortality that at no time is equal to the general population

- There is no modification of the survival curves to equalise hazards (treatment waning).

Total discounted costs associated with NIVO+XELOX (with PAS), accrued over the modelled time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with comparator XELOX were lower ([redacted]). Incremental discounted costs for were predicted to be [redacted], under base case assumptions. The incremental discounted QALYs were predicted to be [redacted]. The resulting ICER estimate was £43,889 per QALY. The results of the

base-case analysis (without treatment waning assumption) are summarised in **Table 1**. The probabilistic analysis (PSA) results of the base case analysis without any treatment waning assumption are shown in **Table 2**.

Table 1. Results of base case analysis without treatment waning

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£43,889**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

Table 2. PSA results of base case analysis without treatment waning (CE prob 52.6%)

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£46,221**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

Comparison with ERG scenarios

For the purpose of demonstrating the sensitivity of the model to alternative assumptions, the model incorporating ERG modifications was run. The survival assumptions used for this model are that:

- PFS modelled by relative survival, using rates from Kaplan-Meier estimator until month 6.44, and a log-normal extrapolation thereafter, informed by the CPS ≥ 5% subgroup of CM649. The NIVO+XELOX and XELOX models are derived independently. The relative survival is NOT multiplied by baseline (lifetable) survival, the relative survival directly informs all-cause PFS until intercept with the general population mortality hazard

- OS modelled by relative survival, using rates from Kaplan-Meier estimator until month 6.44, and a Gompertz extrapolation thereafter, informed by the CPS ≥ 5% subgroup of CM649. The NIVO+XELOX and XELOX models are derived independently. The relative survival is NOT multiplied by baseline (lifetable) survival, the relative survival directly informs all-cause OS until intercept with the general population mortality hazard

- Intercept with the general population mortality occurs in both arms, and at this point the curves are modified to use the general population mortality hazard

- There is no arbitrary modification of the survival curves to equalise hazards (treatment waning)

With the ERG preferred modifications to the model the total discounted costs associated with NIVO+XELOX (with PAS), accrued over the modelled (lifetime) time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with comparator XELOX were lower ([redacted]). Incremental discounted costs were [redacted]. The incremental discounted QALYs for NIVO+XELOX were predicted to be [redacted]. The resulting ICER estimates for NIVO+XELOX were £40,418 per QALY. The results of the ERG modified scenario without any treatment waning assumption are summarised in **Table 3**.

Table 3. Results of ERG modified scenario analysis without treatment waning

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]				
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,418**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

PSA results of the ERG modified scenario analysis without any treatment waning assumption are shown in **Table 4**. PSA indicates that NIVO+XELOX has a [redacted]% probability of being cost-effective with a willingness to pay threshold of £50,000.

Table 4. PSA results of ERG modified scenario analysis without treatment waning

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]				
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£41,527**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

Treatment waning

A scenario incorporating treatment waning was run, as described in Section **Error! Reference source not found.**. In brief, the hazard of mortality by any cause upon the NIVO+XELOX arm was assumed to be modified by a time-varying hazard ratio informed by CM649 until intercept with the hazard of the XELOX arm.

As reasoned in Section 2.1, this treatment waning profile started at 6.5 years, the time of greatest follow-up of CM067 as until this time the continued smooth reduction in marginal hazard is known within this external population, and there is no reason to believe that the CM649 hazard profile requires modification to be consistent with these external data. For this this reason, a scenario based on treatment waning at 6.5 years has been applied. In addition, this assumption would align with a similar precedent used in TA737 where waning ended at 7 years for pembrolizumab in a similar patient population.

The effective modelled rise in hazard after this period remains uncertain, and these results should be viewed as a response to the arbitrary and implausible scenario presented by the ERG in which the modelled hazard more than doubles and dramatically rises at 5 years. The

company does not take the position that this modelled loss of treatment effect should be expected but wishes to demonstrate the effect of this uncertainty upon the decision problem using the best available evidence.

The total discounted costs associated with NIVO+XELOX (with PAS), accrued over the modelled (lifetime) time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with comparator XELOX were notably lower ([redacted]). Incremental discounted costs for NIVO+XELOX was reduced to [redacted] (versus XELOX), under base case assumptions. The incremental discounted QALYs for NIVO+XELOX were predicted to be [redacted]. The resulting ICER estimates for NIVO+XELOX were £47,137 per QALY. The results of the base-case analysis with treatment waning assumption are summarised in **Table 5**.

Table 5. Results of base case analysis with treatment waning at 6.5 years

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,137**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

PSA results of the base case analysis with treatment waning assumption are shown in **Table 6**. The PSA indicates that NIVO+XELOX has a [redacted]% probability of being cost-effective with a WTP of £50,000.

Table 6. PSA results of base case analysis with treatment waning at 6.5 years (prob ce 47%)

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,365**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

Comparison with ERG scenarios with treatment waning

The ERG treatment waning scenario was re-run to demonstrate sensitivity to the ERG's assumptions. This scenario consisted of a modification of the ERG Gompertz model with modification of the NIVO+XELOX all-cause mortality hazard, set equal to the XELOX hazard at 5 years until time horizon.

The total discounted costs associated with NIVO+XELOX (with PAS), accrued over the modelled (lifetime) time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with comparators were notably lower ([redacted]). Incremental discounted costs for NIVO+XELOX was [redacted] (versus XELOX). The incremental discounted QALYs for NIVO+XELOX were predicted to be [redacted]. The resulting ICER estimates for NIVO+XELOX

were £47,988 per QALY. The results of the ERG modified scenario with treatment waning assumption are summarised in **Table 7**.

Table 7. Results of ERG modified scenario analysis with treatment waning at 5 years

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,988**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

PSA results of the ERG modified scenario analysis with treatment waning assumption are shown in **Table 8**. PSA indicates that NIVO+XELOX has a [redacted]% probability of being cost-effective with a WTP of £50,000 (Table 10).

Table 8. PSA results of ERG modified scenario analysis with treatment waning at 5 years

Technology	Total costs (£)	Total life years*	Total QALYs	Inc. costs (£)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Nivolumab + XELOX	[redacted]	[redacted]	[redacted]	-	-	-	-
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£49,869**
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; *Total life years undiscounted							

Deterministic and probabilistic results (including probability of cost-effectiveness) for various starting points of treatment waning for the company's base case and the modified ERG base case are provided in Table 10 and Table 10.

Table 9. Deterministic results of ICER with various starting times of waning – comparison of base case scenario with ERG modified scenario

Scenario	Treatment waning starting at			
	5 years	**6.5 years**	**8 years**	**9 years**
Base case	£49,784	£47,137	£45,778	£45,227
ERG modified base case	£47,988	£ 44,323	£42,346	£41,545

Table 10. PSA results for various starting times of waning – comparison of base case scenario with ERG modified scenario

Scenario	Treatment waning starting at							
	5 years		6.5 years		8 years		9 years	
	ICER	Prob of CE	ICER	Prob of CE	ICER	Prob of CE	ICER	Prob of CE
Base case	£51,331	[redacted]	£49,365	[redacted]	£48,859	[redacted]	£48,611	[redacted]
ERG modified base case	£49,869	[redacted]	£46,460	[redacted]	£44,686	[redacted]	£43,888	[redacted]
CE: cost-effective; ICER: incremental cost-effectiveness ratio; Prob: probability								

Model predicted survival

Survival at key time points from the above scenarios are given in **Table 11**. To avoid confusion regarding the reduction of mortality hazards towards the general population, and the survival rates in this population, the general population survival from the model is also presented in **Table 11**.

It is of note that the survival estimates in **Table 11** are relatively similar, with only minor differences between scenarios, providing certainty around the duration of survival anticipated for patients in this population.

Survival at 20 years for NIVO+XELOX ranged from 3.10% (ERG treatment waning at 5 years) to 5.86% (ERG no treatment waning) compared to 54.28% in the general population. The company base case analysis predicts survival of 4.61% (no treatment waning), which lies between the values presented to clinical experts at ACM2 (i.e. 5.9% Gompertz, 3.1% Gompertz with treatment waning, and 0.5% generalised gamma).

However, it should be noted that the application of a conservative treatment waning scenario had limited impact on the ICER, which increased by £3,464/QALY (£3,301/QALY in probabilistic ICER) (difference of ICER from base case treatment waning starting at 6.5 years compared to ICER from base case with no treatment waning).

Table 11. Survival at key time points from the base case and ERG modified scenario analysis

Technology	Percent alive at each time point					
	Company Base case			ERG scenario		
	5 years	10 years	20 years	5 years	10 years	20 years
Survival in general population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Without waning						
NIVO+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With waning at 5 years						
NIVO+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With waning at 6.5 years						
NIVO+XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Discussion

The company believes that the base case analysis presented in **Table 12** is the best available estimate of the cost-effectiveness of nivolumab + XELOX versus XELOX in the NHS England setting, presenting a deterministic ICER of £43,889 per QALY and a probabilistic ICER of £46,221 per QALY.

In this response, the company have provided overall survival estimates at 5 years, 10 years and 20 years, which are relatively similar to the ERG's, with only minor differences between scenarios. The similarity between these estimates reduces the uncertainty around the duration of survival anticipated for patients in this population.

The predicted survival at 20 years (4.61%) remains above that preferred by clinical experts at the previous appraisal committee meeting. However, this value lies between the values presented to clinical experts (i.e., 5.9% Gompertz, 3.1% Gompertz with treatment waning, and 0.5% generalised gamma). Further, this aligns with previous comments from clinical experts related to the long-lasting impact of immunotherapies, as outlined in Section 2.

BMS' preferred treatment waning scenario of 6.5 years was applied resulting in a deterministic ICER of £47,137. This assumption aligns with a similar precedent used in TA737 where waning ended at 7 years.

Further, it should be noted that all scenarios explored, including those considering treatment waning at different timepoints, provide deterministic ICERs below the £50,000/QALY willingness-to-pay threshold but the most conservative treatment-waning scenario (waning at 5 years). Therefore, these analyses demonstrate that there is relatively little uncertainty around the impact of different modelling assumptions on the cost-effectiveness of nivolumab with XELOX.

Table 12. Summary of cost-effectiveness analysis results

		Deterministic			Probabilistic		
		Inc. life years	Inc. QALYs	ICER (£/QALY)	Inc. life years	Inc. QALYs	ICER (£/QALY)
Company base case	Without waning	[redacted]	[redacted]	£43,889	[redacted]	[redacted]	£46,221
	With waning at 6.5 years	[redacted]	[redacted]	£47,137	[redacted]	[redacted]	£49,365
ERG scenario	Without waning	[redacted]	[redacted]	£40,418	[redacted]	[redacted]	£41,527
	With waning at 5 years	[redacted]	[redacted]	£47,988	[redacted]	[redacted]	£49,869

NICE National Institute for Health and Care Excellence

Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma [ID1465]

Consultation on the appraisal consultation document – deadline for comments 5pm on Wednesday 13 April 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
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	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.
Example 1	We are concerned that this recommendation may imply that ……..
1	**The UK patients will be significantly disadvantaged as nivolumab + chemotherapy is now the standard of care chemotherapy globally for her-2 negative non resectable gastric and gastro-oesophageal adenocarcinoma patients**. There is an acknowledgment that the end of life criteria are met which implies a survival advantage would be lost if UK patients were denied this treatment. This would result in a significant inequity in care in the UK compared to the rest of the world.
2	**UK R+D will fall behind**: UK will struggle to attract multi-national studies that use chemotherapy + nivolumab as the standard arm in their design.
3	**Concerns the this decision has been made based on less than robust overall survival modelling and waning effect estimates** There have been difficulties reconciling differences in opinion regarding the overall survival modelling and the waning effect between the company and the ARG. However, there is an absence of actual long term data on survival and waning effect of chemotherapy + nivolumab which, in my opinion, limits the conclusions that can be drawn. Nivolumab is an agent which utilises a patient's immune system to mount an anti-cancer effect. In doing so, it also employs memory T cells which continue to provide immune protection against the cancer beyond the last dose of nivolumab. Hence, using modelling which is ordinarily used for standard chemotherapies (which does not continue to work beyond its last administration) is dubious – especially when looking at the waning effect).
4	**Practicalities in clinic:** The Keynote 590 trial testing pembrolizumab + chemotherapy was similar in design and outcomes compared to the Checkmate 649 trial. If use of Nivolumab is not approved for the gastric cancer patients, there will become a clear divide in clinic where both oesophageal/ gasto-oesophageal patients sit next to (and share notes with) gastric cancer patients. We will have created division in therapy based on anatomy (often dependent on a rough guess by the diagnostic pathway) and factors other than survival outcomes. This will become problematic
5	**Emphasis on long term benefits (which benefit the few) rather than shorter term benefits (which benefit most)** The natural history of this cancer is associated with a poor prognosis. Even with the introduction of nivolumab, unfortunately the prognosis for the majority of patients will remain poor. However, the cost effectiveness analysis and NICE decision not to fund for this population seems to be heavily influenced by long term survival outcomes (i.e. 5 years or more) which are only relevant to minor cohort of patients. For this specific population of patients, where the prognosis is poor (less than 18 months), should more consideration be made of the benefits of this treatment during the first 18-24 months which is relevant to the majority of patients.
6	

Insert extra rows as needed

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- Do not include medical information about yourself or another person from which you or the person could be identified.
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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]
Conflict	
Notes	
Comments on the ACD:	

- Recommendations – section 1

I would like to express my dismay for this recommendation on behalf of my patients at Lancashire Teaching Hospitals NHS foundation trust.

I am very concerned that this recommendation would mean that the UK falls behind in its ability to participate in global phase 3 trails as we will not be offering what is now the global standard of care.

I am also concerned that the survival data used is not reflective of this patient group where the survival is sadly a lot less and treatment is about improving quality of life.

This recommendation would create a lack of equity among oesophageal and gastric cancer patients where one group can access immunotherapy and the other can't when in reality they are similar diseases.

Name	[redacted]
Conflict	
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?I would like to express my dismay for this recommendation on behalf of my patients at Lancashire Teaching Hospitals NHS foundation trust. Yes

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Mostly.

  I was surprised to see survival was so good in the standard arm (19% at 2 years). I wonder if this is a reflection on patient selection.
  I would think the benefit of 2 year survival would greater than this in real world data

- Are the recommendations sound and a suitable basis for guidance to the NHS?
  I would like to see nivolumab available for patients with a PDL-1 CPS score of greater than 5. Currently a score of greater than 10 is required for immunotherpay use and I believe patients are missing out on effective therapy as a result.

- 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? Nil

Name	[redacted]
Conflict	
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account?

  Yes checkmate 649 trial is a large phase 3 RCT with demonstrates the benefit of the addition of NIvolumab to chemotherapy in this patient cohort providing level 1A evidence.

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

  We agree that there has been a systematic and balanced assessment of the available evidence; however the findings for cost effectiveness analysis for this population may be overly skewered towards to longer term survival outcomes (i.e. 5 years or more). For this specific population of patients, where the prognosis is poor (less than 18 months) we do not feel that sufficient consideration to the benefits for this treatment in terms outcomes have been fully considered. It would appear that although the committee acknowledged the findings of the checkmate 649 trial was generalisable to the NHS, the outcome to not fund was weighted more heavily on the long term remission / cure which is represents very small proportion of patients. The issue appears to be predicated on the role of maintenance therapy beyond 2 years which is uncommon and further discussion with the commercial company on this would be encouraged to mitigate the ICER threshold.

  We note and agree with the conclusion of the end of life criteria being met. We recognise the uncertainty and difficulties in modelling beyond this period of time and we note the remit for these decisions as outlined in the technology appraisal. However, as part of this process there would need to be consideration towards the “natural history of the disease”. The population involved with the pre-defined characteristic, as noted by the committee have “a poor prognosis and a large impact on quality of life.” As noted by the committee these patients have a higher burden of care, throughout their treatment journey including, but not restricted to issues relating to poor nutrition due to poor intake as a direct complication of the disease. The improvement in the ORR would invariably lead to improvements in quality of care and reduce the burden on the NHS with reduced inpatient care for nutritional support, ongoing nutritional interventions e.g maintenance of feeding tubes / stents etc. the burden of supportive care in this cohort of patients is considerable (and costly) and reflects the natural history of the disease.

  Furthermore, the improved responses (e.g. 60% vs 45% response rate in PDL- CPS ≥ 5 and 12% vs 7% complete response in PDL- CPS ≥ 5 in the chemo plus Nivo vs. chemo alone group) will facilitate the potential use of alternative and less costly treatments to further improve patient outcomes, for instance increased use of targeted therapies like radiotherapy to reduce the need for further systemic therapies either to the primary disease1,2 or metastasis directed therapies. As outlined by the committee the role of

maintenance Nivolumab beyond 2 years in uncertain but it may facilitate more access to alternative options to improve / sustain outcomes.

We would also like to highlight that this indication would expand access to the use of effective immunotherapies in this group of patient. Currently, based on the NICE TA 737, patients with HER 2 negative oesophageal and GOJ adenocarcinoma which express PD L1 with a CPS of 10 or more are eligible to receive pembrolizumab with systemic chemotherapy. The approval of the current application will enable and expanded cohort to include the same group of patients, but also those gastric cancer and those who express PD L1 with CPS of 5 or more to access this treatment. From a clinical perspective, this would enable a consistent and more equitable access to an effective treatment for more patients in this cohort which would further improve outcomes.

It is unclear if the detail on health burden has been accounted for, but as it may have significant implications on the NHS costs, we think that it should be considered and included in the overall evaluation. It may be a specific area for research / prospective data collection to ascertain the impact on clinical, patient quality of life and health care costs prospectively. In this context, without taking into account the implications of the burden on healthcare it is unclear if the assessment of the benefit of cost effectiveness has been fully addressed and it would be useful for the commercial company's analysis on this area.

Ref

1. Hingorani M, Dixit S, Johnson M, et al. Palliative Radiotherapy in the Presence of Well-Controlled Metastatic Disease after Initial Chemotherapy May Prolong Survival in Patients with Metastatic Esophageal and Gastric Cancer. Cancer Res Treat. 2015;47(4):706-717. doi:10.4143/crt.2014.174
2. SP Parikh, R Goody, O Coen, G Radhakrishna, P Hatfield, M Hingorani. Palliative radiotherapy to the oesophagus: Less is just as good. Clin Onc 2019. 31(suppl1)

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

  In this instance, we feel that more detailed analysis on the cost effectiveness in this vulnerable group of patients is required and we would encourage ongoing dialogue and review of the decision. We think that to not approve this drug on the current analysis would significantly disadvantage this patient group and potentially lead to considerable health inequalities and poorer outcomes for our patients compared to others globally. The option, for ongoing prospective analysis on impact on health care costs and outcomes may be mutually useful to both NHS and commercial partners and should be pursued as an active area of research / innovation.

- 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?
  No

Name	[redacted]
Notes	
Comments on the ACD:	

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

  HCUK believe the recommendations are sound and suitable guidance for the NHS because for this specific cohort of patients the options for quality of life and support relating to immunotherapy are very limited and this provides a vitally needed additional option.
  - There are very limited options for OGJ patients and this provides an additional option
  _ Pembro is only suitable for patients with a CPS of 10 or above, this solution gives hope to an additional cohort of
  patients as this Nivolumab treatment cater for a CPS of 5 or above
  -With such limited solutions available and chemo alone causing significant problems for a patient, this treatment provides greater life expectancy and greater life quality
  - The UK has the largest incidence of adenocarcinoma in the world, we can't exclude patients from a treatment that might work
  - We don't want disparity between treatment options available in Europe and the UK

Name	[redacted]
Notes	
Comments on the ACD:	

- Has all of the relevant evidence been taken into account? Yes

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence? Yes

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

  I have some reservations as stated below: Improvement of survival outcomes for upper GI cancers in an area of unmet need and a priority for GI cancer patients in the UK.

  In gastric cancer patients, there is currently no chemotherapy plus immuno-oncology options for patients. If Nivolumab is not available for this group of patients, it will seriously limit survival outcomes for these patients.

  In patients with CPS between 5-10 there is currently no immuno-oncology treatment options. If Nivolumab is not available, it will seriously limit survival outcomes for these patients.

  Availability of chemotherapy + immuno-oncology treatments for oesophageal and GOJ tumours but not for gastric cancer patients is unfair to patients and denies them a clinically effective treatment for this devastating disease. I have treated gastric cancer patients with Nivolumab in clinical trials and have seen their lives transform for the better whilst on therapy.

  Nivolumab is a standard of care therapy in Europe and elsewhere. Not having this treatment available for patients in the UK will impact out standards of care. UK is heavily involved in cancer clinical trial research. To not be able to recommend such UK trial generated treatment, will in the long term, also adversely affect UK's ability to attract future cancer clinical trials.

- 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? None

Name	[redacted]
Notes	
Comments on the ACD:	

- Has all the relevant evidence been taken into account? Yes

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

  No, the over reliance on long term curability of outcomes following systemic therapy of advanced OG cancer is an unreasonable model

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

  No this will not allow for a very effective treatment for patients with advanced OG cancer and not any immunotherapy for gastric cancer (which pembrolizumab is not licensed for)

- 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?

  Yes one should look at hazard ratios of differential outcomes compared with standard chemotherapy or median survival, not 5, 10, 20 year survival given the uncertainty regarding long term outcomes

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Nivolumab in combination with chemotherapy for untreated advanced gastric, gastro-oesophageal junction, or oesophageal adenocarcinoma [ID1465]

ERG response to company response to ACD2

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 133505

Completed 13 May 2022

DOES NOT CONTAIN CIC/AIC

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 ERG RESPONSE TO COMPANY RESPONSE TO ACD2

The ERG is satisfied that the company's approach to modelling overall survival (OS) is reasonable; the results of the model checks that the ERG was able to carry out suggest that the company's approach has been implemented correctly. The company's approach generates incremental cost effectiveness ratios (ICERs) per quality adjusted life year (QALY) gained that are similar to, but lower than, the ICERs per QALY gained generated by the ERG's approach.

Long-term OS estimates associated with treatment with nivolumab remain uncertain. Both the ERG's model and the company's model generate similar OS estimates.

The company has provided evidence to demonstrate that applying 'treatment effect waning' at 5 years is too pessimistic. The ERG agrees with the company that robust evidence to support treatment effect waning is lacking and that the available evidence (provided by the company) suggests that immunotherapies are likely to confer a survival advantage to patients for at least 5 years. Given the available evidence presented by the company, the ERG considers that the company approach of applying a treatment effect waning at 6.5 years is not implausible.

The ERG confirms that the cost effectiveness results generated by the company model and presented in the company response are accurate.