NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of renal cell carcinoma

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Pembrolizumab for adjuvant treatment of renal cell carcinoma [ID3810]

Contents:

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30th June 2022

Merck Sharp & Dohme (UK) Limited
Registered in England No. 233687
Registered Office: 120 Moorgate,
London, United Kingdom EC2M 6UR
T: 0208 1548000
E: carl.selya-hammer@msd.com

To: Helen Knight; Programme Director, Centre for Health Technology Evaluation

Dear Helen,

RE: Pembrolizumab for adjuvant treatment of renal cell carcinoma [ID3810] ACD

Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) for pembrolizumab for adjuvant treatment of renal cell carcinoma (RCC) [ID3810].

We agree with the Committee's view that there is an unmet need for adjuvant treatments for renal cell carcinoma and people with the condition would welcome new treatment options. We are disappointed with the decision not to recommend pembrolizumab in this indication for routine commissioning on the NHS.

We have addressed the Committee's key areas of uncertainty as described in the ACD in our response and kindly request the negative decision is revised on the basis of this additional information, which confirms the cost-effectiveness of pembrolizumab in this indication. [redacted]

We understand that NICE seeks to understand the impact of the assessment of disease-free survival (DFS) as measured by both investigator-assessed (IA) and blinded independent central review (BICR) in order to better understand the efficacy of pembrolizumab in this indication. MSD have provided the incremental cost-effective ratio (ICER) estimates for both IA and BICR as part of our ACD consultation comments. However, MSD's position has not changed:

- IA is the more appropriate measure of efficacy: IA is the primary trial outcome. The trial was powered to measure DFS as determined by IA.

- The economic analysis informed by the IA DFS dataset is more generalisable to UK clinical practice than the BICR DFS dataset considering i) the patients included in the IA DFS analysis compared with BICR and ii) the far closer alignment of costs in the analysis to costs as they would be incurred by the NHS in the real world, which would be driven by IA of DFS

- BICR is associated with limitations when implemented in this clinical study and therefore should not be used as the primary decision-making outcome:

  i) a “retrospective” form of BICR was used in KEYNOTE-564 which is associated with significant limitations (compared to the “real-time” form of BICR),

  ii) the IA and BICR analyses of DFS used different datasets,

  iii) DFS by BICR is not a formal trial endpoint and it is not statistically powered in KEYNOTE-564

Despite limitations of using BICR DFS, the cost-effectiveness analysis was updated using formal curve fitting methods. This produced ICER estimates of £17,821/QALY, demonstrating that the choice of assessment of DFS does not have a large effect on the ICERs. The estimates generated using BICR DFS are similar to company base-case ICERs based on IA DFS and remain below the typical decision-making threshold.

We have also provided additional analyses exploring assumptions around long-term risk of relapse with pembrolizumab, an issue the Committee has identified as needing additional clarity. Based on plausible assumptions informed by evidence from the KEYNOTE-564 trial and clinical opinion, the resulting cost-effectiveness estimates in these scenarios do not show sensitivity to these assumptions and further demonstrate that pembrolizumab provides value for money to the NHS in this indication.

MSD’s priority is to ensure patients have access to innovative treatments and so we are grateful for the invitation to submit a proposal for including pembrolizumab in the Cancer Drugs Fund (CDF) for this indication. However, the clinical trial data are robust and the majority of plausible ICERs are well below usual decision-making thresholds, making this a strong candidate for baseline commissioning.

Particularly in the light of changes to CDF exit process in the new NICE Manual, MSD is concerned that any decision to provide access in the CDF will not give patients and treating clinicians the sustainable access to treatment as might have previously been the case.

We kindly request the Committee revises its decision based on the information contained in this response.

Kind regards,

[redacted]

[redacted], MSD

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Consultation on the appraisal consultation document – deadline for comments end of 30 June 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):	**Merck Sharp & Dohme (UK) Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**
Name of commentator person completing form:	**Carl Selya-Hammer**

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Consultation on the appraisal consultation document – deadline for comments end of 30 June 2022. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Is Investigator Assessed (IA) or blinded independent central review (BICR) review of disease-free survival DFS more methodologically robust, for the purposes of decision making? (3.9)** The way the BICR DFS analysis was conducted in KEYNOTE-564 limits its usefulness in demonstrating the value and clinical effectiveness of pembrolizumab in this indication when used in routine UK clinical practice. IA is more statistically appropriate and more generalisable to clinical practice in the UK. There are a number of reasons that DFS by BICR, as specifically implemented in KEYNOTE-564, does not measure what we think the Committee thinks its measures. These reasons are discussed in more detail below: 1) Instead of “real-time” BICR, KEYNOTE-564 used “retrospective” BICR 2) The IA and BICR analyses of DFS are based on different datasets 3) Analysis of DFS by BICR in the KEYNOTE-564 study was not statistically powered <u>Instead of “real-time” BICR, KEYNOTE-564 used “retrospective” BICR</u> • The ideal method of evaluation of DFS by BICR would be “real-time” BICR, where the BICR assessment and decision happens at the same time as the treating clinician (i.e. at the same time as the IA). The BICR decision could be used as the basis for any decision to continue or alter patients’ treatment (1, 2). While this approach is the ideal approach to assess treatment efficacy, real-time BICR is rarely implementable in either trials or real world due to practical, ethical, and legal barriers. Specifically, the patient’s treating clinician may be unable or unwilling to cede the authority of final determination of a patient’s status and treatment to a BICR. The method of evaluation of DFS by BICR used in the KEYNOTE-564 study was a form of “retrospective” BICR, whereby BICR assessment and final decision happened at a later timepoint following IA of DFS. In the trial, only the investigator’s decision could affect any decision to continue or alter patients’ treatment (1, 2). The KEYNOTE-564 study protocol specified that scanning of patients stopped at the point the investigator determined disease recurrence to have occurred (see section 9.2.1.3 of the KEYNOTE-564 study protocol provided in section 16.1.1.1 of the KEYNOTE-564 Clinical Study Report: "*For participants who discontinue study treatment due to disease recurrence, the initial imaging demonstrating recurrence is the final required imaging, unless recurrence is confirmed with a*

repeat scan. In this case, the confirmatory scan is the final required imaging"[1]). A problem therefore arises when the IA determines disease recurrence to be before the time BICR would determine disease recurrence. The patient in this case would never have an opportunity to have a (later) DFS event by BICR logged. The original trial protocol did not permit the use of later scans to reveal that how premature the IA determination was[1].

Without the possibility to follow up patients to the BICR-determined time of disease recurrence, patients were censored at time of last BICR tumour assessment showing no disease recurrence (19 patients [3.8%] in the pembrolizumab arm and 29 patients [5.8%] in the placebo arm, as shown in Table 15 of Document B section B.2.6 of the company submission). This censoring may be informative, in that a determination of recurrence by IA may be considered prognostic of a BICR-determined recurrence but cannot be assessed due to a lack of further imaging data to confirm if and when this occurs.

<u>The IA and BICR analyses of DFS are based on effectively different datasets, which may contribute to differences in efficacy results observed between the two analyses</u>

- The DFS BICR analysis was only conducted on patients who were determined to have no evidence of disease (NED) at baseline by BICR. Any patients participating in the study that had been determined to have no evidence of disease at baseline according to the trial enrolment protocol, who were later determined to actually have had disease at baseline based on BICR assessment were censored in the BICR DFS analysis given that disease recurrence is not a relevant outcome for patients who have evidence of disease at baseline. Nineteen patients (3.8%) in the pembrolizumab arm and 29 patients (5.8%) in the placebo arm were censored in this way (as shown in Table 15 and Figure 4 of section B.2.6 of Document B of the company submission).

- Not only does censoring these patients at baseline and removing them from the analysis reduce the quality of the BICR analysis results compared to IA DFS, it also means the BICR analysis is less generalisable to real world clinical practice. In practice, a small proportion of patients may be erroneously declared to have NED following nephrectomy by their treating clinician and consequently initiated on adjuvant therapy based on the clinician's determination of eligibility.

  These non-NED patients, i.e. those who actually had a tumour present at baseline, are more likely to have had a DFS event identified in one of the early follow-up scans. Censoring these patients in the DFS by BICR analysis is likely to influence the results toward the hazards being better in both arms compared to the DFS by IA analysis which did not censor these patients. As pembrolizumab is more likely than placebo to have a positive effect on these patients (i.e. pembrolizumab is more likely than placebo to shrink or remove the tumour that had not originally been identified in the baseline scan and to reduce the likelihood that the tumour would be detected as a "disease recurrence" event later on), censoring these patients from the DFS by BICR analysis could contribute toward the tendency of the DFS by BICR results to be less favourable toward pembrolizumab than the DFS by IA results.

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	Analysis of DFS by BICR in the KEYNOTE-564 study was not statistically powered • The primary efficacy endpoint assessed in the KEYNOTE-564 study, specifically DFS by IA (as described in Document B section B.2.3 of the company submission), and the key sample size and statistical power for the analysis of DFS (as described in Appendix L of the company submission) were calculated based on informed assumptions of hazard ratios (HRs) expected specifically for DFS by IA. The DFS by BICR analysis was a sensitivity analysis only, without any considerations of it being statistically powered. Consequently, only the DFS by IA results are formally statistically powered and appropriate for use in decision making. Indeed, the marketing authorisation for pembrolizumab in this indication was granted on the basis of the DFS by IA results from KEYNOTE-564 study, which met the pre-specified primary endpoint (calculated for DFS by IA) and unambiguously demonstrated that pembrolizumab was effective in this indication (3). • Whilst the DFS by BICR results from KEYNOTE-564 are interesting as a sensitivity analysis of IA DFS, it is important to note that DFS by BICR is not a formal endpoint in the study. Therefore, it would be inappropriate to consider the results of the DFS by BICR analysis in KEYNOTE-564 to be a more methodologically robust or a plausible representation of the true underlying relative efficacy of pembrolizumab versus placebo than the results of DFS by IA. The difference in the results of the DFS analyses by BICR and by IA result are driven by differences in patients included as well as the censoring in each analysis.
2	**Accurate ICER estimates when comparing investigator DFS with BICR DFS, when formal curve fitting methodology is followed (3.10)** Use of BICR DFS data requires the same selection process to choose the most appropriate parametric fitting • The ad hoc method described in the ERG report used to estimate the impact of using BICR DFS rather than IA DFS in the economic analysis has a large effect on the ICERs. Conducting formal curve fitting of the BICR DFS dataset to select the most plausible parametric models to extrapolate the DF→DM and DF→LR transitions demonstrated a much smaller impact on the ICER estimates. • The ACD notes that an updated analysis by the company using BICR data from KEYNOTE-564 should be presented for the Committee to more accurately assess the impact of the use of BICR DFS on the ICER. To that end, the cost-effectiveness model originally informed by IA DFS was updated to include BICR DFS data. To select the most appropriate parametric fitting to model transitions from the disease free (DF) health state using BICR DFS, we have applied the same selection process presented in Company base case (Figure 19 in CS). Figure 1 presents an update of Figure 19 in the CS with changes being marked in red for selection of the most plausible parametric fitting of BICR DFS. Three combinations were identified as plausible, all of which had been included in the six most plausible combinations identified in company's original submission (CS Page 84). Of these six combinations of most plausible combinations of parametric models, the remaining three combinations were excluded based on statistical fit

	and validation of results using external data (see Table 3). Notably, estimated DFS based on BICR for the placebo arm of KEYNOTE-564 matched the placebo arms of previous TKI trials in adjuvant RCC less closely than did estimates based on IA DFS, which further highlights the increased relevance of IA DFS in the economic analysis. The inclusion criteria for a combination of parametric models to be considered plausible therefore had to be relaxed to include a wider range than when using IA DFS: within ±6% (rather than ±2.5%) of 5-year predicted DFS for placebo in KEYNOTE-564 in range of 45.0-57.0% (~51% in 3 external trials). As presented in Table 1, of the three combinations of parametric models which met this criterion, only Approach 3 exponential/Gompertz resulted in a plausible incremental DFS gain versus placebo at 7-years (12.2%). The other two options [Approach 1 exponential/Generalized gamma; Approach 2 exponential/Gompertz] resulted in an incremental DFS gain which was lower than that observed for sunitinib versus placebo (10.5%) in the S-TRAC trial in adjuvant RCC at 7-years (see Table 2). The suitability of plausible parametric fits summarized in Table 3 shows Approach 3 exponential/Gompertz to also have good statistical fit in terms of rank of MSE for both arms and Figure 3 highlights its good visual fit to the observed BICR DFS data. <u>Incorporating DFS based on BICR assessment into the economic analysis does not have a large impact on the ICER when selecting the most appropriate parametric fitting to model transitions from the DF health state</u> • Using the most plausible approach to extrapolation transitions from the DF state using on BICR DFS data results in an ICER of £17,821 (see Table 5) compared to £22,367 in the original ERG-preferred base case analysis reflecting IA DFS (see Table 4). Therefore, choice of BICR assessment DFS does not have a large effect on the cost-effectiveness estimates compared with the use of the primary endpoint from the KEYNOTE-564 trial (IA DFS), with cost-effectiveness estimates remaining below what is usually considered an acceptable use of NHS resources.
3	**Whether the pattern of relapse is the same for renal cell carcinoma treated with pembrolizumab as with routine surveillance is uncertain (3.8)** • The ACD reports that more scenario analyses assessing treatment effect (TE) waning assumptions may resolve the uncertainty associated with the long-term risk of relapse with pembrolizumab. The Committee noted that there was a precedent of applying a waning effect in other NICE technology appraisals for immunotherapies with a treatment duration or maximum treatment time. • Whilst the above point is accurate for some metastatic indications, it is not accurate for IO treatments in the adjuvant setting due to the likely mechanism of action for treatments accompanying surgery with curative intent. We were unable to identify any NICE HTAs in the adjuvant setting that included TE waning. The following HTAs all had a treatment stopping rule and no assumptions regarding waning in the NICE documentation: o TA761 Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (ADAURA study) o TA746 Nivolumab for adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer (CheckMate 577 study)

	○ TA684 Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (CheckMate 238 study) ○ TA544 Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (COMBI-AD study) ○ TA766 Pembrolizumab for adjuvant treatment of completely resected stage 3 melanoma (KEYNOTE-054) <u>In exploratory analysis of the long-term pattern of relapse, it is implausible that an increase in the hazards to match those of routine surveillance would apply to all disease-free patients</u> • The ERG considered that the risk of relapse may increase over time to match routine surveillance and did 3 scenario analyses exploring risk of relapse for the pembrolizumab group at 4, 7 and 10 years. As the ACD notes, MSD have previously cited the lack of evidence of TE waning observed in KEYNOTE-564 trial and the implausibility of an abrupt waning of treatment effect at the proposed time points. • Given the curative intent of adjuvant pembrolizumab, MSD believe it is implausible that TE waning would necessarily apply to all patients who remain disease free. Clinical experts have posited that some patients who remain disease free in the long term may never experience disease recurrence. For patients who undergo nephrectomy followed by routine surveillance and later experience recurrence, a likely hypothesis as to the why their disease recurs is because of residual tumor cells or micro-metastases following nephrectomy. For those patients whose disease recurs following immunotherapy it is understood that acquired tumor resistances to evade T cell-mediated cytotoxicity will be responsible for a proportion of these cases. Although the mechanisms for acquired resistance are not fully understood, there is no evidence to suggest that this would occur in all patients who remain disease free in the long term. <u>Waning of treatment effect, were it to occur, would be unlikely to have an immediate 'cliff's edge' effect</u> • Whilst MSD do not agree the data support an assumption of TE waning for pembrolizumab in adjuvant RCC, we have included a waning functionality in the economic model that takes into account the proportion of patients affected by a waning of treatment effect and the time period required for the DFS hazards in the pembrolizumab arm to fully merge with the hazards in the placebo arm for the specified proportion of patients. In this so-called 'washout' period, pembrolizumab DFS hazards increase linearly from the start to the end of this duration until they equal the hazards of the placebo arm. <u>The cost-effectiveness estimates show limited sensitivity to varying assumptions on the long-term risk of relapse using both IA and BICR assessment of DFS</u> • The results of the requested exploratory analysis are presented in Table 6 for the revised ERG base case and company base case, including analyses based on

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	assessment of DFS by both IA and BICR which also vary TE waning parameters related to time of onset, 'washout' period and proportion of patients affected. • The scenario of TE waning at 4-years is considered highly implausible given the absence of evidence in the observed trial data in KEYNOTE-564 at 3.5 years' follow-up to indicate the hazards in the treatments appearing converge at any timepoint. Furthermore, there is no evidence of waning at this timepoint in the clinical trial assessing pembrolizumab in adjuvant melanoma, nor is there evidence of TE waning within this time frame in metastatic pembrolizumab indications. Therefore, exploring TE waning starting at 4-years is not an analysis MSD can accept. • In the scenario with onset of TE waning at 7 years, the proportion assumed to be impacted by TE waning was set at 15% given the lack of evidence of a waning of treatment effect for sunitinib observed in the S-TRAC trial at up to 8+ years' follow-up. At 10-years, the proportion of patients assumed to be impacted by TE waning is increased to 20% to reflect the lack of external data available at 10 years' follow up in the adjuvant RCC setting as well as the increased plausibility of patients who remain disease free in the long term to have increasingly similar risk of recurrence, as highlighted by Leibovich et al (4). For all scenarios, the 'washout' period was assumed to last for 2 years. The results of these exploratory analyses as reported in Table 6 show a limited impact on the base-case cost-effectiveness estimates whether using assessment of DFS by BICR or IA. In both the company and ERG base case the ICERs remain below what is usually considered an acceptable use of NHS resources.
4	**The cost-effectiveness estimates are uncertain and include ICERs higher than what is usually considered an acceptable use of NHS resources (3.11)** • As detailed above, across a variety of exploratory scenarios including assessment of DFS by BICR as well as the exploratory analyses on the long-term risk of relapse with pembrolizumab, and even in analyses combining these scenarios, the ICERs remain below what is usually considered an acceptable use of NHS resources. • Whilst the Committee notes that the cost-effectiveness estimates include ICERs higher than what is usually considered an acceptable use of NHS resources, the cost-effectiveness estimates also include plausible ICERs far below this threshold. This includes the ICER associated with the company base case (£11,138), which was based on an approach to DFS extrapolation that the Committee described as justifiable, as noted in the ACD.
5	**Pembrolizumab is not innovative (3.13)** Section 3.13 of the ACD states that when focusing specifically on relevant benefits associated with innovation, the Committee considered that there were no additional benefits that had not been captured in the QALY. However, it should be noted that there is currently no NICE recommended active adjuvant therapy for RCC post-nephrectomy and so pembrolizumab would be the first effective and well tolerated adjuvant treatment option for patients RCC post-nephrectomy. Pembrolizumab in this setting would offer a significant step-change in benefit for these patients in the UK and alleviate some of the

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	uncertainty, feelings of being abandoned, low emotional status, and anxiety about the cancer returning that patients would otherwise have with access to routine surveillance only.
6	**Amends to the ERG base case, which are reflected in the cost-effectiveness estimates included in this ACD response** The cost-effectiveness estimates presented in this ACD response reflect a revised assumption from the ERG-preferred base case, based on the following: • The ERG base case includes an erroneous set of assumptions requiring a correction: Relative dose intensity (RDI) for pembrolizumab has been set at 100% and the time on treatment (ToT) curve is not truncated at 51 weeks. The current assumption in the ERG base case effectively calculates drug costs for pembrolizumab assuming no missed or delayed doses for all patients remaining on treatment, whilst also allowing patients to continue treatment beyond 1 year (17 cycles), which patients would only do in the event the missed or delayed doses of pembrolizumab in the first 1 year of treatment. The correct approach would be to truncate the ToT curve at 1 year whilst assuming 100% RDI, or conversely, not to truncate the ToT curve at 1 year but to reflect RDI as observed in the trial. • MSD note that the company base case originally included both a truncation of the ToT curve at 51 weeks as well as including RDI for pembrolizumab. As described above, only one or the other assumption should be included and MSD regret the error. Consistent with the revised ERG base case, the cost-effectiveness estimates for the revised company base case exclude the remove of RDI for pembrolizumab but does exclude truncation of the ToT curve at 51 weeks. • To this end, in the revised ERG base case reflected in the cost-effectiveness estimates in this document we have excluded the ERG's previous removal of applying RDI to pembrolizumab drug costs. The cost-effectiveness estimates using BICR DFS in Table 5 and Table 6 reflect the described revisions to the ERG base case. • [redacted]

[1] However, in a very small number of patients in the KEYNOTE-564 study (4 in the pembrolizumab arm and 3 in the placebo arm) additional scans were taken after disease recurrence according to IA had been declared and were then assessed by BICR and included in the analyses.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.

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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Appendices

Figure 1 Selection process of parametric models for transitions from disease free health state

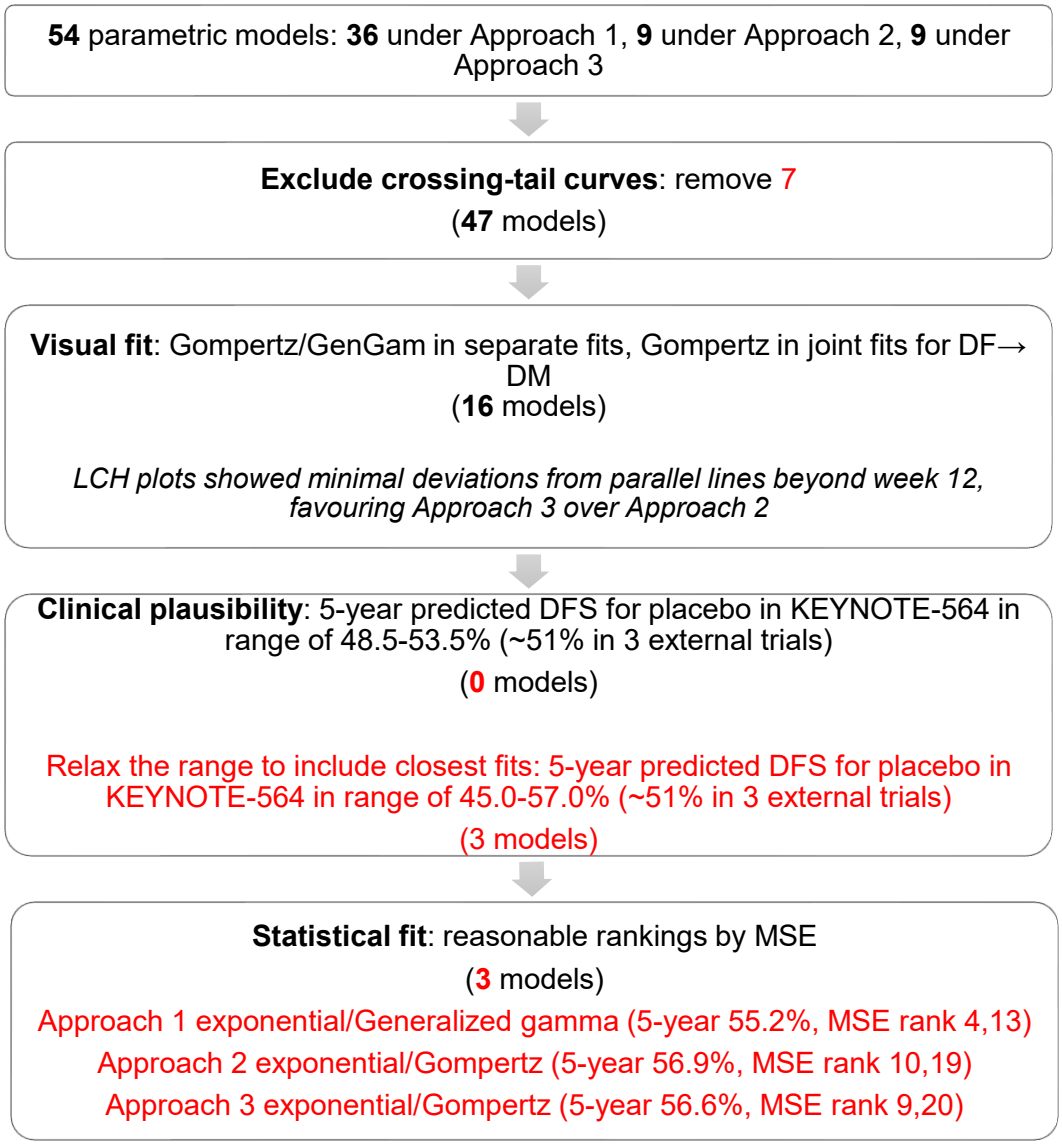

Figure 2 Modelled BICR DFS using Company base case modelling assumptions (Approach 3 exponential/Gompertz) versus observed BICR DFS in KEYNOTE-564 for the placebo arm (data cutoff date: 14 June 2021) and placebo arms from previous trials assessing TKIs in the adjuvant RCC setting

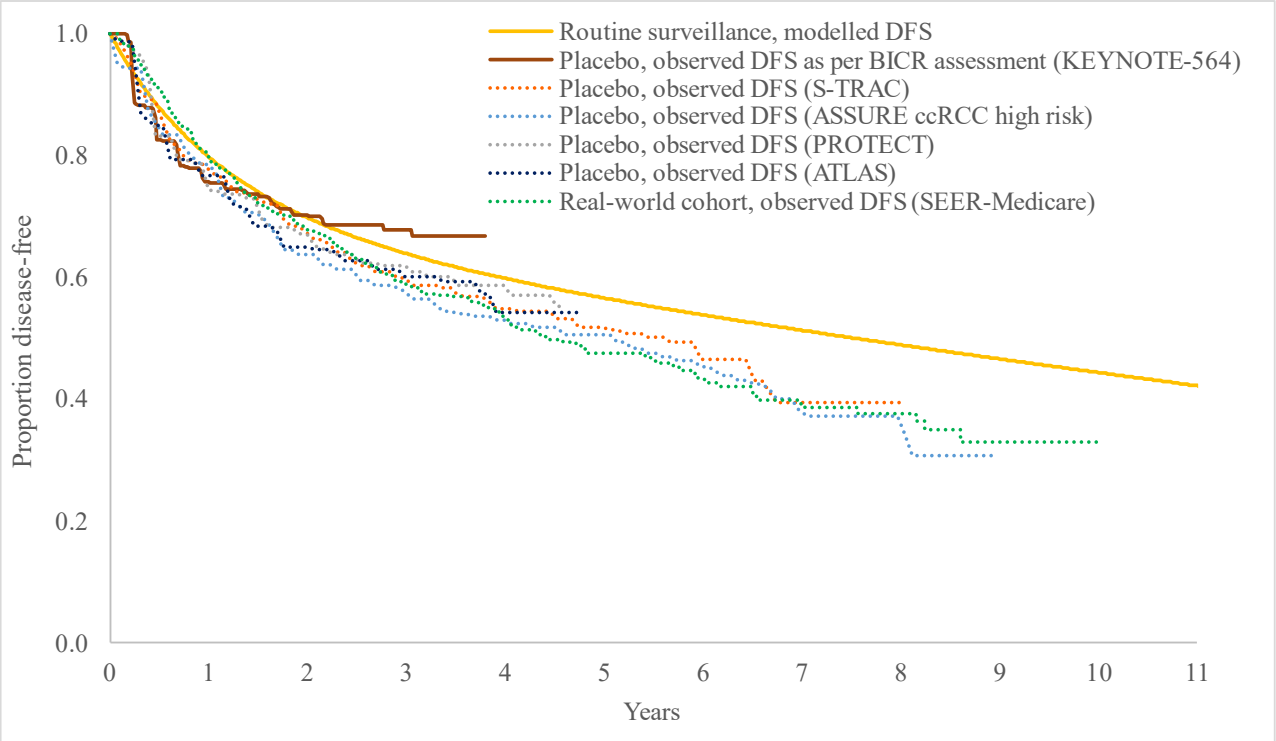

Figure 3 Modelled BICR DFS using Company base case modelling assumptions (Approach 3 exponential/Gompertz) versus observed BICR DFS in KEYNOTE-564 (data cutoff date: 14 June 2021)

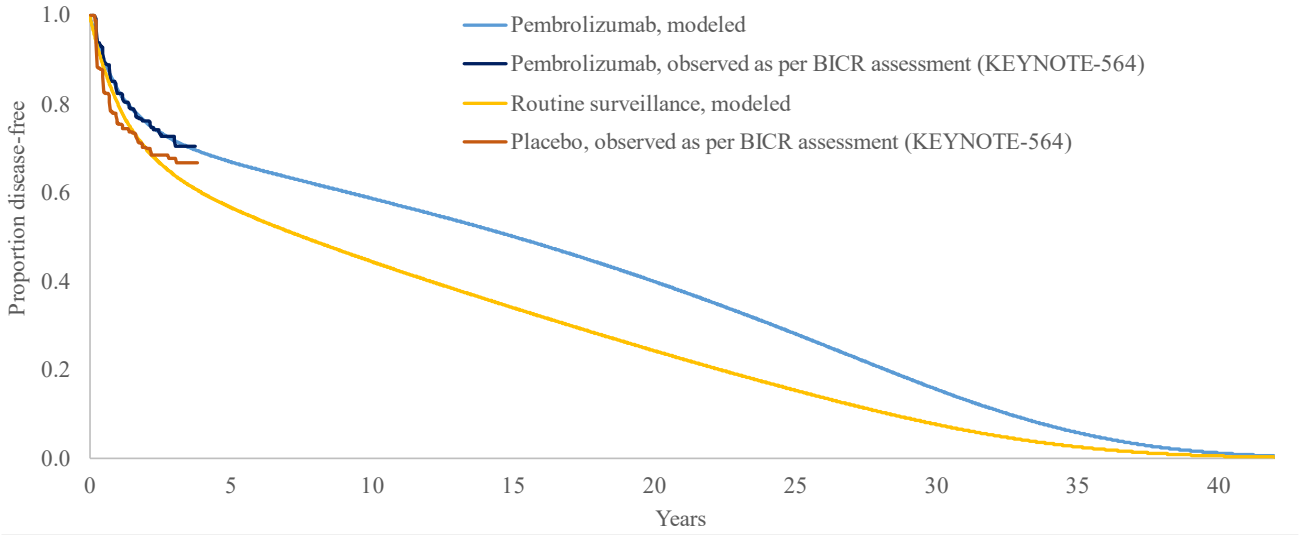

Table 1 External and predictive validation of long-term DFS for routine surveillance versus placebo arms in previous trials of adjuvant therapy

DFS by year	1	2	3	3.5	4	5	7
Placebo, observed DFS (S-TRAC)	77.7%	67.3%	59.5%	57.1%	54.7%	51.3%	39.5%
Placebo, observed DFS (ASSURE ccRCC high risk)	78.6%	63.6%	57.6%	54.3%	53.0%	50.6%	38.2%
Placebo, observed DFS (PROTECT)	74.3%	67.0%	61.9%	60.2%	58.7%	50.8%	--
Placebo, observed DFS (ATLAS) (5)	76.7%	65.0%	60.2%	59.2%	54.3%	--	--
Placebo, observed DFS (KEYNOTE-564, data cut-off: 14-JUN-2021, BICR)	75.6%	70.3%	67.7%	66.7%	--	--	--
Placebo, modelled DFS - Approach 1 exponential/Generalized gamma (BICR)	78.7%	69.7%	63.8%	61.4%	59.2%	55.2%	48.5%
Placebo, modelled DFS - Approach 2 exponential/Gompertz (BICR)	79.7%	69.8%	64.0%	61.9%	60.0%	56.9%	51.6%
Placebo, modelled DFS - Approach 3 exponential/Gompertz (BICR)	79.8%	69.8%	63.9%	61.7%	59.9%	56.6%	51.3%

Table 2 Landmark incremental DFS gain for three most plausible parametric fits based on BICR DFS in KEYNOTE-564 versus S-TRAC

	1	2	3	5	7
Observed, sunitinib vs. placebo (S-TRAC)	10.3%	4.4%	5.4%	8.0%	10.5%
Modelled, pembrolizumab vs. placebo – Approach 1 exponential/Generalized gamma (BICR)	4.4%	6.2%	7.3%	8.9%	10.0%
Modelled, pembrolizumab vs. placebo – Approach 2 exponential/Gompertz (BICR)	4.1%	6.1%	7.2%	8.8%	9.9%
Modelled, pembrolizumab vs. placebo – Approach 3 exponential/Gompertz (BICR)	3.2%	6.0%	7.8%	10.3%	12.2%

Table 3 Comparison of plausible extrapolation approaches according to statistical fit and external validation

		Based on BICR assessment of DFS			
	Selection based on DFS IA	Selection based on DFS BICR	Statistical fit: Rank of MSE for Pembro and placebo	Alignment with external data for the routine surveillance arm: 51% at 5 years in S-TRAC	Plausible incremental DFS gain vs placebo compared to: 10.5% at 7 years S-TRAC
Approach 1 - Exponential/ Generalized gamma	√	×	4, 13	55.2%	10.0%
Approach 3 - Exponential/ Gompertz	√ (company base case)	√ (company base case)	9, 20	56.6%	12.2%
Approach 2 - Exponential/ Gompertz	√	×	10, 19	56.9%	9.9%
Approach 1 - Exponential/ Gompertz	√ (ERG base case)	×	24, 15	58.0%	6.8%
Approach 3 - Weibull/ Gompertz	√	×	15, 16	58.9%	9.3%
Approach 2 - Weibull/ Gompertz	√	×	13, 14	59.2%	8.5%

Table 4 Company base case post clarification and ERG base case including proposed revision

	DFS data (IA) *Table 6 in ERG report*		
Scenario	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£/QALY)**
Company base case post clarification	[redacted]	[redacted]	11,138
Approach 1 combination exponential/ Gompertz	[redacted]	[redacted]	21,927
Removal of oral administration costs	[redacted]	[redacted]	11,413
Removal of truncation to the ToT curve for pembrolizumab	[redacted]	[redacted]	11,138
Removal of pembrolizumab RDI	[redacted]	[redacted]	10,997
Alternative 2L subsequent treatment market share estimates - 50% cabozantinib and 50% no active treatment	[redacted]	[redacted]	9,937
ERG's preferred deterministic base case - combination of all scenarios	[redacted]	[redacted]	22,717
Proposed revision to ERG deterministic base case			
Remove exclusion of pembrolizumab RDI i.e. revised ERG base case	[redacted]	[redacted]	22,367
[redacted]			

Table 5 Comparison of cost effectiveness estimates BICR DFS with IA DFS

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Using IA DFS			
Company base case post clarification	[redacted]	[redacted]	11,138
ERG's preferred deterministic base case - combination of all scenarios removing exclusion of pembrolizumab RDI	[redacted]	[redacted]	22,367
Using BICR DFS **Revised ERG-preferred base case; combination of ERG scenarios, reflecting proposed revision**			
Approach 3 combination exponential/ Gompertz	[redacted]	[redacted]	17,821

Table 6 Treatment effect waning scenarios in revised ERG and company base case cost-effectiveness estimates[1]

Treatment effect waning parameters	IA DFS					
	Revised ERG base case			Revised company base case		
	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Onset: 7-years, **Washout**: 2 years, **Proportion**: 15%	[redacted]	[redacted]	23,750	[redacted]	[redacted]	12,201
Onset: 10-years, **Washout**: 2 years, **Proportion**: 20%	[redacted]	[redacted]	23,732	[redacted]	[redacted]	12,093
	BICR DFS[2]					
Onset: 7-years, **Washout**: 2 years, **Proportion**: 15%	[redacted]	[redacted]	19,757	[redacted]	[redacted]	19,882
Onset: 10-years, **Washout**: 2 years, **Proportion**: 20%	[redacted]	[redacted]	19,572	[redacted]	[redacted]	19,695

[1]All cost-effectiveness estimates reported above reflect [redacted] the inclusion of nivolumab in combination with ipilimumab as an available treatment for 1L aRCC following disease recurrence

[2]For the BICR DFS scenario analysis results, revised ERG and company base cases share the same survival modelling assumption (since the ERG have not yet reviewed the economic model which including the BICR DFS data) but differ in other assumptions listed in Table 4.

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Comments on the ACD received from Action Kidney Cancer

Name	[redacted]
Role	
Other role	
Organisation	Action Kidney Cancer
Location	

Response to specific questions:

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

In a clinical trial, adjuvant pembrolizumab significantly reduced the relative risk of the cancer returning by about one third (32%) compared to placebo. After 2 years, 77.3% of the patients on pembrolizumab remained disease-free. However, disease-free survival and overall survival endpoints have not yet been met in this study.

During the trial, quality of life was assessed. There was only a minor deterioration of quality of life for patients treated with pembrolizumab compared to placebo, and quality of life remained stable over time (2 and a half years). Patients reported that pembrolizumab was also well tolerated. This has a big impact on the quality of life of patients, reducing the stress and worry of the cancer returning. Improved quality of life and wellbeing in the patient has a knock-on effect to those around them, leading to an improvement in the wellbeing and quality of life for carers and the family overall.

Better quality of life and improvement in the psychosocial wellbeing of patients after surgery allows them to get on with their lives without the constant worry of the disease returning and a terminal prognosis. An enhanced quality of life enables them to contribute socially and economically to society.

The committee's decision not to recommend adjuvant pembrolizumab was based upon a lack of follow-up data from clinical trials. However, this does not necessarily reflect routine clinical practice. We are pleased to see that NICE are considering funding through the Cancer Drugs Fund (CDF) to enable collection of real-world survival data for intermediate/high risk patients, which could potentially impact the final recommendation. However, since patients can live for many years after nephrectomy without recurrence of their disease, we are concerned that it will be unlikely that the data collected during the CDF for two years will show a statistically significant difference between adjuvant pembrolizumab and placebo with respect to disease-free survival and overall survival. We would prefer adjuvant pembrolizumab to be recommended for reimbursement on the NHS.

Comments on the ACD:

Pembrolizumab is the first immune checkpoint inhibitor to be assessed as an adjuvant treatment for locally advanced renal cell carcinoma (RCC). Currently, adjuvant treatment to prevent the spread of intermediate/high risk RCC following surgery is an area of serious unmet need in England. An adjuvant treatment is desperately needed for these people to improve their wellbeing and quality of life

following surgery. Carers, family members and friends of kidney cancer patients would also benefit from less worry about disease recurrence.

The current treatment pathway for locally advanced RCC is either radical or partial nephrectomy (surgery). Patients are then followed for up to 5 years after surgery. During this time, no further treatment is given to prevent or reduce the risk of spread of the cancer following surgery. Vascular endothelial growth factor receptor (VEGFR) inhibitors, such as sunitinib, pazopanib, axitinib and sorafenib have all been investigated in randomised controlled clinical trials as potential adjuvant treatments. None significantly improved patient survival, although patients were subject to the toxicities of these medicines for a year without receiving any benefit. However, sunitinib has been approved by the US Food and Drug Administration (FDA) for such use.

If the cancer spreads, an immunotherapy plus VEGFR inhibitor combination is given in the first-line setting. Monotherapy VEGFR inhibitors, mTOR inhibitors or immunotherapies can be given in the second and third line. However, once spread, patients face a terminal prognosis.

Patients with intermediate/high risk, locally advanced RCC are desperate for an adjuvant treatment that will prevent recurrence of their disease without affecting their quality of life. This will help address the stress and anxiety felt by patients and their families and improve their psychosocial wellbeing after surgery for RCC.

The benefits of adjuvant pembrolizumab to patients are reduced recurrence of disease with a tolerable side effect profile and little effect on quality of life. This improves the psychosocial wellbeing of both the patient and their families, allowing them to get on with their lives without the constant worry of the disease returning and a terminal prognosis.

The impact of this on the family, as well as the patient, also needs consideration; these families need support during the most difficult time in their lives when a loved one is diagnosed with a potentially terminal disease.

Adjuvant pembrolizumab is the first immune checkpoint inhibitor proven to be a clinically effective and well-tolerated for people with intermediate/high risk locally advanced RCC. This treatment has been granted a license by the US Food and Drug Administration (FDA) and the European Commission (EC). The European Association of Urology (EAU) guidelines have been updated to recommend the use of the adjuvant pembrolizumab for people with RCC at high risk of recurrence after nephrectomy.

We are disappointed that this innovative and clinically effective treatment for intermediate/high risk, locally advanced RCC has been declined on the basis of the use of an unsuitable health economic assessment for small patient groups (a rare or less common cancer): Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) is used in assessment of cost effectiveness for all cancer drugs and is based on a threshold of an ICER per QALY of £30,000, set in 1999 (although recently a threshold of £50,000 has been quoted for life-extending drugs). These assessments have time and again been shown to be unfair for many rare and less common cancer patient groups, denying these patients access to life-

prolonging treatments during a desperately difficult time for both themselves and their families.

The committee's decision to not recommend adjuvant pembrolizumab for intermediate/high risk locally advanced RCC patients denies these people access to an innovative and effective treatment within NHS England, despite the drug being available for kidney cancer patients living in the US and other European countries. This is confusing for the patient community because the European Commission and the FDA have acknowledged the fact that the treatment is effective but NICE recommends the drug as not a good use of NHS England resources. The committee does not attempt to explain how they reconcile these two positions to those directly affected by their decision.

Before the COVID-19 pandemic, cancer survival rates trailed about 10 years behind other comparable European countries, including Italy and Austria. If NHS England is to improve patient outcomes, including the patient experience as well as overall survival, it is vital that a tolerable and effective adjuvant treatment is made available to patients in order that they have the best possible care. If adjuvant treatment is not accessible, it leaves NHS England patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to other kidney cancer patients in the rest of Europe and North America. Poor survival rates might possibly be due to the restrictions in clinical choice brought about by regulatory authorities leading to health inequalities between countries.

Adjuvant pembrolizumab clinical trials have been conducted in patients with locally advanced RCC in the UK. The patients who participated in these trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of adjuvant pembrolizumab on the NHS, we question whether patients will continue to support future research by taking part in clinical trials.

Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative, and clinically effective drugs if the precedent for these drugs is rejection by NICE.

Now that the European Commission has approved adjuvant pembrolizumab, the treatment is available to patients who have private health insurance or who can afford a private prescription, thus creating two-tier access for patients. The NICE appraisal process, therefore, disadvantages less affluent patients, who rely on NHS England to care for them in the later stages of their lives.

In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which patients will respond to which drug, and drug selection is accomplished by trial and error. Clinicians should have the ability to choose the most effective treatment pathway for individual patients, and without an adjuvant treatment, the clinician's choice is seriously compromised. Some patients will face disease progression following surgery and will ultimately be diagnosed with a terminal condition. They will require treatment for metastatic RCC, along with the

psychosocial support and increased cost of treatment that comes with a terminal diagnosis. An adjuvant treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life.

Nowadays, kidney cancer patients do not exist in silos. They communicate widely within online patient communities. International discussion forums exist where patients talk to one another daily, and patients are more aware of the experiences of others, including their access to innovative treatments, quality of life, and treatment successes and failures. News about lack of access to effective medicines ripples out to other patients and families, destroying their hope and positivity.

Information about adjuvant treatments is readily available to patients around the world on websites and discussion forums. Patients and clinicians are right to expect NICE and the pharmaceutical industry to find a way to bring new and innovative treatments to kidney cancer patients in NHS England, so that English patients have the same choices as patients in other countries and to improve outcomes.

Pembrolizumab for adjuvant treatment of renal cell carcinoma [ID3810]

EAG response to company ACD comments

July 2022

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135377.

1 Introduction

This document provides the Evidence Assessment Group's (EAG's) critique of the company's response to the appraisal consultation document (ACD) produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of pembrolizumab for adjuvant treatment of renal cell carcinoma.

The company has revised their base case to remove the truncation of the time on treatment (ToT) curve (previously capped at 1 year to reflect that maximum of 17 cycles of treatment in KEYNOTE-564). In addition, the company has provided a revised patient access scheme (PAS) discount of [redacted]. No further changes have been made to the company's base case analysis, but the company has provided a scenario exploring disease-free survival (DFS) as assessed by blinded independent central review (BICR) as per the committee's request as well as additional scenarios exploring treatment effect waning.

The company's revised base case is presented in Table 1.

Table 1. Company's revised base case results post ACM 1

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine Surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	11,138
Probabilistic results							
Routine Surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	11,821

Abbreviations: ACM, appraisal committee meeting; LYG, life year gained; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio.

Section 2 presents the EAG's critique of the company's scenarios and Section 3 presents the EAG's updated base case and scenarios.

2 Company additional analysis

2.1 Blinded Independent Central Review Disease-Free Survival analysis

As described in the Evidence Assessment Group (EAG) report, disease-free survival (DFS) and overall (OS) data from KEYNOTE-564 are extremely immature ([redacted]). The company has indicated that the next readout from KEYNOTE-564 will be when 332 DFS events have occurred (Figure 3 of the company submission [CS], Document A) and the final analysis for DFS is anticipated to be available in 2024. As such, the EAG maintains that only mature data will alleviate the uncertainties around the modelling of DFS and OS. Nonetheless, exploration of the appropriateness of DFS assessment (either Investigator assessment [IA] or blinded independent central review [BICR]) is independent of the maturity of the data.

In the appraisal consultation document (ACD), the committee noted the difference in hazard ratios between the analyses based on IA and BICR in KEYNOTE-564. The committee was uncertain about why the IA and BICR-assessed results differed but noted that using IA or BICR results had a large effect on the ICER, based on scenario analysis conducted by the EAG. It concluded that IA reflected what is done in UK clinical practice, but it also acknowledged that the BICR data was plausible and may be more methodologically robust. Despite the trial being double blind, the clinical experts at the appraisal committee meeting (ACM) noted that blinding may have been an issue for IA because the adverse events profile.

In their response to the ACD, the company has expanded on their arguments for why they consider the BICR analysis to be less appropriate than the IA analysis:

- The BICR analysis was retrospective rather than real-time (as is commonly done in clinical studies);
- The IA and BICR analyses of DFS are based on different datasets;
- Analysis of DFS by BICR was not statistically powered (as DFS by BICR was not the primary outcome of the study).

The EAG acknowledges the retrospective nature of the BICR analysis and that this can lead to informative censoring. As the company has described, informative censoring can lead to overestimations of the median DFS as patients who are deemed to have disease recurrence by the investigator but not the BICR, would be censored at that point. The EAG notes that median DFS was not reached for either analysis and it is unclear from the data provided how many patients were

censored due to a difference in disease assessment between the IA and the BICR. According to table 15 in the CS, patients were either censored at baseline (due to no evidence of disease [NED]) or at the last tumour assessment showing no disease recurrence in the BICR analysis. The proportion of patients censored at the last assessment showing no disease recurrence was lower in the pembrolizumab arm of the BICR than of the IA analysis, and therefore unlikely to overestimate the median DFS.

A second potential reason for the numerical difference in the results between the two analyses is, as the company points out, that the IA and BICR analyses of DFS are based on different datasets. The BICR analysis included patients who were determined to have no evidence of disease (NED) at baseline as assessed by BICR, which is not affected by the BICR of scans being retrospective. As reported in Table 15 of the CS, nineteen patients (3.8%) in the pembrolizumab arm and 29 patients (5.8%) in the placebo arm were censored at baseline due to evidence of disease according to BICR.

Finally, the EAG agrees that the analysis of DFS by BICR in the KEYNOTE-564 study was not powered to detect a statistically significant difference in DFS between pembrolizumab and placebo but notes that the results of the analysis show a statistically significant difference at the 0.05 level.

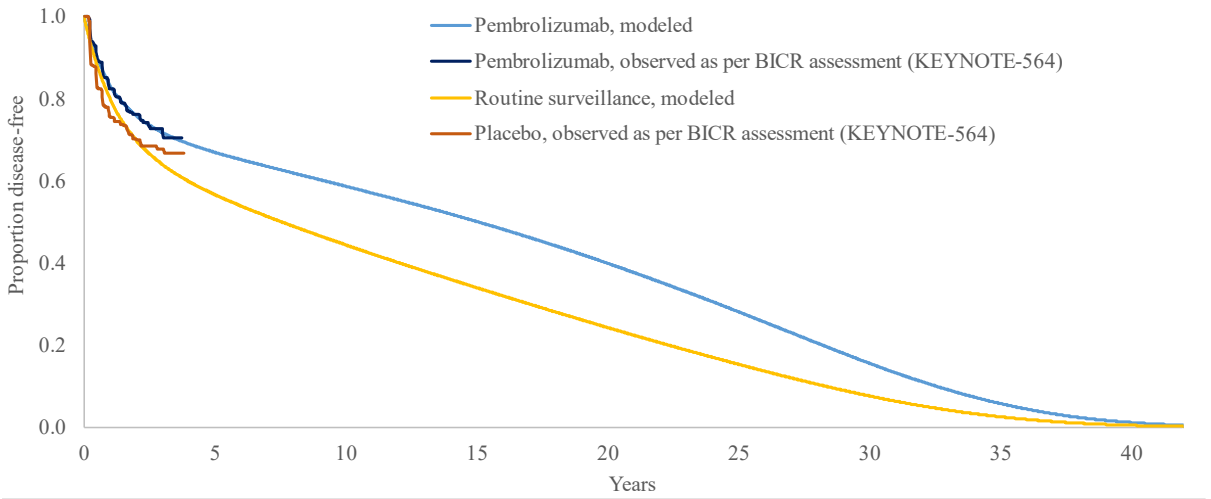
The EAG reiterates that both analyses are methodologically robust and the results of the two analyses should be expected to be similar. However, there is a numerical difference between the results of the analyses, which has an impact on the cost effectiveness. It is unclear why the results differ but there are likely to be several reasons including the different datasets used.

Addressing the request from committee, the company provided a scenario using BICR DFS data to inform the disease-free (DF) to locoregional recurrence (LR) and distant metastases (DM) transition probabilities. The company's method of selecting extrapolations is consistent with the approach described in the CS and the EAG report (Section 4.2.5.1). Out of 56 parametric models using 3 approaches, the company narrowed down the plausible options to the following three models:

- Approach 1 (independently fitted model) combination of exponential (DF to LR) and generalised gamma (DF to DM);
- Approach 2 (proportional hazards [PH] model) combination of exponential (DF to LR) and Gompertz (DF to DM); and
- Approach 3 (time-varying PH model) combination of exponential (DF to LR) and Gompertz (DF to DM).

For the BICR scenario, the company selected the Approach 3 option aligned with their base case approach for IA DFS. Figure 1 presents the company's modelled BICR DFS based on Approach 3. Using BICR DFS increases the company's base case ICER from £11,138 to £17,950.

Figure 1. Company's modelled DFS using BICR data (Figure 3 of the company's comments to the ACD)



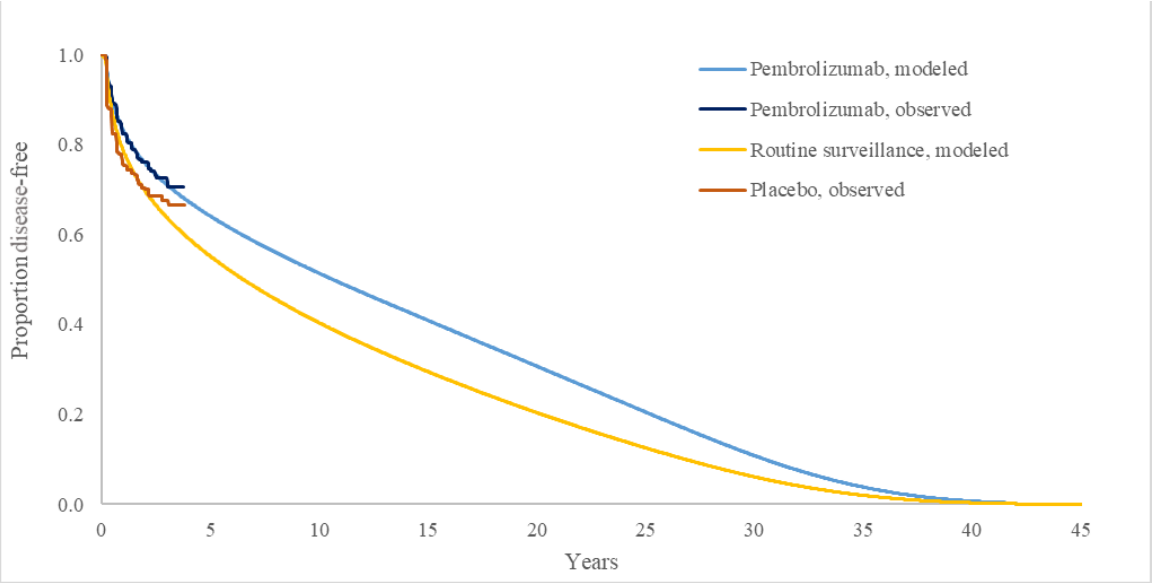
Abbreviations: ACD, appraisal consultation document; BICR, blinded independent central review; DFS, disease-free survival.

As per the original EAG report, the EAG considers that where patient level data are available from a trial, the use of proportional hazards modelling is not necessary and considers that independent models for each treatment arm are preferred, as per the NICE Decision Support Unit Technical Support Document 14[1] (DSU TSD 14). As such, the EAG maintains that the company's Approach 1, which fitted independent models to each treatment arm, is a more robust method for extrapolation of the cause-specific time-to-event data used in the model. However, the EAG cautions that even though Approach 1 is more robust, it is still informed by immature DFS data from KEYNOTE-564 and thus is subject to substantial uncertainty.

The EAG explored the company's selected Approach 1 combination of exponential/generalised gamma extrapolations and found that estimates were slightly more conservative than the Approach 3 for both pembrolizumab and routine surveillance (see Table 2 and Table 3). Figure 2 presents the modelled BICR DFS based on Approach 1. Using Approach 1 increases the ICER from £11,138 to £28,112.

As per their approach in the CS, the company used external sources to validate their choice of extrapolation. The company considered pembrolizumab is expected to have at least a similar magnitude of clinical benefit as adjuvant sunitinib. As such, the company compared the DFS gain at 7 years between the various approaches against the 10.5% DFS gain observed in S-TRAC (adjuvant sunitinib vs placebo) and found that Approach 3 produced a greater gain in DFS (12.2%), whereas the DFS gain for Approach 1 was similar to S-TRAC (10%). As such, the EAG considers Approach 1 for the BICR analysis to be reasonable and presents a version of the EAG base case using these data (see Section 1).

Figure 2. Approach 1 modelled DFS using BICR data



Abbreviations: BICR, blinded independent central review; DFS, disease-free survival.

Table 2. Disease-free and overall survival predictions of BICR scenario parametric models – routine surveillance

Approach/ source	Parametric model combination	Disease-free survival by year					Overall survival by year				
		1 year	3 years	5 years	10 years	30 years	1 year	3 years	5 years	10 years	30 years
Company scenario – Approach 3	**Exponential (DF → LR) and Gompertz (DF → DM)**	79%	65%	58%	46%	8%	98%	89%	81%	64%	13%
Approach 1	**Exponential (DF → LR) and generalised gamma (DF → DM)**	79%	64%	55%	40%	6%	98%	89%	80%	61%	10%
S-TRAC (observed)	-	78%	60%	51%	-	-	99%	91%	82%	-	-
SEER data (observed)	-	80%	59%	48%	33%	-	98%	82%	68%	48%	-
SEER data (extrapolated)	Lognormal (DFS and OS)	82%	59%	47%	31%	12%	97%	82%	69%	45%	10%

Abbreviations: BICR, blinded independent central review; DF, disease-free; DFS, disease-free survival; DM, distant metastases; LR, locoregional recurrence; OS, overall survival.

Table 3. Disease-free and overall survival predictions of BICR scenario – pembrolizumab

Outcome	1 year	3 years	5 years	10 years	30 years
Company scenario - Approach 3 - exponential/Gompertz					
Disease-free survival by year	83%	72%	67%	59%	16%
Overall survival	98%	91%	83%	69%	18%
Approach 1 - exponential/ generalised gamma					
Disease-free survival by year	83%	71%	64%	51%	11%
Overall survival	98%	91%	83%	67%	15%

Abbreviations: BICR, blinded independent central review.

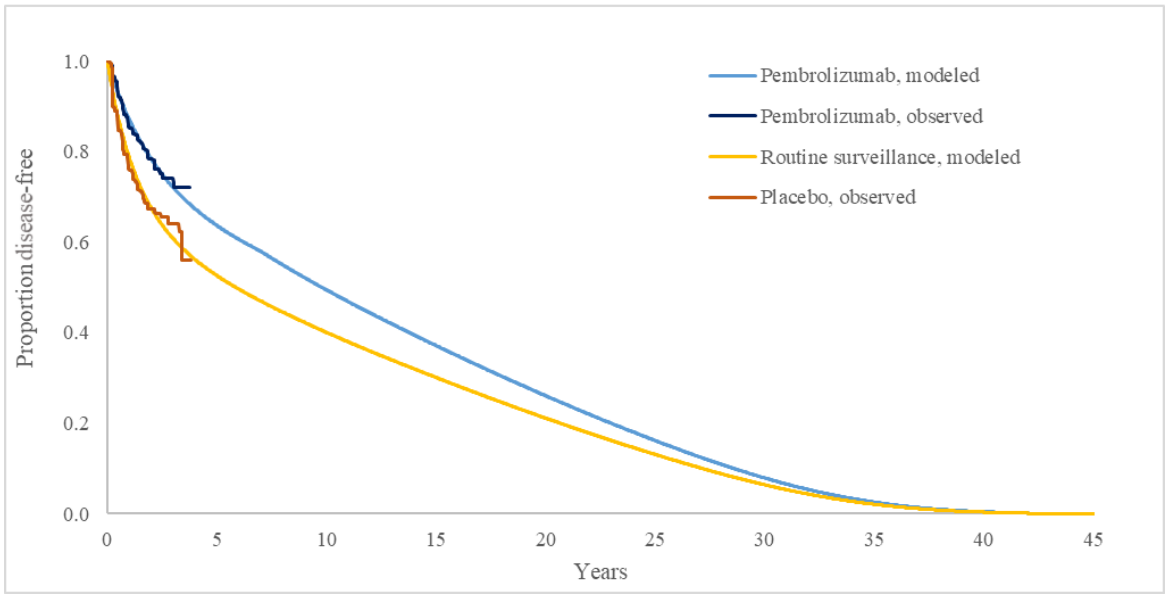
2.2 Treatment waning

In the ACD, the committee considered that the long-term treatment effect of pembrolizumab was uncertain and requested further scenarios with different treatment effect waning assumptions to be explored. Previously, the EAG conducted three scenarios exploring risk of relapse for the pembrolizumab DF to LR and DF to DM transitions equal to routine surveillance at 4, 7 and 10 years.

Preferred treatment effect waning scenarios were not specified in the ACD. Nonetheless, the company explored assumptions around treatment effect waning that were less conservative than the EAG's assumptions, and as such had very little impact on the ICER (Table 4). The company's scenarios assumed that after a certain time point (7 or 10 years) either 15% or 20% of pembrolizumab patients will experience risk of relapse equal to that of routine surveillance patients. This assumes that either 80% or 85% of pembrolizumab patients achieve long term remission. Additionally, the company included a 'wash out' period, where the risk of relapse gradually increases over two years until they equal that of the routine surveillance arm for the proportion of pembrolizumab patients assumed to be affected by treatment effect waning.

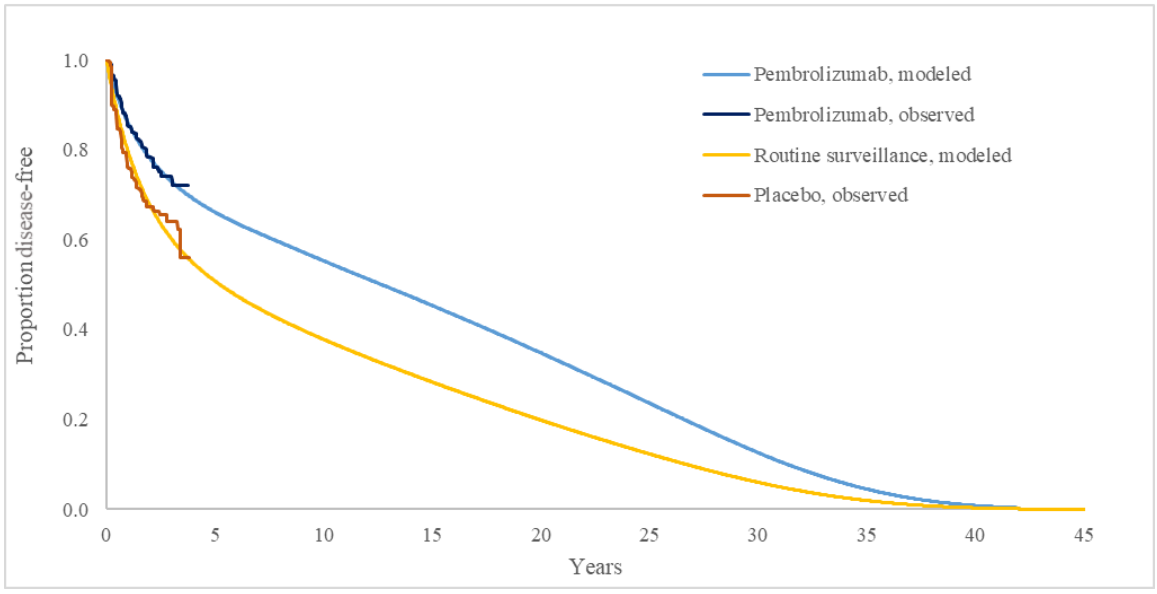
The company stated that the EAG's approach, which assumes the risk of relapse is equal to routine surveillance at a specified time point, results in a 'cliff edge' effect. The EAG considers the company's comment about a 'cliff edge' effect for treatment effect waning refers to "immediate waning", i.e. when the survival curve of the active treatment immediately drops down to the survival curve of the comparator. However, this is not the case in the EAG risk of relapse scenario, which presents a more "gradual waning". Figure 3 presents the EAG's risk of relapse scenario using a time point of 7 years and demonstrates that there is a gradual convergence of the pembrolizumab DFS curve to the routine surveillance curve. Figure 4 presents the company's treatment effect scenario, assuming a time point for waning of 7 year, with a 2-year washout period for 15% of DFS patients.

Figure 3. Example of the EAG risk of relapse scenario - Approach 1 Investigator assessed DFS, waning timepoint of 7 years, 100% of patients affected.



Abbreviations: DFS, disease-free survival; EAG, Evidence Assessment Group.

Figure 4. Company's treatment effect waning scenario - Approach 3 Investigator assessed DFS, waning timepoint of 7 years, 2-year wash out period, 15% of patients affected.



Abbreviations: DFS, disease-free survival.

It is unclear how the company selected the proportion of 15% or 20% of pembrolizumab patients affected by treatment effect waning. However, as acknowledged in the EAG report, an unknown and currently unknowable proportion of pembrolizumab patients may achieve long-term remission. As

such, the EAG presents additional scenarios to illustrate the potential impact of pembrolizumab waning (Table 4), combining the EAG's and company's treatment waning assumptions, removing the washout period (akin to the EAG's assumptions), and including a proportion of patients affected by treatment effect waning (akin to the company's assumptions). Please see Section 3.2 for the same treatment effect waning scenarios applied to the EAG revised base case.

Table 4. Company and EAG treatment effect waning scenarios

Treatment effect parameters			Incremental costs	Incremental QALYs	ICER (£/QALY)
Onset	**Washout**	**Proportion**			
Company revised base case					
No treatment effect waning			[redacted]	[redacted]	**11,138**
Company scenarios					
7 years	2 years	15%	[redacted]	[redacted]	12,201
10 years	2 years	20%	[redacted]	[redacted]	12,093
EAG scenarios					
4 years	Not applied	**100% (EAG original assumption)**	[redacted]	[redacted]	**27,303**
		15%	[redacted]	[redacted]	13,056
		20%	[redacted]	[redacted]	13,726
		50%	[redacted]	[redacted]	18,119
7 years	Not applied	**100% (EAG original assumption)**	[redacted]	[redacted]	**19,754**
		15%	[redacted]	[redacted]	12,350
		20%	[redacted]	[redacted]	12,760
		50%	[redacted]	[redacted]	15,281
10 years	Not applied	**100% (EAG original assumption)**	[redacted]	[redacted]	**16,538**
		15%	[redacted]	[redacted]	11,954
		20%	[redacted]	[redacted]	12,225
		50%	[redacted]	[redacted]	13,849

Abbreviations: EAG, evidence assessment group; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year.

3 EAG analysis

3.1 Correction to the EAG base case

The company highlighted that the EAG's approach to modelling time on treatment (ToT), which removes both the truncation to the pembrolizumab ToT curve and relative dose intensity (RDI), contains a flawed assumption. The company explained that the untruncated curved estimates treatment beyond one year because of missed or delayed doses and removing RDI assumes no missed or delayed doses. Instead, the company suggests that either the ToT curve is untruncated and RDI is applied (98.9%) or the curve is truncated and RDI is 100%. The EAG agrees with the company's assessment of estimating ToT for pembrolizumab accurately and has accepted the company's correction to the EAG base case of removing the truncation to the pembrolizumab ToT curve and applying RDI (which is also now part of the company's revised base case). The corrected EAG base case is presented in Table 5.

For the extrapolation of disease-free (DF) to locoregional recurrence (LR) and distant metastases (DM) transitions, the EAG presents its corrected base case also using blinded independent central review (BICR) DFS data for committee consideration in Table 6. Please note, that when using BICR DFS, the model does not allow for probabilistic sensitivity analysis (PSA) to be run, thus a probabilistic EAG ICER cannot be presented. The EAG considers that the probabilistic BICR ICER is likely to be higher than the deterministic ICER, primarily because of the small QALY gain and large incremental cost, resulting in a highly sensitive ICER. The sensitivity in the ICER is demonstrated when comparing the deterministic and probabilistic ICERs for the IA analysis.

The following assumptions that deviate from the company's revised base case, previously presented to committee, are as listed below:

- Disease-free survival (DFS) modelled using Approach 1 combination of exponential and Gompertz for disease-free (DF) to locoregional recurrence (LR) and distant metastases (DM) transitions;
- Removal of oral administration costs; and
- Alternative subsequent second-line treatment for advanced renal cell carcinoma (aRCC) scenario - 50% cabozantinib and 50% no active treatment.

Table 7 presents the cumulative impact of each change on the ICER.

Table 5. Corrected EAG base case - investigator assessed DFS

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Routine Surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	22,367
Probabilistic results							
Routine Surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	27,872

Abbreviations: DFS, disease-free survival; LYG, life year gained; ICER, incremental cost effectiveness ratio; QALY, quality adjusted life year.

Table 6. Corrected EAG deterministic base case - BICR DFS*

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]	[redacted]	-	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	27,996

Abbreviations: BICR, blinded independent central review; DFS, disease-free survival; ICER, incremental cost effectiveness ratio; LYG, life year gained; QALY, quality adjusted life year.

*Model does not contain functionality to run PSA using the BICR scenario.

Table 7. EAG's preferred model assumptions

Preferred assumption	Deterministic ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	11,138	11,138
Removal of oral administration costs	11,787	11,787
Alternative 2L subsequent treatment market share estimates - 50% cabozantinib and 50% no active treatment	10,311	11,026
Approach 1 combination exponential/ Gompertz - investigator assessed DFS	**22,479**	**22,367**
Approach 1 combination exponential/ generalised gamma - BICR DFS	**28,112**	**27,996**

Abbreviations: 2L, second-line; BICR, blinded independent central review; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

3.2 Scenarios around the EAG base case

Table 8 presents the treatment effect waning scenarios applied the EAG base case using either IA or BICR DFS.

Table 8. Treatment effect waning scenarios applied to the EAG base case

Treatment effect parameters			Investigator assessed DFS			BICR DFS		
Onset	Washout	Proportion	Incremental costs	Incremental QALYs	ICER (£/QALY)	Incremental costs	Incremental QALYs	ICER (£/QALY)
Corrected EAG base case								
No treatment effect waning			[redacted]	[redacted]	**22,367**	[redacted]	[redacted]	**27,996**
Company scenarios								
7 years	2 years	15%	[redacted]	[redacted]	23,750	[redacted]	[redacted]	29,821
10 years	2 years	20%	[redacted]	[redacted]	23,732	[redacted]	[redacted]	29,548
EAG scenarios								
4 years	Not applied	**100% (EAG original assumption)**	[redacted]	[redacted]	**34,472**	[redacted]	[redacted]	**59,011**
		15%	[redacted]	[redacted]	24,062	[redacted]	[redacted]	31,298
		20%	[redacted]	[redacted]	24,635	[redacted]	[redacted]	32,474
		50%	[redacted]	[redacted]	28,174	[redacted]	[redacted]	40,481
7 years	Not applied	**100% (EAG original assumption)**	[redacted]	[redacted]	**32,833**	[redacted]	[redacted]	**44,321**
		15%	[redacted]	[redacted]	23,855	[redacted]	[redacted]	30,106
		20%	[redacted]	[redacted]	24,356	[redacted]	[redacted]	30,832
		50%	[redacted]	[redacted]	27,433	[redacted]	[redacted]	35,449

10 years	Not applied	**100% (EAG original assumption)**	[redacted]	[redacted]	**30,136**	[redacted]	[redacted]	**37,464**
		15%	[redacted]	[redacted]	23,514	[redacted]	[redacted]	29,346
		20%	[redacted]	[redacted]	23,897	[redacted]	[redacted]	29,801
		50%	[redacted]	[redacted]	26,214	[redacted]	[redacted]	32,587

Abbreviations: BICR, blinded independent central review; EAG, evidence assessment group; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year.

4 References

1. Latimer N. NICE DSU Technical Support Document 14. Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013 [Available from: http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf accessed May 2021.