NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

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.

Appraisal title

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	MSD	The Appraisal Consultation Document states on page 7 (Section 3.4) that "The final overall survival data cut is expected in the third quarter of 2023." MSD wish to clarify that this data is currently expected in the third quarter of 2022, with data analysis to follow shortly afterwards.	Thank you for your comment. The date has been corrected in Section 3.4 of the FAD.
2	Consultee	Eisai	Section 1, page 3 – The appraisal consultation document states, "*Clinical trial evidence suggests that people having lenvatinib plus pembrolizumab have longer before their disease gets worse than people having sunitinib, but this is uncertain for people with favourable-risk cancer*". Eisai believe that this statement is inaccurate for people with favourable-risk cancer, given a statistically significant improvement was observed with lenvatinib plus pembrolizumab for progression-free survival and progression after next line of therapy in this population in the pivotal trial (CLEAR). At the time of the final progression-free survival analysis (interim analysis 3), the hazard ratio for progression-free survival was 0.41 (95% confidence interval: 0.28, 0.62); p<0.0001, and the hazard ratio for progression after next line of therapy was 0.57 (95% confidence interval: 0.32, 1.00); [redacted]. In relation, the appraisal consultation document contradicts this statement in Section 3.4, page 7; "*The trial results demonstrated a progression-free survival benefit with lenvatinib plus pembrolizumab over sunitinib in the whole population and across all risk groups*". Therefore, we request "*but this is uncertain for people with favourable-risk cancer*" is removed from the statement on page 3.	Thank you for your comment. The specified text has been removed from the FAD.
3	Consultee	Eisai	Section 3.2, page 5 – The appraisal consultation document states, "*The committee heard that clinicians assess advanced renal cell carcinoma on presentation using the International Metastatic Renal Cell Carcinoma (IMDC) risk score. This measure uses a range of criteria to determine whether a person has favourable, intermediate or poor risk of* ***experiencing disease progression***". Eisai believe that this statement is inaccurate, as the IMDC-risk model predicts survival in patients with metastatic renal cell carcinoma treated with systemic therapy, not risk of experiencing disease progression. Therefore, we recommend that this statement is corrected.	Thank you for your comment. This statement has been corrected in Section 3.2 of the FAD.
4	Consultee	Eisai	Section 3.3, page 7 – The appraisal consultation document states, "*The trial stratified people by IMDC risk score*". People were stratified based on the Memorial Sloan-Kettering Cancer Center (MSKCC) risk score for metastatic renal cell carcinoma in the CLEAR trial, therefore this statement should be corrected.	Thank you for your comment. We have removed reference to MSKCC risk score in Section 3.3 of the FAD for clarity.
5	Consultee	Eisai	Section 3.6, page 8 – The title states, "*The EAG prefers a Bayesian network meta-analysis because of*	Thank you for your comment.

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			uncertainty in the proportional hazards assumption". Eisai believe this statement is unclear, as: 1. Both the proportional hazards-based network meta-analysis (referred to as the 'Bayesian network meta-analysis' in the appraisal consultation document) and the fractional polynomial analysis are performed using a Bayesian framework 2. Preferring the proportional hazards-based network meta-analysis (referred to as the 'Bayesian network meta-analysis' in the appraisal consultation document) *because of uncertainty in the proportional hazards assumption* is not a logical statement Eisai propose that the 'Bayesian network meta-analysis' is renamed as the 'proportional hazards network meta-analysis' (or similar) throughout, and the title of this section is re-worded to: "The EAG prefers a **proportional hazards network meta-analysis despite the** uncertainty in the proportional hazards assumption", or similar.	All previous references to "Bayesian network meta-analysis" have been replaced with "proportional hazards network meta-analysis" in the FAD.
6	Consultee	Eisai	Section 3.6, page 8 – The appraisal consultation document states, "*The committee recalled that previous NICE technology appraisals (tivozanib for treating advanced renal cell carcinoma, cabozantinib for untreated advanced renal cell carcinoma, nivolumab with ipilimumab for untreated advanced renal cell carcinoma and avelumab with axitinib for untreated advanced renal cell carcinoma) had concluded that sunitinib and pazopanib are likely of equivalent clinical effectiveness, and that tivozanib may have a similar effect to sunitinib or pazopanib. The committee agreed with these decisions and so focused on the comparisons with cabozantinib, and nivolumab plus ipilimumab*". It is unclear why the assumption that pazopanib and tivozanib have equivalent effectiveness to sunitinib means the only relevant comparisons are with cabozantinib and nivolumab plus ipilimumab in the intermediate and poor risk population. We suggest this is clarified further in Section 3.6.	Thank you for your comment. Section 3.6 of the FAD has been amended for clarity on this issue.
7	Consultee	Eisai	Section 3.7, page 9 – The title states, "*The companies prefer the results from fractional polynomial NMAs, but these are highly uncertain".* Base-case analyses submitted by Eisai used proportional hazards network meta-analyses, and this was Eisai's preferred base case. Therefore, we request this statement is corrected accordingly.	Thank you for your comment. The title of Section 3.7 has been corrected in the FAD.
8	Consultee	Eisai	Section 3.12, page 14 – The appraisal consultation document states, "*The committee noted that the Kaplan–Meier plots for the observed overall survival data for lenvatinib plus pembrolizumab in the favourable-risk subgroup was very close to that for sunitinib, with the curves almost overlaid. The overall survival extrapolation for sunitinib was therefore not clinically plausible because the gamma distribution likely overestimated survival for sunitinib compared with lenvatinib plus pembrolizumab. The committee agreed that this discrepancy might be attributable to low patient numbers and the low number of events experienced by people in the favourable-risk subgroup, and concluded that the overall survival extrapolations in the favourable-risk subgroup are not clinically plausible*." As the committee agreed that the evidence assessment group's overall survival extrapolations are not clinically plausible in the favourable risk group, Eisai are concerned about the implications of the associated results being in the public domain without appropriate caveats, due to the potentially damaging interpretation of the cost-	Thank you for your comment. No change to FAD required.

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			effectiveness of lenvatinib plus pembrolizumab. Therefore, Eisai request that all cost-effectiveness results for the favourable risk group are redacted. The results and corresponding discussion for the favourable risk group are included in the following sections in the committee papers: • Section 5.22.2 (favourable risk), results discussion within the paragraph and results presented within Table 66 and Table 67 • Section 5.23.2, results discussion within the paragraphs and results presented within Table 70 and Table 71 • Section 5.24.1 (favourable risk; sensitivity analyses), discussion within the paragraph • Section 5.24.3 (favourable risk; scenario results), last sentence of the paragraph and the results presented in Table 74, Table 75, Table 76 • Section 5.25 (discussion of cost-effectiveness analyses), paragraph 4 • Section 6.1.3 (cost-effectiveness results), paragraph 2 • In 'Assessment group response to Company consultations comments'; Section 1.2.2, Table 3, Table 4, and Table 5 • In 'Assessment group response to company consultations comments'; Section 1.2.3, Table 6 Eisai have a similar concern regarding the results for the all-risk population. The appraisal consultation document does not include a statement regarding the plausibility of the overall survival extrapolations for the all-risk population. However, as stated by Eisai in response to the evidence assessment group's report, the overall survival extrapolations used by the evidence assessment group led to a long-term hazard ratio of approximately [redacted] for lenvatinib plus pembrolizumab vs sunitinib, which contradicts the results from the CLEAR trial, which showed Kaplan Meier curves with a statistical significance in favour of lenvatinib plus pembrolizumab (hazard ratio of 0.72 [95% CI: 0.55, 0.93]), based on the updated overall survival analysis. In the context of the committee's main concern for the favourable risk population being that the extrapolated overall survival for sunitinib is likely overestimated compared with the Kaplan Meier data, Eisai believe this also applies for the all-risk population, and request that cost-effectiveness results for the all-risk population are also redacted on the same basis. The results and corresponding discussion for the all-risk population are included in the following sections within the committee papers: • Appendix 17; Section 9.17.13 (deterministic results), Table 128 and Table 129 • Appendix 17; Section 9.17.14 (probabilistic sensitivity analysis results), Table 130 and Table 131 • Appendix 17; Section 9.17.16 (Assessment group deterministic scenario analysis results (all-risk population)), Table 132, Table 133, and Table 134 In 'Assessment group response to Company consultation comments'; Section 1.2.3, Table 6, Table 7, and Table 8	
9	Consultee	Eisai	There is a factual inaccuracy in the data presented on slide 16 of the public committee slides. In the last row, the	Thank you for your comment.

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			PFS-rate time points should read 6-, 12-, 18-, and 24 months, not 12-, 18-, 24- and 36 months.	No change to FAD required.
10	Consultee	BMS	BMS are concerned that the recommendation (ACD section 1.1) of pembrolizumab with lenvatinib (PEMBRO+LENVA) for untreated advanced renal cell carcinoma (RCC) in adults, in the intermediate or poor IMDC risk population only if "nivolumab with ipilimumab would otherwise be offered" is open to misinterpretation for the following reasons: • There are no NICE restrictions as to which intermediate or poor risk patients nivolumab with ipilimumab (NIVO+IPI) can be offered. • The mode of action and trial data for the two treatment combinations treatments do not support the implication that the patient populations are equivalent. • It is unclear how this guidance will/ should be implemented in clinical practice BMS request an update to the recommendation to remove the restriction of "patients for whom nivolumab with ipilimumab would otherwise be offered" to ensure clarity of the recommendation, in line with appropriate clinical decision-making criteria. It is understood that this recommendation is intended to prevent the use of PEMBRO+LENVA in patients who would be suitable for cabozantinib, as PEMBRO+LENVA is not considered cost-effective against cabozantinib. The inclusion of NIVO+IPI within the NICE recommendation may not result in such a restriction as the NICE recommendation for NIVO+IPI includes all untreated advanced RCC patients with intermediate-/poor IMDC risk, which will not help achieve a cost-effective use of PEMBRO+LENVA and will likely complicate clinician decision-making. Given that sunitinib, pazopanib, tivozanib and avelumab with axitinib (AVE+AXI) are currently recommended for patients regardless of IMDC risk (i.e. all risk), this also means they are recommended for intermediate-/poor- IMDC risk patients, who are a subset of the all-risk patients, along with NIVO+IPI and cabozantinib (see Figure 1). Therefore, the current wording of the NICE recommendation of PEMBRO+LENVA would enable prescribing to any intermediate or poor risk patient, despite not being cost-effective against cabozantinib. It should be noted that sunitinib, pazopanib, and tivozanib have not been appraised against PEMBRO+LENVA in the intermediate-/poor- risk advanced RCC population despite being available treatment options on the NHS for these patients. **Figure 1. Proposed treatment options for patients with untreated advanced RCC with intermediate-/poor-IMDC risk**	Thank you for your comment. In order to provide further clarity, section 3.19 of the FAD has been updated to include a summary of the preferred treatment pathway for people with intermediate or poor risk, as confirmed by clinical experts.

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			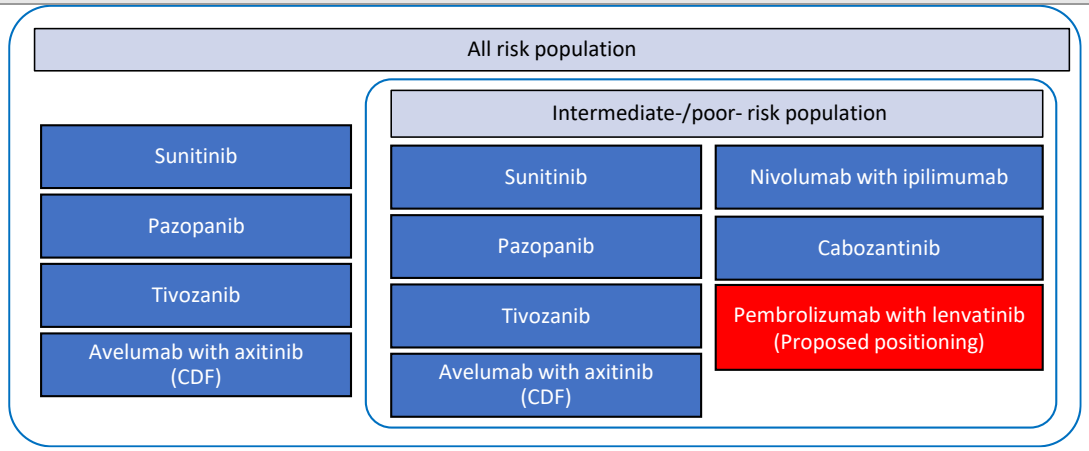 In Technology Appraisal Guidance TA780, NIVO+IPI has been demonstrated to be cost-effective for untreated advanced RCC with intermediate-/poor- IMDC risk when compared with single agent tyrosine kinase inhibitor (TKI) sunitinib and pazopanib (comparators at the time of the submission)[i]. The ACD draft recommendation for PEMBRO+LENVA states that it was not cost-effective versus cabozantinib, but was cost effective against NIVO+IPI, a conclusion which is also dependent on the evidence included and scientific approaches used in this assessment, which differ from those in TA780 and prior 1L RCC assessments by NICE (see comments in section 2, 3 and 4). Tying the NICE recommendation of PEMBRO+LENVA to the populations suitable for NIVO+IPI will not ensure the cost-effective use of PEMBRO+LENVA by precluding use in patients who are candidates for single agent TKI, as NIVO+IPI can be offered to those patients. In addition, it is unclear what clinical decision-making criteria should be applied to enable clinicians to identify patients suitable for PEMBRO+LENVA. For example, current NICE guidance does not distinguish how a clinician should decide which 1L advanced RCC intermediate-/poor- IMDC risk patients should be offered NIVO+IPI versus who should be offered cabozantinib. At present, patients are able to be offered both NIVO+IPI or cabozantinib, along with other single agent TKIs and IO+TKI (AVE+AXI) not included in the scope of this assessment by the EAG and NICE committee. Therefore, being suitable to be offered NIVO+IPI is not mutually exclusive to suitability for single agent TKI or AVE+AXI. During the PEMBRO+LENVA ACM, clinical experts stated that "*for people with intermediate- and poor-risk disease, cabozantinib, and nivolumab plus ipilimumab are treatment options, with nivolumab plus ipilimumab usually preferred for people who are fit enough to receive it*". It is not clear if the guidance is intended to restrict treatment to the "fit" subgroup, with unfit patients being suitable for single agent TKI, or AVE+AXI via the CDF. When deciding to treat a patient, several factors are taken into account, including but not limited to, clinical status, fitness and patient preference. Fitness is one, but not the only, factor in deciding a course of treatment, and it is important for all factors to be considered when deciding which first-line therapy to take.	

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			To avoid confusion in clinical decision-making and ensure appropriate prescribing of PEMBRO+LENVA within cost-effective criteria, BMS request the removal of the restriction of PEMBRO+LENVA to "patients for whom nivolumab with ipilimumab would otherwise be offered" and update to the recommendation to ensure clarity of the recommendation.	
11	Consultee	BMS	BMS are concerned that not all relevant evidence has been taken into account for the appraisal of PEMBRO+LENVA, resulting in unreasonable interpretations and conclusions of the evidence. BMS believe the evidence around the CDF Review of NIVO+IPI, appropriateness of the systematic literature review (SLR) and NICE appraisal precedence presented are relevant to the current appraisal and should have been consider by the appraisal committee. The SLR performed by the EAG does not capture all relevant comparator publications which were available at the time of the search performed in October 2021 and November 2021, for databases and conference proceedings, respectively. At the time of the database search, CheckMate 214 trial with 48-month follow-up (published November 2020) as a scientific paper and 60-month minimum follow-up (published September 2021) as a conference poster were published and available in the public domain.[ii,iii] This evidence would provide an additional 6- to 18-months of additional follow-up to the included CheckMate 214 trial (minimum 42-months follow-up). The additional follow-up which has not been appropriately captured or included within the current appraisal demonstrates that a greater proportion of patients are continuing to benefit across all endpoints when treated with NIVO+IPI compared with sunitinib. The CDF review of NIVO+IPI included the 60-month minimum follow-up data from CheckMate 214, an additional 30-months of follow-up than was available at the time of the initial appraisal and CDF entry. At the time of the PEMBRO+LENVA Assessment Group (AG) Report (March 2022), NIVO+IPI was subject to an ongoing CDF review which resulted in a draft positive FAD in February 2022 and positive TA guidance in March 2022 (TA780).[i] Given NICE's decision to include NIVO+IPI as a comparator prior to the positive CDF review, TA780 should be retrospectively included as a NICE technology appraisal source for clinical effectiveness studies (see AG Report, page 40, Table 8). The inclusion of TA780 and the 60-month minimum-follow-up of CheckMate 214 would help address a number of key uncertainties raised by the committee and EAG during the appraisal of PEMBRO+LENVA, given the shorter follow-up of the CLEAR study. **Duration of follow-up** From the CLEAR trial, PEMBRO+LENVA has a short follow-up with median follow-up of 26.6 months for progression-free survival (PFS) and 33 months for OS compared with the minimum follow-up of 60 month from the CheckMate 214 study of NIVO+IPI in TA780. With minimum follow-up of 30-months (median follow up: 32.4 months), NIVO+IPI entered into the CDF in order to address clinical uncertainties including the long-term benefit of NIVO+IPI relative to sunitinib, subsequent treatments in clinical practice, and the proportion of intermediate- and poor- risk in clinical practice (See NIVO+IPI CDF Review submission, section A.1 page 7). **Overall Survival** Consistent with the 30-month data cut; the 42-month, 48-month and 60-month data cut shows patients treated with NIVO+IPI continue to demonstrate a statistically significant improvement in OS compared with patients	Thank you for your comment. Including the updated data from the CheckMate 214 trial in the EAG NMAs has had little impact on the results, and the conclusions drawn in the original EAG report remain the same. Section 3.17 has been updated to confirm that this was understood and considered by the committee.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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<tr><td></td><td></td><td></td><td>
treated with sunitinib across the observed study period. With the 30-month data cut, the median OS for the NIVO+IPI arm had not been reached; and with the 60-month data cut, this was realized at 47.0 (95% confidence interval [CI]: 35.4, 57.4) months compared with 26.6 (95% CI: 22.1, 33.5) months with sunitinib, a gain in median OS of 20 months for NIVO+IPI versus sunitinib (see Table 1 and Figure 2). This additional evidence demonstrates that, with further follow-up, the long-term OS benefit of NIVO+IPI is maintained versus sunitinib.

Table 1. Summary of key CheckMate 214 trial OS results
<table>
<tr><th>Outcome</th><th>Treatment</th><th>Median, months (95% CI)</th><th>HR (95% CI)</th></tr>
<tr><td colspan="4">Overall survival</td></tr>
<tr><td rowspan="2">30 month minimum follow up[iv]</td><td>NIVO+IPI (n=425)</td><td>NA (35.6 to NA)</td><td rowspan="2">0.66 (0.54 to 0.80)</td></tr>
<tr><td>Sunitinib (n=422)</td><td>26.6 (22.1 to 33.4)</td></tr>
<tr><td rowspan="2">42-month minimum follow-up[v]</td><td>NIVO+IPI (n=425)</td><td>47.0 (35.6 - NA)</td><td rowspan="2">0.66 (0.55-0.80)</td></tr>
<tr><td>Sunitinib (n=422)</td><td>26.6 (22.1 - 33.5)</td></tr>
<tr><td rowspan="2">48-month minimum follow-up[ii]</td><td>NIVO+IPI (n=425)</td><td>48.1 (35.6, NA)</td><td rowspan="2">0.65 (0.54, 0.78)</td></tr>
<tr><td>Sunitinib (n=422)</td><td>26.6 (22.1, 33.5)</td></tr>
<tr><td rowspan="2">60 month minimum follow up[iii]</td><td>NIVO+IPI (n=425)</td><td>47.0 (35.4 to 57.4)</td><td rowspan="2">0.68 (0.58 to 0.81)</td></tr>
<tr><td>Sunitinib (n=422)</td><td>26.6 (22.1 to 33.5)</td></tr>
</table>
CI=confidence interval; HR=hazard ratio; NA=not applicable

Figure 2. KM curve of OS by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)
</td><td></td></tr>
</table>

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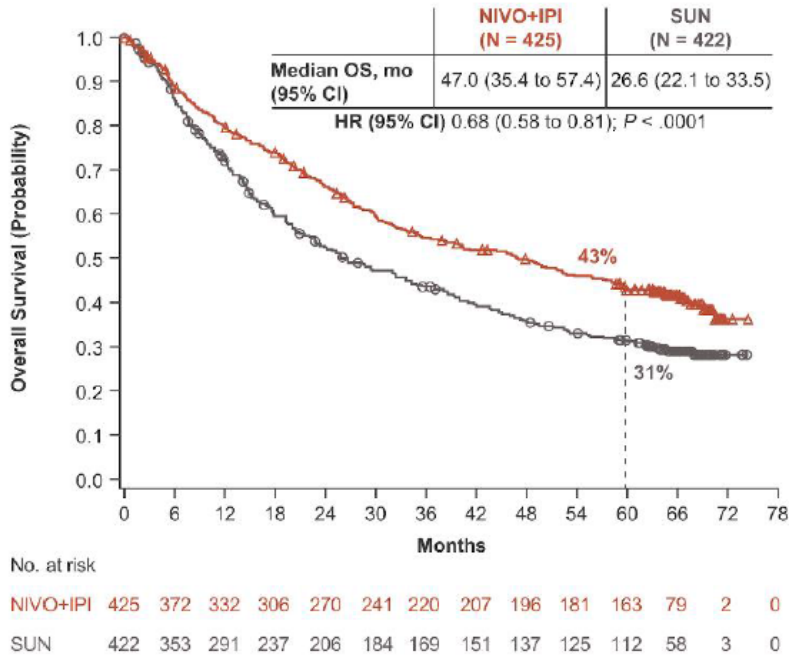

Key: KM, Kaplan–Meier; OS, overall survival.

Table 2. OS rates by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)

Timepoint in months	OS rates by treatment, %	
	NIVO+IPI	Sunitinib
1	[redacted]	[redacted]
3	[redacted]	[redacted]
6	[redacted]	[redacted]
12[iv]	80.0	72.0
24[ii]	66.4	52.4

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36	[redacted]	[redacted]
48[ii]	50.0	35.8
60	43.0	31.3

One of the key uncertainties raised during the PEMBRO+LENVA Appraisal Committee Meeting (ACM) was around the modelling of OS, PFS and TTD. During the initial appraisal of NIVO+IPI with 30-months of minimum follow-up (TA581), the committee considered "both the log-normal, and Kaplan–Meier with exponential extrapolation, curves clinically plausible, concluding that it would take both into account in its decision making".[vi] The CDF review of NIVO+IPI with 60-months of minimum follow-up demonstrated the grossly underpredicted OS for both treatment arms in CheckMate 214 when using the KM+exponential extrapolation versus the 60-month CheckMate 214 data, as seen in Figure 3 (reproduced from CDF review submission. Section A.7.2, Figure 5). During the CDF review of NIVO+IPI, the ERG report stated that the ERG "at the time of the initial appraisal (using 30-month minimum follow-up CheckMate 214 trial data) were both overly pessimistic" (TA780 ERG report section 4.1.1 page 23), with both the ERG and committee concluding that the extrapolations of overall survival using log-normal function were appropriate for both treatment arms. Therefore, if log-normal is appropriate to model sunitinib from CheckMate 214, and KM+exponential underestimates OS over the longer term, it should be considered that in this assessment of PEMBRO+LENVA, with the same comparator arm of sunitinib, the KM+exponential is inappropriate to model the control arm. Further, given that the KM+exponential also underestimated the longer-term survival of NIVO+IPI, the application of a single constant HR, as based on the NMA to the sunitinib arm, is likely to underestimate the longer-term data from CheckMate 214.

The CDF appraisal of NIVO+IPI TA780 FAD states, "The committee considered that the updated data supported the company's choice of the log-normal hazard function and that a proportion of people in CheckMate 214 would effectively be 'cured' with immunotherapy. The committee concluded that the extrapolations of overall survival were appropriate but, to explore uncertainty, it considered sensitivity analyses using other assumptions around extrapolating how the rate of death changes over time in its decision-making."[i] Therefore, as the committee wanted to explore different assumptions around rate of death changing over time, it would be fair to conclude that it is inappropriate to model NIVO+IPI using a constant hazard rate via the exponential function.

As such, BMS would encourage, for validation, to compare absolute reported landmark OS data from TA780 (NIVO+IPI: 43.0%, sunitinib: 31.3%) as reported in **Error! Reference source not found.** and Table 2 above, with the 5-year predicted OS using the KM+exponential approach in this assessment.

Figure 3. OS extrapolations based on 30-month CheckMate 214 (KM + exponential, log-logistic, and log-normal) versus OS 60-month CheckMate 214 KM data – intermediate-/poor-risk patients (Reproduced from NIVO+IPI CDF Review, A.7.2 page 33 figure 5)

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			[redacted] The PEMBRO+LENVA ACD states that the "EAG's extrapolation of overall survival in the intermediate and poor-risk group is suitable for decision making" (ACD section 3.11) even though the updated OS analysis for PEMBRO+LENVA (median 33-months follow-up for OS) is still relatively immature with [redacted] and [redacted] of deaths occurring in the PEMBRO+LENVA and sunitinib groups, respectively (median OS not reached for both treatment arms; PEMBRO+LENVA ACM slides). When compared with NIVO+IPI on entry to the CDF, 43% of NIVO+IPI and 54% of sunitinib OS events had occurred with the 30-month minimum follow-up data (median follow-up of 32.4 months [IQR: 13.4,36.3]) and the committee noted that "given the immaturity of the data, there was substantial clinical uncertainty about the long-term effectiveness of nivolumab with ipilimumab".[vi] Despite the immature data from the CLEAR study, the AG has considered the KM+exponential extrapolation appropriate for OS on the basis that the CLEAR trial PEMBRO+LENVA OS hazard was constant beyond week 50. However, it is clear from the OS smoothed hazard plots for both NIVO+IPI and sunitinib from CheckMate 214 that with 60-month minimum follow-up data, a non-constant hazard is observed for both treatment arms; therefore, a constant hazard is highly unlikely to provide a good fit to the data as the extrapolated portion of these models consistently underestimates OS (see Figure 3, Figure 4 and Figure 5). Goodness-of-fit statistics from the CDF review of NIVO+IPI indicated that the exponential extrapolation provided the worst statistical fit to	

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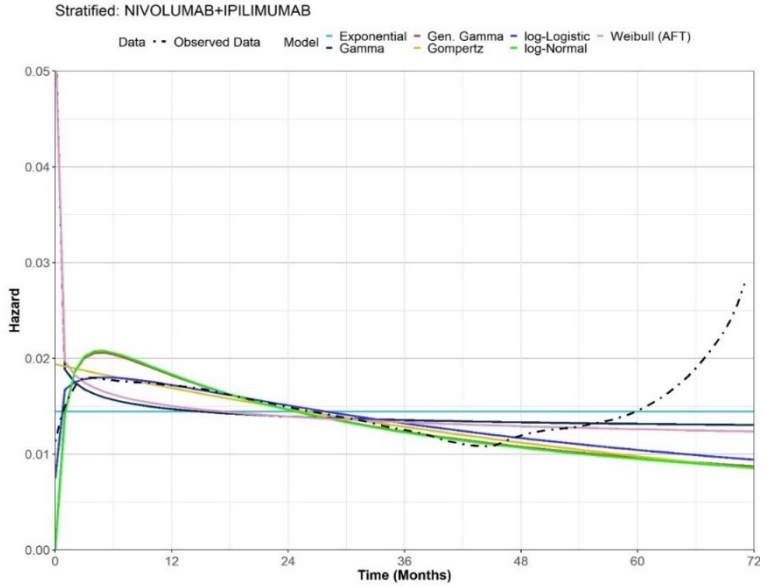
			the data as it has the highest Akaike information criterion (AIC) and Bayesian information criterion (BIC) values across both treatment arms (see also NIVO+IPI CDF Review, section A.15.2.2 page 63, table 19). **Figure 4. NIVO+IPI smoothed hazard plots for OS and fitted parametric survival models – CheckMate 214 intermediate/poor risk patients (60-month minimum follow-up) (Reproduced from NIVO+IPI CDF Review A.15.2.2 Figure 19)**  **Figure 5. Sunitinib smoothed hazard plots for OS and fitted parametric survival models – CheckMate 214 intermediate/poor risk patients (60-month data cut) (Reproduced from NIVO+IPI CDF Review document A.15.2.2 Figure 20)**	

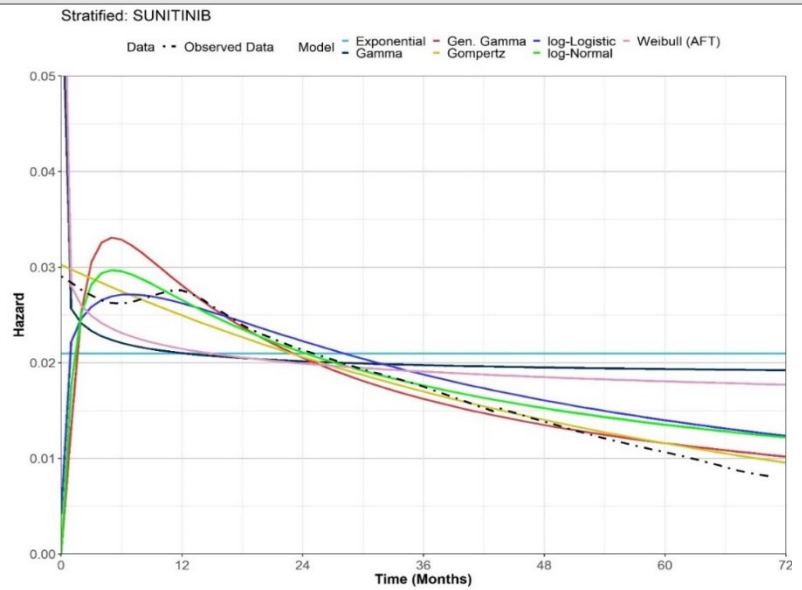
Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 **Progression-Free Survival** In both the original submission for NIVO+IPI and CDF review, both the ERG and committee preferred analysis was to use the secondary definition of PFS, which does not censor on receipt of subsequent therapy. This appraisal of PEMBRO+LENVA considers the primary definition of IRRC-assessed PFS from CheckMate 214, which was part of the co-primary endpoint of the trial. Both the PFS (per IRRC) by primary definition and secondary definition demonstrate a consistently improved PFS versus sunitinib across the observed study period, with an increasing incremental gain in absolute PFS versus sunitinib with additional follow-up (see Table 3). As seen in the KM curve, a plateau appears to be forming from approximately 2 years for NIVO+IPI, which is not observed for sunitinib (see Figure 6, Figure 7 and Figure). Patients treated with NIVO+IPI have a significantly longer median PFS compared with sunitinib, further supporting the unique durable response seen with NIVO+IPI, as otherwise evidenced in the gain in median DoR versus sunitinib. It is clear from the plateau seen in the KM curves and the continuous improvement in HR that NIVO+IPI offers significant and clinically relevant benefit for patients in terms of PFS versus sunitinib, which is sustained with longer term follow-up which has not been captured in the current appraisal. In addition, the application of a single hazard ratio from an NMA, as per the AG's approach in this appraisal, is inappropriate for extrapolation of NIVO+IPI PFS as it is unlikely to capture the observed PFS as reported from the CheckMate 214 study. BMS would encourage, for validation, to compare the predicted landmark PFS for NIVO+IPI using the approach in this appraisal versus landmark PFS (per IRRC) as reported in the CheckMate 214 publications (PFS per IRRC for NIVO+IPI: 32.7% at 48 months and 31% at 60 months; Figure 6 and Figure 7). As the intermediate/poor risk information is redacted, we cannot provide the comparison as a matter of validation for the PFS predictions.	

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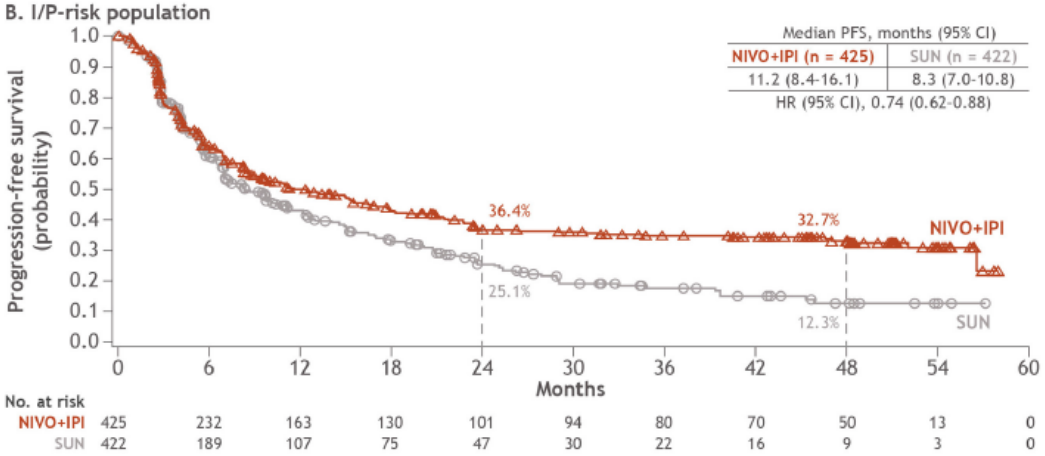
			Figure 6 KM curve of PFS by treatment arm - CheckMate 214 intermediate-/poor-risk patients (48-month data cut; IRRC primary definition)[ii]  **Figure 7. KM curve of PFS by treatment arm - CheckMate 214 intermediate-/poor-risk patients (60-month data cut; IRRC primary definition)**	

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			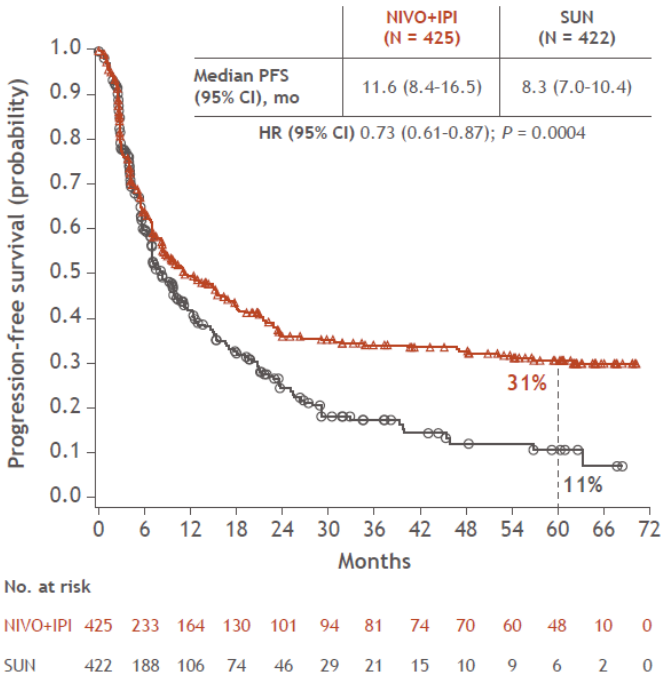 **Figure 8: KM curve of PFS by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut, IRRC secondary definition)**	

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
			[redacted]	

Table 3 Summary of key CheckMate 214 trial PFS results

Outcome	Treatment	Median, months (95% CI)	HR (95% CI)
Progression-free survival (IRRC secondary definition)			
18 month minimum follow up	NIVO+IPI (n=425)	[redacted]	[redacted]
	Sunitinib (n=422)	[redacted]	
60 month minimum follow up	NIVO+IPI (n=425)	[redacted]	[redacted]
	Sunitinib (n=422)	[redacted]	

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td colspan="4">Progression-free survival (Investigator-assessed, primary definition)</td></tr>
<tr><td rowspan="2">30 -month minimum follow-up[iv]</td><td>NIVO+IPI (n=425)</td><td>8.2 (6.9-10.0)</td><td rowspan="2">0.77 (0.65 - 0.91)</td></tr>
<tr><td>Sunitinib (n=422)</td><td>8.3 (7.0-8.8)</td></tr>
<tr><td colspan="4">Progression-free survival (IRRC-assessed, primary definition)</td></tr>
<tr><td rowspan="2">42-month minimum follow-up[v]</td><td>NIVO+IPI (n=425)</td><td>11.6 (8.4-15.5)</td><td rowspan="2">0.75 (0.62-0.90)</td></tr>
<tr><td>Sunitinib (n=422)</td><td>8.3 (7.0-10.8)</td></tr>
<tr><td rowspan="2">48-month minimum follow-up[ii]</td><td>NIVO+IPI (n=425)</td><td>11.2 (8.4-16.1)</td><td rowspan="2">0.74 (0.62 - 0.88)</td></tr>
<tr><td>Sunitinib (n=422)</td><td>8.3 (7.0-10.8)</td></tr>
<tr><td rowspan="2">60-month minimum follow-up[iii]</td><td>NIVO+IPI (n=425)</td><td>11.6 (8.4 - 16.5)</td><td rowspan="2">0.73 (0.61 to 0.87)</td></tr>
<tr><td>Sunitinib (n=422)</td><td>8.3 (7.0 - 10.4)</td></tr>
</table>
Please note that in the 30-month minimum follow-up data set of CheckMate 214, independent radiology review committee (IRRC)-assessed PFS was not available and only investigator-assessed PFS was published.[iv] Later data cuts published IRRC-assessed PFS, which should be considered in this appraisal.

The committee concluded the EAG's exponential extrapolation for PFS to be plausible , but there was some uncertainty due to the limitations of the network meta-analysis (ACD section 3.11). Similar to NIVO+IPI, on CDF entry with 30-months minimum follow-up, the KM+exponential extrapolation was preferred by the ERG and NICE committee despite BMS preferring the hazard spline (2-knots).With an additional 30-months of follow-up at CDF exit (60-month minimum), TA780 has demonstrated that NIVO+IPI does not exhibit a constant hazard over the observed follow-up (see Figure 9 and Figure 10). Visual assessment of the smoothed hazard plots and fitted hazard functions of standard parametric survival models did not adequately capture the shape of the hazard functions (see Figure 9 and Figure 10). Goodness of fit statistics, visual inspection and clinical validation suggested that the hazard spline model (2 knots) was the best fitting extrapolation for the updated clinical data to capture the observed emerging plateau, this was consistent with the original submission when the 30-month data cut was used as cubic splines were preferred. Clinical validation for the CDF review of NIVO+IPI also confirmed that spline 2-knots hazard extrapolations were reflective of clinical practice.[vii]
The final analysis of PFS for PEMBRO+LENVA was performed using the 26.6 months median OS follow-up. Evidence from the CDF exit of NIVO+IPI not only demonstrates the extent to which the exponential model fits the data poorly, but also that there is a visible plateau after 2 years. Given the short length of follow-up of the CLEAR trial with PEMBRO+LENVA it is too early to determine whether or not a similar plateau may be observed, highlighting the long-term uncertainty associated with PEMBRO+LENVA when basing 40-year extrapolations on limited follow-up.

Figure 9. NIVO+IPI smoothed hazard plots and fitted parametric survival models for PFS per IRRC (secondary definition) – CheckMate 214 intermediate/poor risk patients (60-month data cut) ((Reproduced from TA780 CDF Review submission, A.15.3.2, figure 26)</td><td></td></tr>
</table>

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
			 **Figure 10. Sunitinib smoothed hazard plots and fitted parametric survival models for PFS per IRRC (secondary definition) – CheckMate 214 intermediate/poor risk patients (60-month data cut) (Reproduced from TA780 CDF Review submission, A.15.3.2, figure 27).**	

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			 **Notes:** A 12 month smoothing interval was used for hazard data plots. **Duration of response (DoR)** Similar to what is observed in IRRC-assessed PFS, a plateau is observed in the DoR KM plot for patients who received NIVO+IPI in CheckMate 214 and achieved response, which is not observed in the sunitinib arm (Figure 11). With 60 months of minimum follow-up, median DoR has not been met for NIVO+IPI (95% CI: 50.9-not estimable) while median DoR was previously reported for sunitinib as 19.7 months (95% CI: 15.4-25.0 months), reflecting a minimum gain of at least 40.3 months, based on minimum available follow-up of 60 months, (~3.4 years) in median DoR. The median DoR for PEMBRO+LENVA in the intermediate-/poor- risk group was not reported, however using data from the IA3 data cut-off (median follow-up of 26.6 months for OS), the all-risk median DoR has been reached at 25.8 months (95% CI 22.1 to 27.9; see AG MTA report, section 3.8.4, page 56, table 22), and it would likely be plausible to assume that DoR may be shorter in patients with worse prognosis (i.e. intermediate/poor risk) given that median DoR is longer in the ITT (all risk) population for sunitinib in CheckMate 214 (median DoR: 24.8 months in ITT population). Therefore, patients who achieve response with NIVO+IPI have a higher probability of remaining in response over the longer-term than with sunitinib or	

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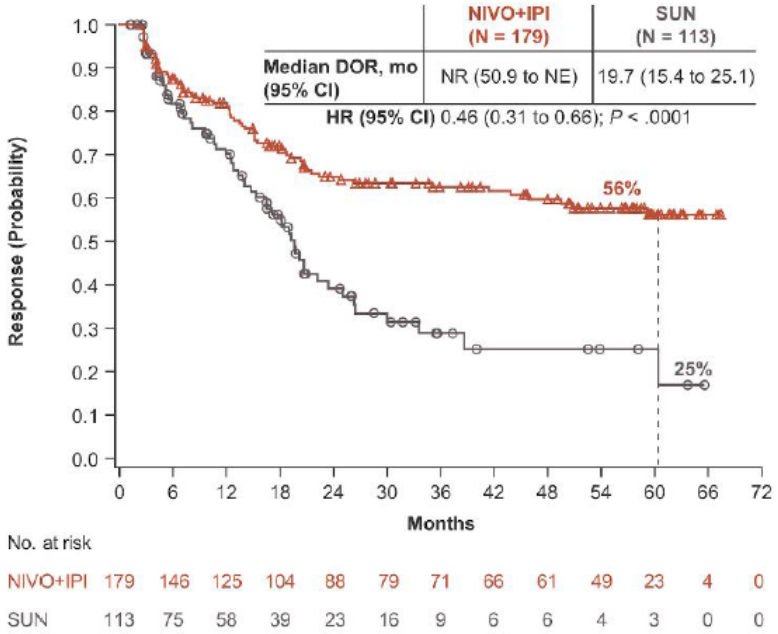
			PEMBRO+LENVA. This is of importance for consideration in this appraisal and recommendation because the current assessment is based on applying a constant HR for PFS and OS from the NMA to model outcomes for NIVO+IPI. However, clinical evidence shows there is a difference in the durability of response over time in NIVO+IPI that is not observed with sunitinib or PEMBRO+LENVA, which brings into question whether the approach used in this appraisal is scientifically appropriate to extrapolate outcomes of NIVO+IPI. **Figure 11. KM curve of DOR by treatment arm - CheckMate 214 intermediate-/poor-risk patients (60-month data cut)**  **Time to Treatment Discontinuation (TTD)** BMS strongly disagree that the TTD curve selected for NIVO+IPI should be set equal to LENVA given published evidence that has been included in this appraisal does not support such an assumption. Clinical evidence shows a large difference in median duration of therapy between the CheckMate 214 trial and the CLEAR trial, which has not been taken into account in this appraisal. The assumption of equal TTD to LENVA has likely resulted in a large overestimation of treatment costs with NIVO+IPI. As reported in the 30-month publication, and also in the 48-month publication, median duration of therapy in the all-treated (all risk) population is 7.9 months in the NIVO+IPI arm and 7.8 months in the sunitinib arm.[iiiv] In	

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			contrast, the CLEAR study reports the median duration of treatment for all risk patients was 17.0 months in the PEMBRO+LENVA arm and 7.8 months in the sunitinib arm. Though these populations include favourable risk patients, the treatment duration for PEMBRO+LENVA is higher than that observed in CheckMate 214 for NIVO+IPI. Moreover, median PFS for PEMBRO+LENVA is 23.9 months in the all risk population (all risk) whereas median PFS (IRRC) in the all risk population for NIVO+IPI is 12.2 months (median PFS: 11.2 months for intermediate/poor risk patients).[viii] This shows a clear difference in the median PFS and median TTD for the NIVO+IPI ITT population of 4.3 months, in favour of PFS. BMS encourage the committee to revisit the TTD assumption of equivalence for NIVO+IPI to LENVA and to also compare this with PFS predictions, considering the previous CDF review NIVO+IPI in which "[redacted] of patients who are progression-free in the NIVO+IPI arm still are receiving treatment, demonstrating the ongoing clinical benefit despite treatment discontinuation. This treatment-free interval is further evidenced by swimmer plots presented in the appendix showing the proportion of patients achieving ongoing response but remaining off treatment and without any subsequent therapy" (NIVO+IPI CDF Review submission, section A.6.1.4, page 22). Therefore, it would be scientifically inappropriate to assume an equal duration of therapy to LENVA or any treatment duration that exceeds PFS for NIVO+IPI. Assuming equivalence, despite the evidence against such an assumption, is likely to overestimate treatment costs for NIVO+IPI, resulting in a more favourable ICER for PEMBRO+LENVA versus NIVO+IPI. The additional follow-up, which has not been appropriately captured for inclusion in the SLR or considered within the current appraisal, further demonstrates that a greater proportion of patients are continuing to benefit across all endpoints when treated with NIVO+IPI compared with sunitinib. With this additional follow-up, PFS has improved over sunitinib, and a plateau appears to be forming from approximately 2 years, which is also seen with the DOR curve as patients are continuing to benefit as demonstrated by the consistently longer OS. With 60-months minimum follow up, an additional 30-months over CDF entry, BMS have demonstrated (whilst following the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 and 21) that the extrapolations selection for NIVO+IPI, were and continue to be the best fitting.[ixx] These extrapolations were clinically validated and reflected expectations in clinical practice. It is unclear if the same process has been followed by the AG as extrapolations do not appear to be clinically validated nor do they seem to have been validated against longer-term data that is available in the public domain. These data should have been captured in this appraisal. Finally, conclusions by the committee in this appraisal appear to conflict with those in TA780, which BMS reiterates also should have been retrospectively considered in this appraisal.	
12	Consultee	BMS	BMS are concerned that available evidence and past precedence have not been considered in the AG NMA, resulting in unreasonable conclusions with a high level of uncertainty, which are unsuitable for decision making. In addition to points demonstrated above, the base case model is likely to overestimate costs of treatment of NIVO+IPI and underestimate long-term benefit (and PFS) by using a HR-based approach, which would deeply favour a lower ICER for PEMBRO+LENVA versus NIVO+IPI. The CDF review of NIVO+IPI with 60-month minimum follow-up assessed the proportional hazards (PH) across	Thank you for your comment. The EAG assessed the proportional hazards assumption using the updated progression-free survival and overall survival data. The EAG maintains its original conclusions and

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			the two treatment arms of CheckMate 214. The plateau in the KM curves, crossing of the log-cumulative hazard plots and rejection of the Schoenfeld residual test (P < 0.01) show evidence that the PH assumption is not supported. Despite the violation in PH assumption with PFS in the NIVO+IPI arm, time-varying hazards were not considered in the AG NMA and so "the AG PFS NMA HRs are not applicable to all time points across the observed follow-up of the trials included in the NMAs" (See AG MTA report, section 5.13.1 page 105). This violation of the PH assumption indicates that a constant HR would not be appropriate for use in this appraisal to estimate outcomes for NIVO+IPI, especially in the case of PFS where a clear and defined plateau has been observed from year 2, which is not observed for other therapies included in the NMA. Past precedence in advanced RCC for the submissions of pembrolizumab with axitinib (PEMBRO+AXI) and AVE+AXI explored both time-constant and time-varying NMAs.[xixii] In the appraisal of AVE+AXI, the ERG and committee conclude that methodological concerns and the immature data informing the model made these results uncertain.".[xi] Similarly, in the appraisal of PEMBRO+AXI, the committee "considered that the evidence base for the intermediate and poor-risk subgroup was weak.".[xii] In addition, application of a constant HR when the PH assumption is violated has previously been shown to substantially underestimate outcomes for NIVO+IPI. In a cost-effectiveness study by Bensimon et al (2020) in first-line RCC, which was not identified in the economic SLR for this appraisal, a HR-based NMA was applied to sunitinib to predict NIVO+IPI (based on 30-month minimum follow-up).[xiii] As can be seen in Figure 12, predicted PFS for NIVO+IPI at five years is approximately <5%, whereas the 60-month minimum follow-up data shows PFS is 31% at five years. Therefore, the application of a HR-based NMA in this appraisal would not capture the plateau observed in CheckMate 214 for NIVO+IPI, which is not seen for the sunitinib arm to which the HR was applied. As such, the clinical benefit of NIVO+IPI has not been appropriately calculated and this method is inappropriate for use in decision making to compare PEMBRO+LENVA versus NIVO+IPI. **Figure 12. Modelled PFS from Bensimon et al, which used a HR-based NMA applied to sunitinib (intermediate/poor risk patients; Supplemental Figure S3B)[xiii]**	preference for the proportional hazards network meta-analysis approach over alternative options. Scenarios that vary the relative overall survival between lenvatinib + pembrolizumab and nivolumab + ipilimumab demonstrate that this has little impact on the cost-effectiveness results. No change to FAD required.

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			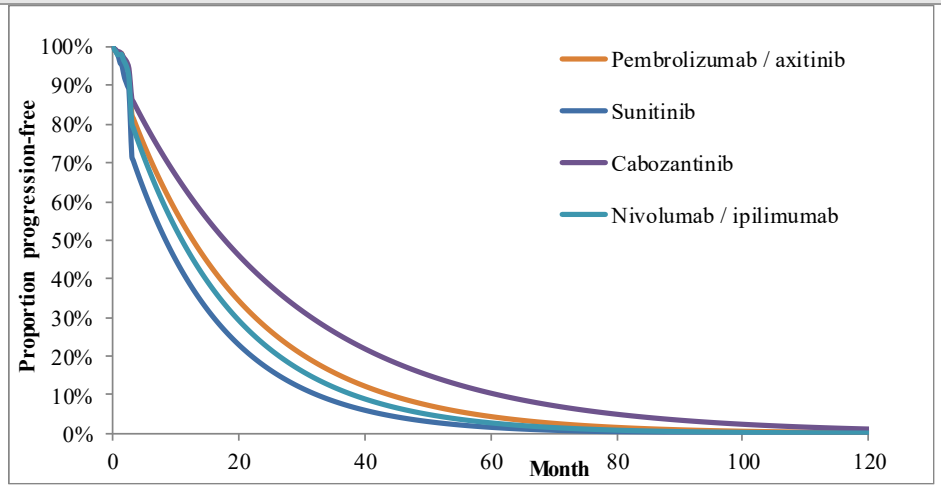 Taking into account the uncertainty surrounding the AG NMA and the omission of the 60-month minimum follow-up data from CheckMate 214, the scenario where OS of PEMBRO+LENVA is equal to NIVO+IPI should be the considered for decision making. Results from the AG OS fixed effects NMA in the intermediate-/poor- risk subgroup demonstrate a minor numerical advantage for PEMBRO+LENVA when compared with NIVO+IPI that is not statistically significant and has a wide confidence interval (HR=0.94, 95% CrI: 0.66 to 1.32). The results show there is no statistical difference in treatment effect between the two combination treatments. When this scenario is further explored (where OS PEMBRO+LENVA is equal to NIVO+IPI) in the deterministic sensitivity analysis of the AG economic model, PEMBRO+LENVA is dominated by NIVO+IPI.	
13	Consultee	BMS	BMS are concerned that treatment waning has not been appropriately accounted for in the PEMBRO+LENVA arm with the inclusion of a two-year stopping rule with pembrolizumab. This infers that whilst pembrolizumab is discontinued by 24 months, the benefit from treatment continues indefinitely, which is subject to uncertainty. The EAG recognise that the “effect of the pembrolizumab 2 year stopping rule on TTD data is unclear”, but do not consider treatment waning within their based case despite precedence from previous NICE appraisals of therapies in RCC (TA645 and TA650) and other immunotherapies with trial driven maximum durations of IO treatment. In the NICE appraisal of PEMBRO+AXI, a 2-year stopping rule was applied to the PEMBRO arm. In that appraisal, the committee noted that in previous NICE appraisals of checkpoint inhibitors when length of treatment was capped at 2 years in the cost-effectiveness model, the committees did not assume lifetime treatment benefit but, instead, examined various analyses of treatment benefit (waning effects). The committee agreed that immunotherapy would likely provide a durable response but concluded that there was insufficient evidence to assume this would be lifelong. The committee considered various model scenarios when the treatment effect of pembrolizumab stopped after 3 years, 5 years and 10 years (that is, treatment effect	Thank you for your comment. While pembrolizumab has a 2-year-stopping rule, there is no treatment stopping associated with lenvatinib. The EAG therefore considered that it was inappropriate to apply a waning of treatment effect based solely on the stopping rule for pembrolizumab when the other active treatment (lenvatinib) continued. The EAG considers that this is analogous to there being no

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			continued to 1 year, 3 years and 8 years after stopping pembrolizumab). Although the committee concluded that the immaturity of the data from KEYNOTE-426 (approximately 20 months follow-up) made any estimation of treatment waning effect highly uncertain, it accepted scenarios when a waning effect was applied after 5 years (TA650 FAD sections 3.10-3.11).[xii] Considering the IO component is the same in the two appraisals and it is the same disease setting, precedent would have required waning to be implemented to PEMBRO+LENVA. In contrast, for the NICE appraisal of AVE+AXI based on clinical evidence from the JAVELIN Renal 101 trial, no stopping rule was applied, the committee concluded that there was no evidence to support a stopping rule as the pivotal trial JAVELIN Renal 101 and marketing authorisation did not include a stopping rule. With the removal of a stopping rule from the modelling, treatment waning was excluded so as to be in line with the trial. The committee agreed that it was not appropriate to include a stopping rule and treatment waning (TA650 FAD sections 3.16-3.17).[xi] In the company's justification for the lack of treatment waning, they state "longer-term follow-up of patients receiving IO in advanced RCC has indicated a maintenance of survival benefit beyond treatment discontinuation (i.e., treatment waning has not been detected)" (PEMBRO+LENVA MSD company submission page 95). The company reference the 5-year minimum follow up of the CheckMate 214 trial to justify the maintenance of survival benefit beyond treatment discontinuation, but neither the market authorisation nor CheckMate 214 trial include a stopping rule. In addition, the assumption of a stopping rule was not accepted in the CDF entry as the committee concluded "that it is not appropriate to include a stopping rule for decision making because its effect on clinical outcomes are untested". Therefore, it is inappropriate to use such evidence from CheckMate 214 or the NIVO+IPI appraisals as justification for lack of treatment waning.[iii]	waning of treatment effect for nivolumab + ipilimumab despite ipilimumab having a four-cycle-stopping rule. No change to FAD required.
14	Consultee	NCRI-ACP-RCP-RCR	Our experts are disappointed that only a subgroup of patients (those with intermediate and poor risk disease) is included in the advice, this is clearly a good outcome for those patients. However, we did wish to at least acknowledge that the excluded group, those with favourable risk disease, are currently treated with avelumab plus axitinib within the CDF, and so this has resulted in a degree of injustice, as this was, by the very nature of the review, excluded as a relevant comparator in this analysis	Thank you for your comment. No change to FAD required.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

[i] National Institute for Health and Care Excellence (NICE). TA780: Nivolumab with ipilimumab for untreated advanced renal cell carcinoma. 2022 Available at: https://www.nice.org.uk/guidance/ta780. Accessed: August 2022.

ii Albiges, L., Tannir, N. M., Burotto, M., et al. (2020). Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. ESMO open, 5(6), e001079. https://doi.org/10.1136/esmoopen-2020-001079

iii Motzer, R. J., Tannir, N. M., McDermott, D. F., et al. Conditional survival and 5-year follow-up in CheckMate 214: first-line nivolumab plus ipilimumab versus sunitinib in advanced renal cell carcinoma. Presented at the ESMO Virtual Congress 2021; 2021.

iv Motzer, R. J., Rini, B. I., McDermott, D. F., et al.(2019). Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. The Lancet. Oncology, 20(10), 1370–1385. https://doi.org/10.1016/S1470-2045(19)30413-9

v Motzer, R. J., Escudier, B., McDermott, D. F., et al. (2020). Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. Journal for immunotherapy of cancer, 8(2), e000891. https://doi.org/10.1136/jitc-2020-000891

vi National Institute for Health and Care Excellence (NICE). TA581: Nivolumab with ipilimumab for untreated advanced renal cell carcinoma. 2019. Data on File.

vii Bristol Myers Squibb. Nivolumab plus ipilimumab in renal cell carcinoma - Cancer Drugs Fund Exit Consult: Clinical validation. 2021. Data on File.

[viii] Motzer, R., Alekseev, B., Rha, S. Y., et al. (2021). Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. The New England journal of medicine, 384(14), 1289–1300. https://doi.org/10.1056/NEJMoa2035716

ix Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. (Updated: March 2013) Available at: https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0089910/pdf/PubMedHealth_PMH0089910.pdf. Accessed: August 2022.

x Rutherford MJ, Lambert PC, Sweeting MJ, et al. NICE DSU TECHNICAL SUPPORT DOCUMENT 21: Flexible Methods for Survival Analysis. 2020. Available at: http://nicedsu.org.uk/wp-content/uploads/2020/11/NICE-DSU-Flex-Surv-TSD-21_Final_alt_text.pdf. Accessed: 30 July 2021

xi National Institute of Health and Care Excellence. TA645: Avelumab with axitinib for untreated advanced renal cell carcinoma. 2020. Available at: https://www.nice.org.uk/guidance/ta645. Accessed: August 2022

xii National Institute for Health and Care Excellence (NICE). TA650: Pembrolizumab with axitinib for untreated advanced renal cell carcinoma 2020. Available at: https://www.nice.org.uk/guidance/ta650. Accessed: August 2022

[xiii] Bensimon, A. G., Zhong, Y., Swami, U., et al. (2020). Cost-effectiveness of pembrolizumab with axitinib as first-line treatment for advanced renal cell carcinoma. Current medical research and opinion, 36(9), 1507–1517. https://doi.org/10.1080/03007995.2020.1799771

Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

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	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 and 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:	[redacted]
Comment	**Comments**

Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

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number	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 Appraisal Consultation Document states on page 7 (Section 3.4) that "*The final overall survival data cut is expected in the third quarter of 2023*." MSD wish to clarify that this data is currently expected in the third quarter of 2022, with data analysis to follow shortly afterwards.
2	
3	
4	
5	
6	

Insert extra rows as needed

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

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

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

Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Eisai Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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	Section 1, page 3 – The appraisal consultation document states, "*Clinical trial evidence suggests that people having lenvatinib plus pembrolizumab have longer before their disease gets worse than people having sunitinib, but this is uncertain for people with favourable-risk cancer*". Eisai believe that this statement is inaccurate for people with favourable-risk cancer, given a statistically significant improvement was observed with lenvatinib plus pembrolizumab for progression-free survival and progression after next line of therapy in this population in the pivotal trial (CLEAR). At the time of the final progression-free survival analysis (interim analysis 3), the hazard ratio for progression-free survival was 0.41 (95% confidence interval: 0.28, 0.62); p<0.0001, and the hazard ratio for progression after next line of therapy was 0.57 (95% confidence interval: 0.32, 1.00); [redacted]. In relation, the appraisal consultation document contradicts this statement in Section 3.4, page 7; "*The trial results demonstrated a progression-free survival benefit with lenvatinib plus pembrolizumab over sunitinib in the whole population and across all risk groups*". Therefore, we request "*but this is uncertain for people with favourable-risk cancer*" is removed from the statement on page 3.
2	Section 3.2, page 5 – The appraisal consultation document states, "*The committee heard that clinicians assess advanced renal cell carcinoma on presentation using the International Metastatic Renal Cell Carcinoma (IMDC) risk score. This measure uses a range of criteria to determine whether a person has favourable, intermediate or poor risk of* ***experiencing disease progression***". Eisai believe that this statement is inaccurate, as the IMDC-risk model predicts survival in patients with metastatic renal cell carcinoma treated with systemic therapy, not risk of experiencing disease progression (1). Therefore, we recommend that this statement is corrected.
3	Section 3.3, page 7 – The appraisal consultation document states, "*The trial stratified people by IMDC risk score*". People were stratified based on the Memorial Sloan-Kettering Cancer Center (MSKCC) risk score for metastatic renal cell carcinoma in the CLEAR trial, therefore this statement should be corrected.

Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

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4	Section 3.6, page 8 – The title states, "*The EAG prefers a Bayesian network meta-analysis because of uncertainty in the proportional hazards assumption*". Eisai believe this statement is unclear, as: 1. Both the proportional hazards-based network meta-analysis (referred to as the 'Bayesian network meta-analysis' in the appraisal consultation document) and the fractional polynomial analysis are performed using a Bayesian framework 2. Preferring the proportional hazards-based network meta-analysis (referred to as the 'Bayesian network meta-analysis' in the appraisal consultation document) *because of uncertainty in the proportional hazards assumption* is not a logical statement Eisai propose that the 'Bayesian network meta-analysis' is renamed as the 'proportional hazards network meta-analysis' (or similar) throughout, and the title of this section is re-worded to: "The EAG prefers a **proportional hazards network meta-analysis despite the** uncertainty in the proportional hazards assumption", or similar.
5	Section 3.6, page 8 – The appraisal consultation document states, "*The committee recalled that previous NICE technology appraisals (tivozanib for treating advanced renal cell carcinoma, cabozantinib for untreated advanced renal cell carcinoma, nivolumab with ipilimumab for untreated advanced renal cell carcinoma and avelumab with axitinib for untreated advanced renal cell carcinoma) had concluded that sunitinib and pazopanib are likely of equivalent clinical effectiveness, and that tivozanib may have a similar effect to sunitinib or pazopanib. The committee agreed with these decisions and so focused on the comparisons with cabozantinib, and nivolumab plus ipilimumab*". It is unclear why the assumption that pazopanib and tivozanib have equivalent effectiveness to sunitinib means the only relevant comparisons are with cabozantinib and nivolumab plus ipilimumab in the intermediate and poor risk population. We suggest this is clarified further in Section 3.6.
6	Section 3.7, page 9 – The title states, "*The companies prefer the results from fractional polynomial NMAs, but these are highly uncertain".* Base-case analyses submitted by Eisai used proportional hazards network meta-analyses, and this was Eisai's preferred base case. Therefore, we request this statement is corrected accordingly.
7	Section 3.12, page 14 – The appraisal consultation document states, "*The committee noted that the Kaplan–Meier plots for the observed overall survival data for lenvatinib plus pembrolizumab in the favourable-risk subgroup was very close to that for sunitinib, with the curves almost overlaid. The overall survival extrapolation for sunitinib was therefore not clinically plausible because the gamma distribution likely overestimated survival for sunitinib compared with lenvatinib plus pembrolizumab. The committee agreed that this discrepancy might be attributable to low patient numbers and the low number of events experienced by people in the favourable-risk subgroup, and concluded that the overall survival extrapolations in the favourable-risk subgroup are not clinically plausible*." As the committee agreed that the evidence assessment group's overall survival extrapolations are not clinically plausible in the favourable risk group, Eisai are concerned about the implications of the associated results being in the public domain without appropriate caveats, due to the potentially damaging interpretation of the cost-effectiveness of lenvatinib plus pembrolizumab. Therefore, Eisai request that all cost-effectiveness results for the favourable risk group are redacted. The results and corresponding discussion for the favourable risk group are included in the following sections in the committee papers: • Section 5.22.2 (favourable risk), results discussion within the paragraph and results presented within Table 66 and Table 67

	• Section 5.23.2, results discussion within the paragraphs and results presented within Table 70 and Table 71 • Section 5.24.1 (favourable risk; sensitivity analyses), discussion within the paragraph • Section 5.24.3 (favourable risk; scenario results), last sentence of the paragraph and the results presented in Table 74, Table 75, Table 76 • Section 5.25 (discussion of cost-effectiveness analyses), paragraph 4 • Section 6.1.3 (cost-effectiveness results), paragraph 2 • In 'Assessment group response to Company consultations comments'; Section 1.2.2, Table 3, Table 4, and Table 5 • In 'Assessment group response to company consultations comments'; Section 1.2.3, Table 6 Eisai have a similar concern regarding the results for the all-risk population. The appraisal consultation document does not include a statement regarding the plausibility of the overall survival extrapolations for the all-risk population. However, as stated by Eisai in response to the evidence assessment group's report, the overall survival extrapolations used by the evidence assessment group led to a long-term hazard ratio of approximately [redacted] for lenvatinib plus pembrolizumab vs sunitinib, which contradicts the results from the CLEAR trial, which showed Kaplan Meier curves with a statistical significance in favour of lenvatinib plus pembrolizumab (hazard ratio of 0.72 [95% CI: 0.55, 0.93]), based on the updated overall survival analysis. In the context of the committee's main concern for the favourable risk population being that the extrapolated overall survival for sunitinib is likely overestimated compared with the Kaplan Meier data, Eisai believe this also applies for the all-risk population, and request that cost-effectiveness results for the all-risk population are also redacted on the same basis. The results and corresponding discussion for the all-risk population are included in the following sections within the committee papers: • Appendix 17; Section 9.17.13 (deterministic results), Table 128 and Table 129 • Appendix 17; Section 9.17.14 (probabilistic sensitivity analysis results), Table 130 and Table 131 • Appendix 17; Section 9.17.16 (Assessment group deterministic scenario analysis results (all-risk population)), Table 132, Table 133, and Table 134 • In 'Assessment group response to Company consultation comments'; Section 1.2.3, Table 6, Table 7, and Table 8
8	There is a factual inaccuracy in the data presented on slide 16 of the public committee slides. In the last row, the PFS-rate time points should read 6-, 12-, 18-, and 24 months, not 12-, 18-, 24- and 36 months.

Insert extra rows as needed

References

1. MDCalc. IMDC Risk Model for Metastatic Renal Cell Carcinoma. Available at: https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-model-metastatic-renal-cell-carcinoma [last accessed: 15th August 2022]. 2021.

Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]
Comment	**Comments**

Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

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number	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to comment as follows.
1	Our experts are disappointed that only a subgroup of patients (those with intermediate and poor risk disease) is included in the advice, this is clearly a good outcome for those patients. However, we did wish to at least acknowledge that the excluded group, those with favourable risk disease, are currently treated with avelumab plus axitinib within the CDF, and so this has resulted in a degree of injustice, as this was, by the very nature of the review, excluded as a relevant comparator in this analysis

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Bristol Myers Squibb
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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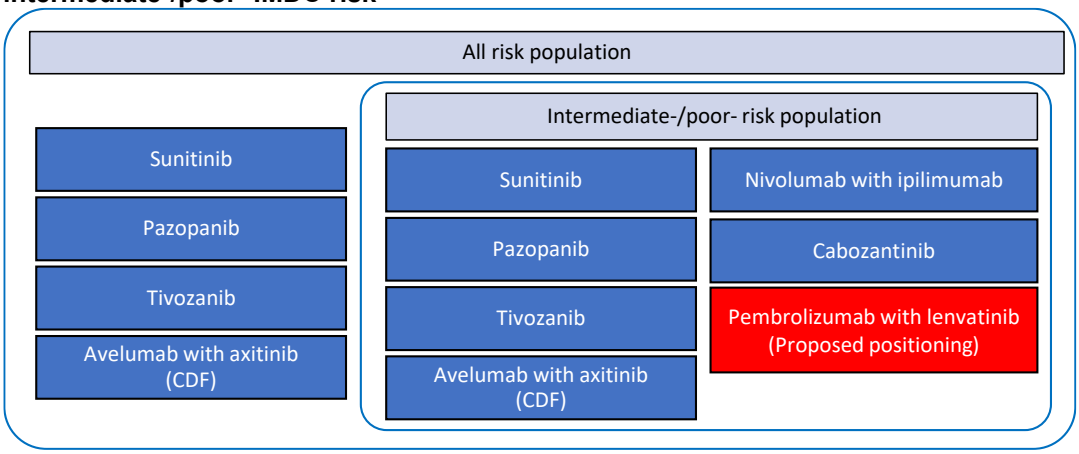
Name of commentator person completing form:	[redacted]

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	BMS are concerned that the recommendation (ACD section 1.1) of pembrolizumab with lenvatinib (PEMBRO+LENVA) for untreated advanced renal cell carcinoma (RCC) in adults, in the intermediate or poor IMDC risk population only if "nivolumab with ipilimumab would otherwise be offered" is open to misinterpretation for the following reasons: • There are no NICE restrictions as to which intermediate or poor risk patients nivolumab with ipilimumab (NIVO+IPI) can be offered. • The mode of action and trial data for the two treatment combinations treatments do not support the implication that the patient populations are equivalent. • It is unclear how this guidance will/ should be implemented in clinical practice BMS request an update to the recommendation to remove the restriction of "patients for whom nivolumab with ipilimumab would otherwise be offered" to ensure clarity of the recommendation, in line with appropriate clinical decision-making criteria. It is understood that this recommendation is intended to prevent the use of PEMBRO+LENVA in patients who would be suitable for cabozantinib, as PEMBRO+LENVA is not considered cost-effective against cabozantinib. The inclusion of NIVO+IPI within the NICE recommendation may not result in such a restriction as the NICE recommendation for NIVO+IPI includes all untreated advanced RCC patients with intermediate-/poor IMDC risk, which will not help achieve a cost-effective use of PEMBRO+LENVA and will likely complicate clinician decision-making. Given that sunitinib, pazopanib, tivozanib and avelumab with axitinib (AVE+AXI) are currently recommended for patients regardless of IMDC risk (i.e. all risk), this also means they are recommended for intermediate-/poor- IMDC risk patients, who are a subset of the all-risk patients, along with NIVO+IPI and cabozantinib (see Figure 1). Therefore, the current wording of the NICE recommendation of PEMBRO+LENVA would enable prescribing to any intermediate or poor risk patient, despite not being cost-effective against cabozantinib. It should be noted that sunitinib, pazopanib, and tivozanib have not been appraised against PEMBRO+LENVA in the intermediate-/poor- risk advanced RCC population despite being available treatment options on the NHS for these patients.

Figure 1. Proposed treatment options for patients with untreated advanced RCC with intermediate-/poor- IMDC risk



In Technology Appraisal Guidance TA780, NIVO+IPI has been demonstrated to be cost-effective for untreated advanced RCC with intermediate-/poor- IMDC risk when compared with single agent tyrosine kinase inhibitor (TKI) sunitinib and pazopanib (comparators at the time of the submission)[1]. The ACD draft recommendation for PEMBRO+LENVA states that it was not cost-effective versus cabozantinib, but was cost effective against NIVO+IPI, a conclusion which is also dependent on the evidence included and scientific approaches used in this assessment, which differ from those in TA780 and prior 1L RCC assessments by NICE (see comments in section 2, 3 and 4). Tying the NICE recommendation of PEMBRO+LENVA to the populations suitable for NIVO+IPI will not ensure the cost-effective use of PEMBRO+LENVA by precluding use in patients who are candidates for single agent TKI, as NIVO+IPI can be offered to those patients.

In addition, it is unclear what clinical decision-making criteria should be applied to enable clinicians to identify patients suitable for PEMBRO+LENVA. For example, current NICE guidance does not distinguish how a clinician should decide which 1L advanced RCC intermediate-/poor- IMDC risk patients should be offered NIVO+IPI versus who should be offered cabozantinib. At present, patients are able to be offered both NIVO+IPI or cabozantinib, along with other single agent TKIs and IO+TKI (AVE+AXI) not included in the scope of this assessment by the EAG and NICE committee. Therefore, being suitable to be offered NIVO+IPI is not mutually exclusive to suitability for single agent TKI or AVE+AXI.

During the PEMBRO+LENVA ACM, clinical experts stated that "*for people with intermediate- and poor-risk disease, cabozantinib, and nivolumab plus ipilimumab are treatment options, with nivolumab plus ipilimumab usually preferred for people who are fit enough to receive it*". It is not clear if the guidance is intended to restrict treatment to the "fit" subgroup, with unfit patients being suitable for single agent TKI, or AVE+AXI via the CDF. When deciding to treat a patient, several factors are taken into account, including but not limited to, clinical status, fitness and patient preference.
Fitness is one, but not the only, factor in deciding a course of treatment, and it is important for all factors to be considered when deciding which first-line therapy to take. To avoid confusion in clinical decision-making and ensure appropriate prescribing of PEMBRO+LENVA within cost-effective criteria, BMS request the removal of the restriction of PEMBRO+LENVA to "patients for whom nivolumab with ipilimumab would

	otherwise be offered" and update to the recommendation to ensure clarity of the recommendation.
2	BMS are concerned that not all relevant evidence has been taken into account for the appraisal of PEMBRO+LENVA, resulting in unreasonable interpretations and conclusions of the evidence. BMS believe the evidence around the CDF Review of NIVO+IPI, appropriateness of the systematic literature review (SLR) and NICE appraisal precedence presented are relevant to the current appraisal and should have been consider by the appraisal committee. The SLR performed by the EAG does not capture all relevant comparator publications which were available at the time of the search performed in October 2021 and November 2021, for databases and conference proceedings, respectively. At the time of the database search, CheckMate 214 trial with 48-month follow-up (published November 2020) as a scientific paper and 60-month minimum follow-up (published September 2021) as a conference poster were published and available in the public domain.[2,3] This evidence would provide an additional 6- to 18-months of additional follow-up to the included CheckMate 214 trial (minimum 42-months follow-up). The additional follow-up which has not been appropriately captured or included within the current appraisal demonstrates that a greater proportion of patients are continuing to benefit across all endpoints when treated with NIVO+IPI compared with sunitinib. The CDF review of NIVO+IPI included the 60-month minimum follow-up data from CheckMate 214, an additional 30-months of follow-up than was available at the time of the initial appraisal and CDF entry. At the time of the PEMBRO+LENVA Assessment Group (AG) Report (March 2022), NIVO+IPI was subject to an ongoing CDF review which resulted in a draft positive FAD in February 2022 and positive TA guidance in March 2022 (TA780).[1] Given NICE's decision to include NIVO+IPI as a comparator prior to the positive CDF review, TA780 should be retrospectively included as a NICE technology appraisal source for clinical effectiveness studies (see AG Report, page 40, Table 8). The inclusion of TA780 and the 60-month minimum-follow-up of CheckMate 214 would help address a number of key uncertainties raised by the committee and EAG during the appraisal of PEMBRO+LENVA, given the shorter follow-up of the CLEAR study. **Duration of follow-up** From the CLEAR trial, PEMBRO+LENVA has a short follow-up with median follow-up of 26.6 months for progression-free survival (PFS) and 33 months for OS compared with the minimum follow-up of 60 month from the CheckMate 214 study of NIVO+IPI in TA780. With minimum follow-up of 30-months (median follow up: 32.4 months), NIVO+IPI entered into the CDF in order to address clinical uncertainties including the long-term benefit of NIVO+IPI relative to sunitinib, subsequent treatments in clinical practice, and the proportion of intermediate- and poor- risk in clinical practice (See NIVO+IPI CDF Review submission, section A.1 page 7). **Overall Survival** Consistent with the 30-month data cut; the 42-month, 48-month and 60-month data cut shows patients treated with NIVO+IPI continue to demonstrate a statistically significant improvement in OS compared with patients treated with sunitinib across the observed study period. With the 30-month data cut, the median OS for the NIVO+IPI arm had not

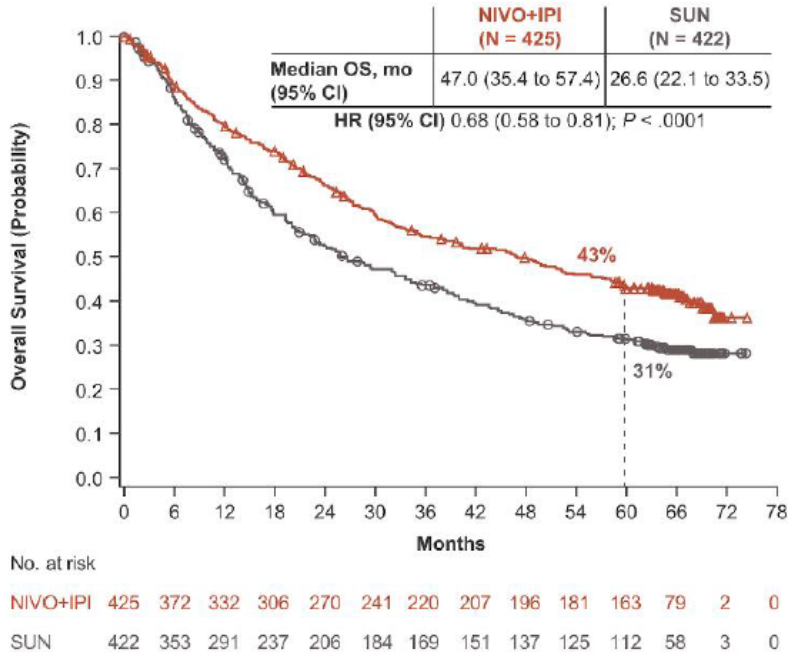
been reached; and with the 60-month data cut, this was realized at 47.0 (95% confidence interval [CI]: 35.4, 57.4) months compared with 26.6 (95% CI: 22.1, 33.5) months with sunitinib, a gain in median OS of 20 months for NIVO+IPI versus sunitinib (see Table 1 and Figure 2). This additional evidence demonstrates that, with further follow-up, the long-term OS benefit of NIVO+IPI is maintained versus sunitinib.

Table 1. Summary of key CheckMate 214 trial OS results

Outcome	Treatment	Median, months (95% CI)	HR (95% CI)
Overall survival			
30 month minimum follow up[4]	NIVO+IPI (n=425)	NA (35.6 to NA)	0.66 (0.54 to 0.80
	Sunitinib (n=422)	26.6 (22.1 to 33.4)	
42-month minimum follow-up[5]	NIVO+IPI (n=425)	47.0 (35.6 - NA)	0.66 (0.55-0.80)
	Sunitinib (n=422)	26.6 (22.1 - 33.5)	
48-month minimum follow-up[2]	NIVO+IPI (n=425)	48.1 (35.6, NA)	0.65 (0.54, 0.78)
	Sunitinib (n=422)	26.6 (22.1, 33.5)	
60 month minimum follow up[3]	NIVO+IPI (n=425)	47.0 (35.4 to 57.4)	0.68 (0.58 to 0.81
	Sunitinib (n=422)	26.6 (22.1 to 33.5)	

CI=confidence interval; HR=hazard ratio; NA=not applicable

Figure 2. KM curve of OS by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)



Key: KM, Kaplan–Meier; OS, overall survival.

Table 2. OS rates by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut)

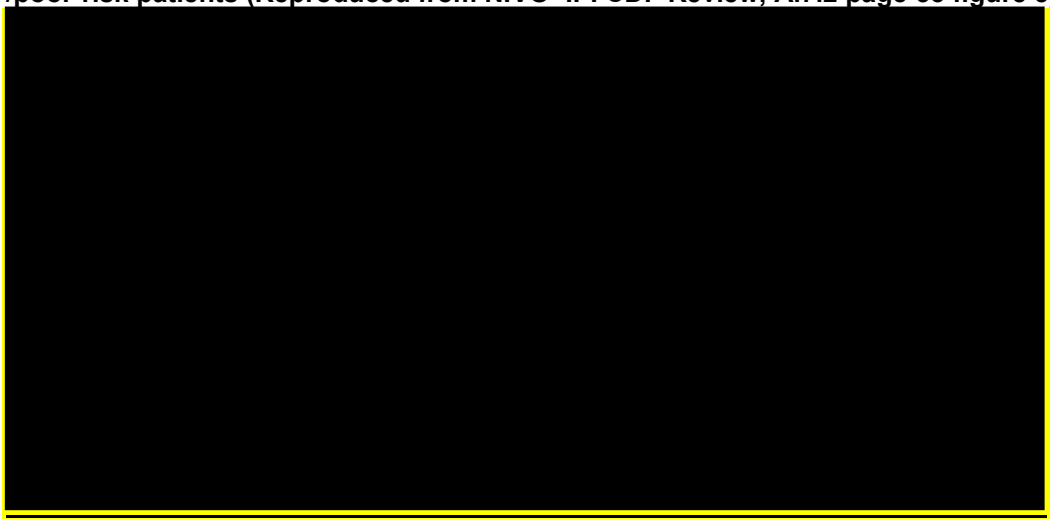
Timepoint in months	OS rates by treatment, %	
	NIVO+IPI	Sunitinib
1	[redacted]	[redacted]
3	[redacted]	[redacted]
6	[redacted]	[redacted]
12[4]	80.0	72.0
24[2]	66.4	52.4
36	[redacted]	[redacted]
48[2]	50.0	35.8
60	43.0	31.3

One of the key uncertainties raised during the PEMBRO+LENVA Appraisal Committee Meeting (ACM) was around the modelling of OS, PFS and TTD. During the initial appraisal of NIVO+IPI with 30-months of minimum follow-up (TA581), the committee considered "both the log-normal, and Kaplan–Meier with exponential extrapolation, curves clinically plausible, concluding that it would take both into account in its decision making".[6] The CDF review of NIVO+IPI with 60-months of minimum follow-up demonstrated the grossly underpredicted OS for both treatment arms in CheckMate 214 when using the KM+exponential extrapolation versus the 60-month CheckMate 214 data, as seen in Figure 3 (reproduced from CDF review submission. Section A.7.2, Figure 5). During the CDF review of NIVO+IPI, the ERG report stated that the ERG "at the time of the initial appraisal (using 30-month minimum follow-up CheckMate 214 trial data) were both overly pessimistic" (TA780 ERG report section 4.1.1 page 23), with both the ERG and committee concluding that the extrapolations of overall survival using log-normal function were appropriate for both treatment arms. Therefore, if log-normal is appropriate to model sunitinib from CheckMate 214, and KM+exponential underestimates OS over the longer term, it should be considered that in this assessment of PEMBRO+LENVA, with the same comparator arm of sunitinib, the KM+exponential is inappropriate to model the control arm. Further, given that the KM+exponential also underestimated the longer-term survival of NIVO+IPI, the application of a single constant HR, as based on the NMA to the sunitinib arm, is likely to underestimate the longer-term data from CheckMate 214.

The CDF appraisal of NIVO+IPI TA780 FAD states, "The committee considered that the updated data supported the company's choice of the log-normal hazard function and that a proportion of people in CheckMate 214 would effectively be 'cured' with immunotherapy. The committee concluded that the extrapolations of overall survival were appropriate but, to explore uncertainty, it considered sensitivity analyses using other assumptions around extrapolating how the rate of death changes over time in its decision-making."[1] Therefore, as the committee wanted to explore different assumptions around rate of death changing over time, it would be fair to conclude that it is inappropriate to model NIVO+IPI using a constant hazard rate via the exponential function.

As such, BMS would encourage, for validation, to compare absolute reported landmark OS data from TA780 (NIVO+IPI: 43.0%, sunitinib: 31.3%) as reported in **Error! Reference source not found.** and Table 2 above, with the 5-year predicted OS using the KM+exponential approach in this assessment.

Figure 3. OS extrapolations based on 30-month CheckMate 214 (KM + exponential, log-logistic, and log-normal) versus OS 60-month CheckMate 214 KM data – intermediate-/poor-risk patients (Reproduced from NIVO+IPI CDF Review, A.7.2 page 33 figure 5)



The PEMBRO+LENVA ACD states that the "EAG's extrapolation of overall survival in the intermediate and poor-risk group is suitable for decision making" (ACD section 3.11) even though the updated OS analysis for PEMBRO+LENVA (median 33-months follow-up for OS) is still relatively immature with [redacted] and [redacted] of deaths occurring in the PEMBRO+LENVA and sunitinib groups, respectively (median OS not reached for both treatment arms; PEMBRO+LENVA ACM slides). When compared with NIVO+IPI on entry to the CDF, 43% of NIVO+IPI and 54% of sunitinib OS events had occurred with the 30-month minimum follow-up data (median follow-up of 32.4 months [IQR: 13.4,36.3]) and the committee noted that "given the immaturity of the data, there was substantial clinical uncertainty about the long-term effectiveness of nivolumab with ipilimumab".[6]

Despite the immature data from the CLEAR study, the AG has considered the KM+exponential extrapolation appropriate for OS on the basis that the CLEAR trial PEMBRO+LENVA OS hazard was constant beyond week 50. However, it is clear from the OS smoothed hazard plots for both NIVO+IPI and sunitinib from CheckMate 214 that with 60-month minimum follow-up data, a non-constant hazard is observed for both treatment arms; therefore, a constant hazard is highly unlikely to provide a good fit to the data as the extrapolated portion of these models consistently underestimates OS (see Figure 3, Figure 4 and Figure 5). Goodness-of-fit statistics from the CDF review of NIVO+IPI indicated that the exponential extrapolation provided the worst statistical fit to the data as it has the highest Akaike information criterion (AIC) and Bayesian information criterion (BIC) values across both treatment arms (see also NIVO+IPI CDF Review, section A.15.2.2 page 63, table 19).

Figure 4. NIVO+IPI smoothed hazard plots for OS and fitted parametric survival models – CheckMate 214 intermediate/poor risk patients (60-month minimum follow-up) (Reproduced from NIVO+IPI CDF Review A.15.2.2 Figure 19)

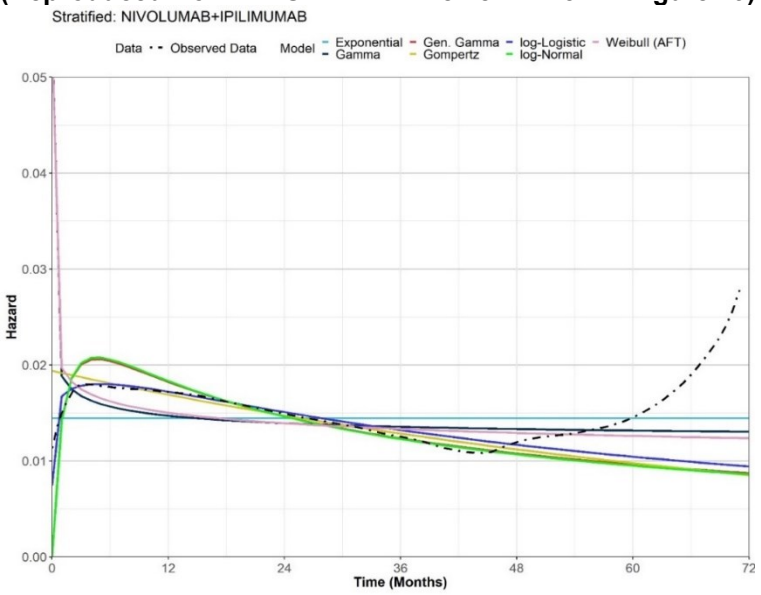
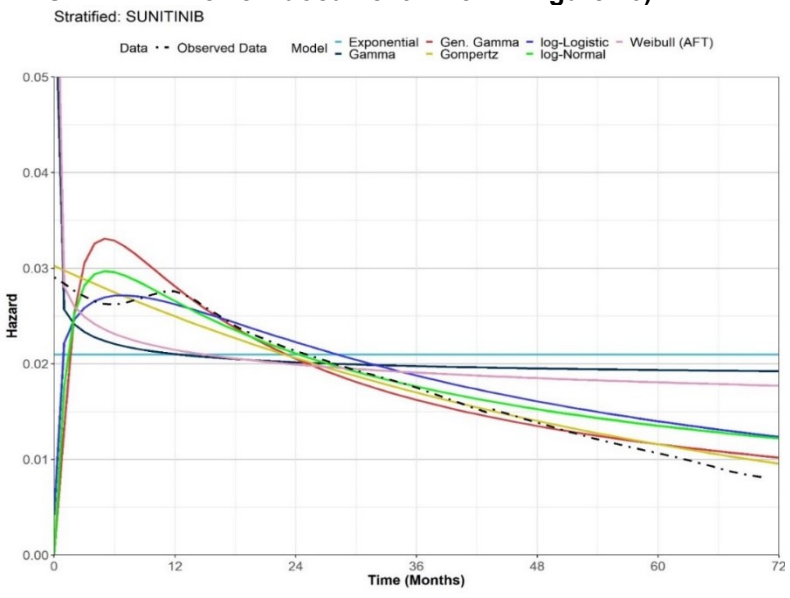


Figure 5. Sunitinib smoothed hazard plots for OS and fitted parametric survival models – CheckMate 214 intermediate/poor risk patients (60-month data cut) (Reproduced from NIVO+IPI CDF Review document A.15.2.2 Figure 20)



Progression-Free Survival

In both the original submission for NIVO+IPI and CDF review, both the ERG and committee preferred analysis was to use the secondary definition of PFS, which does not censor on receipt of subsequent therapy. This appraisal of PEMBRO+LENVA considers the primary definition of IRRC-assessed PFS from CheckMate 214, which was part of the co-primary endpoint of the trial. Both the PFS (per IRRC) by primary definition and secondary definition demonstrate a consistently improved PFS versus

sunitinib across the observed study period, with an increasing incremental gain in absolute PFS versus sunitinib with additional follow-up (see Table 3). As seen in the KM curve, a plateau appears to be forming from approximately 2 years for NIVO+IPI, which is not observed for sunitinib (see Figure 6, Figure 7 and Figure). Patients treated with NIVO+IPI have a significantly longer median PFS compared with sunitinib, further supporting the unique durable response seen with NIVO+IPI, as otherwise evidenced in the gain in median DoR versus sunitinib. It is clear from the plateau seen in the KM curves and the continuous improvement in HR that NIVO+IPI offers significant and clinically relevant benefit for patients in terms of PFS versus sunitinib, which is sustained with longer term follow-up which has not been captured in the current appraisal. In addition, the application of a single hazard ratio from an NMA, as per the AG's approach in this appraisal, is inappropriate for extrapolation of NIVO+IPI PFS as it is unlikely to capture the observed PFS as reported from the CheckMate 214 study. BMS would encourage, for validation, to compare the predicted landmark PFS for NIVO+IPI using the approach in this appraisal versus landmark PFS (per IRRC) as reported in the CheckMate 214 publications (PFS per IRRC for NIVO+IPI: 32.7% at 48 months and 31% at 60 months; Figure 6 and Figure 7). As the intermediate/poor risk information is redacted, we cannot provide the comparison as a matter of validation for the PFS predictions.

Figure 6 KM curve of PFS by treatment arm - CheckMate 214 intermediate-/poor-risk patients (48-month data cut; IRRC primary definition)[2]

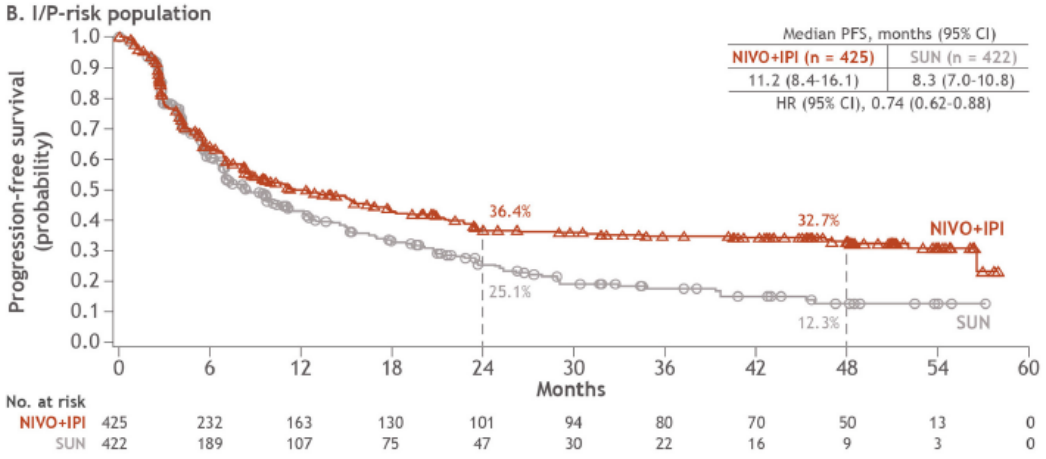


Figure 7. KM curve of PFS by treatment arm - CheckMate 214 intermediate-/poor-risk patients (60-month data cut; IRRC primary definition)

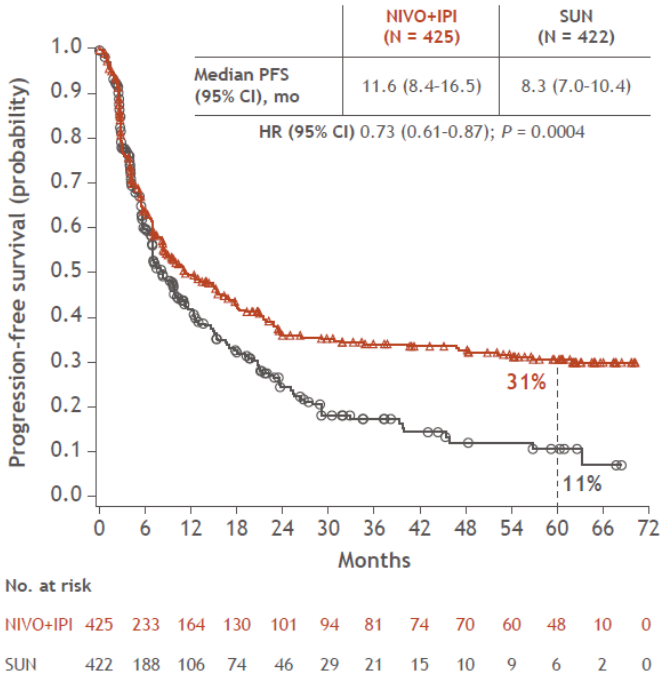


Figure 8: KM curve of PFS by treatment arm – CheckMate 214 intermediate-/poor-risk patients (60-month data cut, IRRC secondary definition)

[redacted]

Table 3 Summary of key CheckMate 214 trial PFS results

Outcome	Treatment	Median, months (95% CI)	HR (95% CI)
Progression-free survival (IRRC secondary definition)			
18 month minimum follow up	NIVO+IPI (n=425)	[redacted]	[redacted]
	Sunitinib (n=422)	[redacted]	
60 month minimum follow up	NIVO+IPI (n=425)	[redacted]	[redacted]
	Sunitinib (n=422)	[redacted]	
Progression-free survival (Investigator-assessed, primary definition)			
30 -month minimum follow-up[4]	NIVO+IPI (n=425)	8.2 (6.9-10.0)	0.77 (0.65 - 0.91
	Sunitinib (n=422)	8.3 (7.0-8.8)	
Progression-free survival (IRRC-assessed, primary definition)			
42-month minimum follow-up[5]	NIVO+IPI (n=425)	11.6 (8.4-15.5)	0.75 (0.62-0.90)
	Sunitinib (n=422)	8.3 (7.0-10.8)	
48-month minimum follow-up[2]	NIVO+IPI (n=425)	11.2 (8.4-16.1)	0.74 (0.62 - 0.88
	Sunitinib (n=422)	8.3 (7.0-10.8)	
60-month minimum follow-up[3]	NIVO+IPI (n=425)	11.6 (8.4 - 16.5)	0.73 (0.61 to 0.87
	Sunitinib (n=422)	8.3 (7.0 - 10.4)	

Please note that in the 30-month minimum follow-up data set of CheckMate 214, independent radiology review committee (IRRC)-assessed PFS was not available and only investigator-assessed PFS was published.[4] Later data cuts published IRRC-assessed PFS, which should be considered in this appraisal.

The committee concluded the EAG's exponential extrapolation for PFS to be plausible , but there was some uncertainty due to the limitations of the network meta-analysis (ACD section 3.11). Similar to NIVO+IPI, on CDF entry with 30-months minimum follow-up, the KM+exponential extrapolation was preferred by the ERG and NICE committee despite BMS preferring the hazard spline (2-knots).With an additional 30-months of follow-up at CDF exit (60-month minimum), TA780 has demonstrated that NIVO+IPI does not exhibit a constant hazard over the observed follow-up (see Figure 9 and Figure 10). Visual assessment of the smoothed hazard plots and fitted hazard functions of standard parametric survival models did not adequately capture the shape of the hazard functions (see Figure 9 and Figure 10). Goodness of fit statistics, visual inspection and clinical validation suggested that the hazard spline model (2 knots) was the best fitting extrapolation for the updated clinical data to capture the observed emerging plateau, this was consistent with the original submission when the 30-month data cut was used as cubic splines were preferred. Clinical validation for the CDF review of NIVO+IPI also confirmed that spline 2-knots hazard extrapolations were reflective of clinical practice.[7]

The final analysis of PFS for PEMBRO+LENVA was performed using the 26.6 months median OS follow-up. Evidence from the CDF exit of NIVO+IPI not only demonstrates the extent to which the exponential model fits the data poorly, but also that there is a visible plateau after 2 years. Given the short length of follow-up of the CLEAR trial with PEMBRO+LENVA it is too early to determine whether or not a similar plateau may be observed, highlighting the long-term uncertainty associated with PEMBRO+LENVA when basing 40-year extrapolations on limited follow-up.

Figure 9. NIVO+IPI smoothed hazard plots and fitted parametric survival models for PFS per IRRC (secondary definition) – CheckMate 214 intermediate/poor risk patients (60-month data cut) ((Reproduced from TA780 CDF Review submission, A.15.3.2, figure 26)

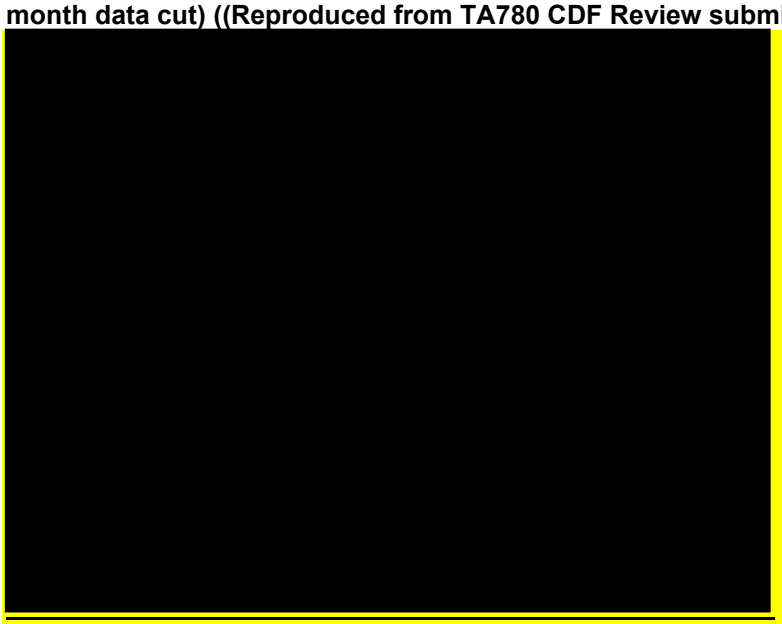


Figure 10. Sunitinib smoothed hazard plots and fitted parametric survival models for PFS per IRRC (secondary definition) – CheckMate 214 intermediate/poor risk patients (60-month data cut) (Reproduced from TA780 CDF Review submission, A.15.3.2, figure 27).

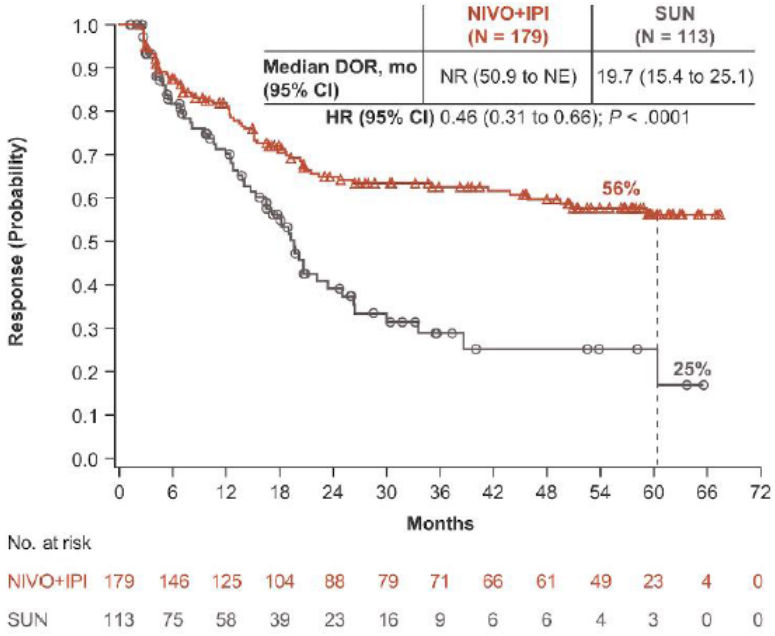
Notes: A 12 month smoothing interval was used for hazard data plots.

Duration of response (DoR)

Similar to what is observed in IRRC-assessed PFS, a plateau is observed in the DoR KM plot for patients who received NIVO+IPI in CheckMate 214 and achieved response, which is not observed in the sunitinib arm (Figure 11). With 60 months of minimum follow-up, median DoR has not been met for NIVO+IPI (95% CI: 50.9-not estimable) while median DoR was previously reported for sunitinib as 19.7 months (95% CI: 15.4-25.0 months), reflecting a minimum gain of at least 40.3 months, based on minimum available follow-up of 60 months, (~3.4 years) in median DoR. The median DoR for PEMBRO+LENVA in the intermediate-/poor- risk group was not reported, however using data from the IA3 data cut-off (median follow-up of 26.6 months for OS), the all-risk median DoR has been reached at 25.8 months (95% CI 22.1 to 27.9; see AG MTA report, section 3.8.4, page 56, table 22), and it would likely be plausible to assume that DoR may be shorter in patients with worse prognosis (i.e. intermediate/poor risk) given that median DoR is longer in the ITT (all risk) population for sunitinib in CheckMate 214 (median DoR: 24.8 months in ITT population). Therefore, patients who achieve response with NIVO+IPI have a higher probability of remaining in response over the longer-term than with sunitinib or PEMBRO+LENVA.

This is of importance for consideration in this appraisal and recommendation because the current assessment is based on applying a constant HR for PFS and OS from the NMA to model outcomes for NIVO+IPI. However, clinical evidence shows there is a difference in the durability of response over time in NIVO+IPI that is not observed with sunitinib or PEMBRO+LENVA, which brings into question whether the approach used in this appraisal is scientifically appropriate to extrapolate outcomes of NIVO+IPI.

Figure 11. KM curve of DOR by treatment arm - CheckMate 214 intermediate-/poor-risk patients (60-month data cut)

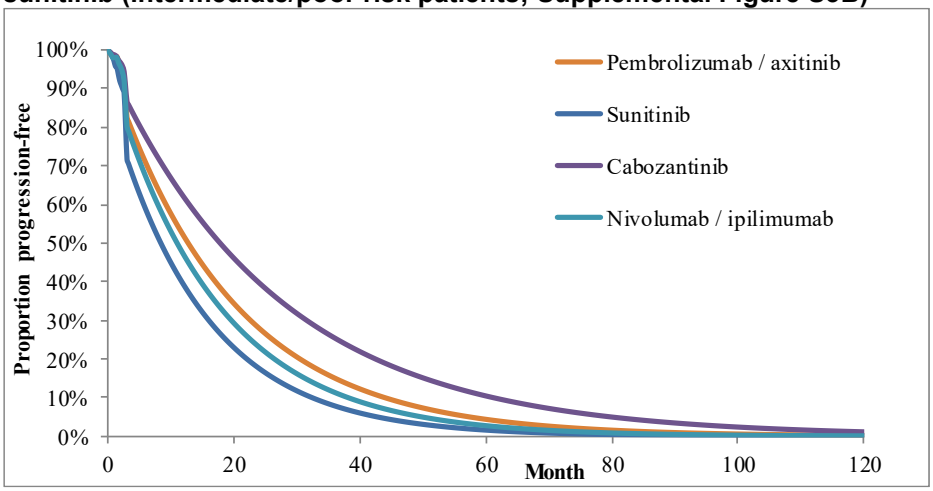


Time to Treatment Discontinuation (TTD)

BMS strongly disagree that the TTD curve selected for NIVO+IPI should be set equal to LENVA given published evidence that has been included in this appraisal does not support such an assumption. Clinical evidence shows a large difference in median

	duration of therapy between the CheckMate 214 trial and the CLEAR trial, which has not been taken into account in this appraisal. The assumption of equal TTD to LENVA has likely resulted in a large overestimation of treatment costs with NIVO+IPI. As reported in the 30-month publication, and also in the 48-month publication, median duration of therapy in the all-treated (all risk) population is 7.9 months in the NIVO+IPI arm and 7.8 months in the sunitinib arm.[24] In contrast, the CLEAR study reports the median duration of treatment for all risk patients was 17.0 months in the PEMBRO+LENVA arm and 7.8 months in the sunitinib arm. Though these populations include favourable risk patients, the treatment duration for PEMBRO+LENVA is higher than that observed in CheckMate 214 for NIVO+IPI. Moreover, median PFS for PEMBRO+LENVA is 23.9 months in the all risk population (all risk) whereas median PFS (IRRC) in the all risk population for NIVO+IPI is 12.2 months (median PFS: 11.2 months for intermediate/poor risk patients).[8] This shows a clear difference in the median PFS and median TTD for the NIVO+IPI ITT population of 4.3 months, in favour of PFS. BMS encourage the committee to revisit the TTD assumption of equivalence for NIVO+IPI to LENVA and to also compare this with PFS predictions, considering the previous CDF review NIVO+IPI in which "[redacted] of patients who are progression-free in the NIVO+IPI arm still are receiving treatment, demonstrating the ongoing clinical benefit despite treatment discontinuation. This treatment-free interval is further evidenced by swimmer plots presented in the appendix showing the proportion of patients achieving ongoing response but remaining off treatment and without any subsequent therapy" (NIVO+IPI CDF Review submission, section A.6.1.4, page 22). Therefore, it would be scientifically inappropriate to assume an equal duration of therapy to LENVA or any treatment duration that exceeds PFS for NIVO+IPI. Assuming equivalence, despite the evidence against such an assumption, is likely to overestimate treatment costs for NIVO+IPI, resulting in a more favourable ICER for PEMBRO+LENVA versus NIVO+IPI. The additional follow-up, which has not been appropriately captured for inclusion in the SLR or considered within the current appraisal, further demonstrates that a greater proportion of patients are continuing to benefit across all endpoints when treated with NIVO+IPI compared with sunitinib. With this additional follow-up, PFS has improved over sunitinib, and a plateau appears to be forming from approximately 2 years, which is also seen with the DOR curve as patients are continuing to benefit as demonstrated by the consistently longer OS. With 60-months minimum follow up, an additional 30-months over CDF entry, BMS have demonstrated (whilst following the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14 and 21) that the extrapolations selection for NIVO+IPI, were and continue to be the best fitting.[910] These extrapolations were clinically validated and reflected expectations in clinical practice. It is unclear if the same process has been followed by the AG as extrapolations do not appear to be clinically validated nor do they seem to have been validated against longer-term data that is available in the public domain. These data should have been captured in this appraisal. Finally, conclusions by the committee in this appraisal appear to conflict with those in TA780, which BMS reiterates also should have been retrospectively considered in this appraisal.

3	BMS are concerned that available evidence and past precedence have not been considered in the AG NMA, resulting in unreasonable conclusions with a high level of uncertainty, which are unsuitable for decision making. In addition to points demonstrated above, the base case model is likely to overestimate costs of treatment of NIVO+IPI and underestimate long-term benefit (and PFS) by using a HR-based approach, which would deeply favour a lower ICER for PEMBRO+LENVA versus NIVO+IPI. The CDF review of NIVO+IPI with 60-month minimum follow-up assessed the proportional hazards (PH) across the two treatment arms of CheckMate 214. The plateau in the KM curves, crossing of the log-cumulative hazard plots and rejection of the Schoenfeld residual test ($P < 0.01$) show evidence that the PH assumption is not supported. Despite the violation in PH assumption with PFS in the NIVO+IPI arm, time-varying hazards were not considered in the AG NMA and so "the AG PFS NMA HRs are not applicable to all time points across the observed follow-up of the trials included in the NMAs" (See AG MTA report, section 5.13.1 page 105). This violation of the PH assumption indicates that a constant HR would not be appropriate for use in this appraisal to estimate outcomes for NIVO+IPI, especially in the case of PFS where a clear and defined plateau has been observed from year 2, which is not observed for other therapies included in the NMA. Past precedence in advanced RCC for the submissions of pembrolizumab with axitinib (PEMBRO+AXI) and AVE+AXI explored both time-constant and time-varying NMAs.[1112] In the appraisal of AVE+AXI, the ERG and committee conclude that methodological concerns and the immature data informing the model made these results uncertain.".[11] Similarly, in the appraisal of PEMBRO+AXI, the committee "considered that the evidence base for the intermediate and poor-risk subgroup was weak.".[12] In addition, application of a constant HR when the PH assumption is violated has previously been shown to substantially underestimate outcomes for NIVO+IPI. In a cost-effectiveness study by Bensimon et al (2020) in first-line RCC, which was not identified in the economic SLR for this appraisal, a HR-based NMA was applied to sunitinib to predict NIVO+IPI (based on 30-month minimum follow-up).[13] As can be seen in Figure 12, predicted PFS for NIVO+IPI at five years is approximately <5%, whereas the 60-month minimum follow-up data shows PFS is 31% at five years. Therefore, the application of a HR-based NMA in this appraisal would not capture the plateau observed in CheckMate 214 for NIVO+IPI, which is not seen for the sunitinib arm to which the HR was applied. As such, the clinical benefit of NIVO+IPI has not been appropriately calculated and this method is inappropriate for use in decision making to compare PEMBRO+LENVA versus NIVO+IPI.

	Figure 12. Modelled PFS from Bensimon et al, which used a HR-based NMA applied to sunitinib (intermediate/poor risk patients; Supplemental Figure S3B)[13]  Taking into account the uncertainty surrounding the AG NMA and the omission of the 60-month minimum follow-up data from CheckMate 214, the scenario where OS of PEMBRO+LENVA is equal to NIVO+IPI should be the considered for decision making. Results from the AG OS fixed effects NMA in the intermediate-/poor- risk subgroup demonstrate a minor numerical advantage for PEMBRO+LENVA when compared with NIVO+IPI that is not statistically significant and has a wide confidence interval (HR=0.94, 95% CrI: 0.66 to 1.32). The results show there is no statistical difference in treatment effect between the two combination treatments. When this scenario is further explored (where OS PEMBRO+LENVA is equal to NIVO+IPI) in the deterministic sensitivity analysis of the AG economic model, PEMBRO+LENVA is dominated by NIVO+IPI.
4	BMS are concerned that treatment waning has not been appropriately accounted for in the PEMBRO+LENVA arm with the inclusion of a two-year stopping rule with pembrolizumab. This infers that whilst pembrolizumab is discontinued by 24 months, the benefit from treatment continues indefinitely, which is subject to uncertainty. The EAG recognise that the “effect of the pembrolizumab 2 year stopping rule on TTD data is unclear”, but do not consider treatment waning within their based case despite precedence from previous NICE appraisals of therapies in RCC (TA645 and TA650) and other immunotherapies with trial driven maximum durations of IO treatment. In the NICE appraisal of PEMBRO+AXI, a 2-year stopping rule was applied to the PEMBRO arm. In that appraisal, the committee noted that in previous NICE appraisals of checkpoint inhibitors when length of treatment was capped at 2 years in the cost-effectiveness model, the committees did not assume lifetime treatment benefit but, instead, examined various analyses of treatment benefit (waning effects). The committee agreed that immunotherapy would likely provide a durable response but concluded that there was insufficient evidence to assume this would be lifelong. The committee considered various model scenarios when the treatment effect of pembrolizumab stopped after 3 years, 5 years and 10 years (that is, treatment effect continued to 1 year, 3 years and 8 years after stopping pembrolizumab). Although the committee concluded that the immaturity of the data from KEYNOTE-426 (approximately 20 months follow-up) made any estimation of treatment waning effect

	highly uncertain, it accepted scenarios when a waning effect was applied after 5 years (TA650 FAD sections 3.10-3.11).[12] Considering the IO component is the same in the two appraisals and it is the same disease setting, precedent would have required waning to be implemented to PEMBRO+LENVA. In contrast, for the NICE appraisal of AVE+AXI based on clinical evidence from the JAVELIN Renal 101 trial, no stopping rule was applied, the committee concluded that there was no evidence to support a stopping rule as the pivotal trial JAVELIN Renal 101 and marketing authorisation did not include a stopping rule. With the removal of a stopping rule from the modelling, treatment waning was excluded so as to be in line with the trial. The committee agreed that it was not appropriate to include a stopping rule and treatment waning (TA650 FAD sections 3.16-3.17).[11] In the company's justification for the lack of treatment waning, they state "longer-term follow-up of patients receiving IO in advanced RCC has indicated a maintenance of survival benefit beyond treatment discontinuation (i.e., treatment waning has not been detected)" (PEMBRO+LENVA MSD company submission page 95). The company reference the 5-year minimum follow up of the CheckMate 214 trial to justify the maintenance of survival benefit beyond treatment discontinuation, but neither the market authorisation nor CheckMate 214 trial include a stopping rule. In addition, the assumption of a stopping rule was not accepted in the CDF entry as the committee concluded "that it is not appropriate to include a stopping rule for decision making because its effect on clinical outcomes are untested". Therefore, it is inappropriate to use such evidence from CheckMate 214 or the NIVO+IPI appraisals as justification for lack of treatment waning.[3]
5	
6	

Insert extra rows as needed

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Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760]

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Addendum to AG MTA report

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Lenvatinib plus pembrolizumab for untreated advanced renal cell carcinoma [ID3760]: A Multiple Technology Appraisal

Addendum following ACD comments

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CONTAINS COMMERCIAL IN CONFIDENCE DATA (CIC) AND ACADEMIC IN CONFIDENCE DATA (ACIC)

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

ALL TABLES IN THIS REPORT ARE CONFIDENTIAL

1 INTRODUCTION

To inform the National Institute for Health and Care Excellence Multiple Technology Appraisal process of the clinical and cost effectiveness of lenvatinib plus pembrolizumab for untreated advanced renal cell carcinoma, Bristol Myers Squibb (BMS) (manufacturer of nivolumab plus ipilimumab [NIV+IPI]) submitted comments on the Appraisal Consultation Document (ACD). This addendum contains the Assessment Group (AG) response to those comments and amendments to the AG network meta-analysis (NMA) and AG cost effectiveness estimates.

2 NETWORK META-ANALYSES

BMS notes that in the AG report, the NMAs for the intermediate/poor risk subgroup incorporate CheckMate 214 trial[1] progression-free survival (PFS) data according to the primary definition, which includes censoring for subsequent anti-cancer therapy. This censoring for subsequent anti-cancer therapy is consistent with the primary definition of PFS in the CLEAR trial[2] (using the censoring method preferred by the US Food and Drug Administration [FDA]) and the definition of PFS in the CABOSUN trial.[3] BMS highlighted that in both the original submission for NIV+IPI[4] and the Cancer Drugs Fund (CDF) review,[5] both the Evidence Review Group and the NICE Appraisal Committee preferred the analysis that used the secondary definition of PFS from the CheckMate 214 trial[1]. This secondary definition of PFS does not apply censoring for subsequent anti-cancer therapy, which is consistent with the secondary definition of PFS in the CLEAR trial[2] (using the censoring method preferred by the European Medicines Agency [EMA]).

The PFS and overall survival (OS) data from the CheckMate 214 trial[1] used in the NMAs presented in the AG report were based on a minimum follow-up time of 42 months. Only results using the primary definition of PFS were available in the publication of the CheckMate 214 trial[1] that reported 42-month follow-up data.

BMS highlighted that there are two sources of data in the public domain[6,7] that report PFS and OS data from the CheckMate 214 trial[1] that are more up-to-date than the data sources used in the AG NMAs. A published paper[6] reports 48-month minimum follow-up PFS and OS data, and a conference poster[7] reports 60-month minimum follow-up PFS and OS data. Both sources[6,7] report PFS data according to the primary definition. In its ACD response, BMS

provided 60-month PFS results according to the secondary definition of PFS. These results were not previously in the public domain (and are marked as academic in confidence).

The AG has updated the intermediate/poor risk group NMAs to include the most recent PFS and OS data from the CheckMate 214 trial (60-month minimum follow-up)[7], and presents these updated NMA results alongside results from the AG original NMAs in Table 1. In all three trials that contributed data to the intermediate/poor risk group NMAs, the primary definition of PFS included censoring on receipt of subsequent anti-cancer therapy. Therefore, the AG has used these primary definitions for its primary analysis. Sensitivity analyses have also been conducted using the secondary definitions of PFS from the CLEAR trial[2] and CheckMate 214 trial.[1] The AG assessed the proportional hazards (PH) assumption for the updated PFS and OS data from the CheckMate 214 trial,[7] and the AG's original conclusions (that PH is violated for PFS data, but not for OS data) remain valid. Including the updated data from the CheckMate 214 trial[7] in the AG NMAs has had little impact on the results, and the conclusions drawn in the original AG report remain the same.

Table 1 Results from the original and updated AG PFS and OS intermediate/poor risk subgroup NMAs

Treatment	Comparator	Fixed effects HR (95% CrI)[a]		Random effects HR (95% CrI)[a]	
		Original	Updated	Original	Updated
PFS – Primary analysis[b]					
Lenvatinib + pembrolizumab	Sunitinib	0.36 (0.28 to 0.46)	0.36 (0.28 to 0.46)	0.40 (0 to 773)	0.40 (0 to 812)
Lenvatinib + pembrolizumab	Cabozantinib	0.75 (0.45 to 1.25)	0.75 (0.45 to 1.25)	0.76 (0 to 25591)	0.76 (0 to 28283)
Lenvatinib + pembrolizumab	Nivolumab + ipilimumab	0.48 (0.35 to 0.66)	0.49 (0.36 to 0.67)	0.53 (0 to 21807)	0.53 (0 to 22471)
Cabozantinib	Sunitinib	0.48 (0.31 to 0.74)	0.48 (0.31 to 0.74)	0.53 (0 to 953)	0.52 (0 to 944)
Nivolumab plus ipilimumab	Sunitinib	0.75 (0.62 to 0.90)	0.73 (0.61 to 0.87)	0.76 (0 to 1339)	0.75 (0 to 1394)
Nivolumab plus ipilimumab	Cabozantinib	1.57 (0.97 to 2.51)	1.52 (0.95 to 2.44)	1.46 (0 to 48050)	1.43 (0 to 54176)
PFS – Sensitivity analysis[c]					
Lenvatinib + pembrolizumab	Sunitinib	0.45 (0.36 to 0.56)	0.45 (0.36 to 0.56)	0.49 (0 to 953)	0.49 (0 to 880)
Lenvatinib + pembrolizumab	Cabozantinib	0.93 (0.57 to 1.52)	0.93 (0.57 to 1.54)	0.92 (0 to 33190)	0.94 (0 to 33860)
Lenvatinib + pembrolizumab	Nivolumab + ipilimumab	0.60 (0.45 to 0.80)	0.69 (0.53 to 0.91)	0.63 (0 to 24343)	0.72 (0 to 26108)
Cabozantinib	Sunitinib	0.48 (0.31 to 0.74)	0.48 (0.31 to 0.74)	0.53 (0 to 973)	0.52 (0 to 1033)
Nivolumab + ipilimumab	Sunitinib	0.75 (0.62 to 0.90)	0.65 (0.55 to 0.76)	0.77 (0 to 1313)	0.68 (0 to 1236)
Nivolumab + ipilimumab	Cabozantinib	1.57 (0.97 to 2.51)	1.35 (0.85 to 2.16)	1.46 (0 to 45707)	1.31 (0 to 52052)
OS					
Lenvatinib + pembrolizumab	Sunitinib	0.62 (0.46 to 0.83)	0.62 (0.46 to 0.83)	0.66 (0 to 1200)	0.65 (0 to 1200)
Lenvatinib + pembrolizumab	Cabozantinib	0.78 (0.47 to 1.28)	0.78 (0.47 to 1.28)	0.80 (0 to 32209)	0.78 (0 to 28854)
Lenvatinib + pembrolizumab	Nivolumab + ipilimumab	0.94 (0.66 to 1.32)	0.91 (0.65 to 1.27)	0.95 (0 to 36680)	0.9 (0 to 31571)
Cabozantinib	Sunitinib	0.80 (0.53 to 1.21)	0.80 (0.53 to 1.21)	0.83 (0 to 1525)	0.84 (0 to 1510)
Nivolumab + ipilimumab	Sunitinib	0.66 (0.55 to 0.79)	0.68 (0.58 to 0.81)	0.69 (0 to 1274)	0.72 (0 to 1326)
Nivolumab + ipilimumab	Cabozantinib	0.83 (0.53 to 1.30)	0.85 (0.55 to 1.32)	0.84 (0 to 30031)	0.87 (0 to 35596)

[a] HR<1 favours the treatment over the comparator
[b] Primary definition of PFS used (includes censoring for subsequent anti-cancer therapy) for all three included trials
[c] Secondary definition of PFS (no censoring for subsequent anti-cancer therapy) used for the CLEAR trial[2] and the CheckMate 214 trial[2] and primary definition of PFS (includes censoring for subsequent anti-cancer therapy) for the CABOSUN trial[3]
CrI=credible interval; HR=hazard ratio; OS=overall survival; PFS=progression-free survival

3 AG RESPONSE TO BMS COMMENTS: COST EFFECTIVENESS ESTIMATES

The AG intermediate/poor risk subgroup NMAs have been updated with the addition of the CheckMate 214 trial 60-month minimum follow-up data suggested by BMS. The AG intermediate/poor risk subgroup base case cost effectiveness analyses have been re-run using these results. The key drivers of cost effectiveness in the MSD/AG model for the comparison of lenvatinib plus pembrolizumab (LEN+PEM) versus NIV+IPI are differences in OS and costs.

The long-term OS for patients treated with LEN+PEM is uncertain; the updated AG FE NMA hazard ratio (HR) suggests that, versus NIV+IPI, treatment with LEN+PEM may lead to improved OS; however, this result is not statistically significant (HR=0.91; 95% CrI: 0.65 to 1.27). As there is no statistically significant OS difference between treatment with LEN+PEM and treatment with NIV+IPI, the same OS extrapolation can be used to model the experience of both sets of patients (this means that the actual OS extrapolation chosen will have a negligible impact on cost effectiveness results). The AG has run a scenario in which there is no OS difference between treatment with LEN+PEM and treatment with NIV+IPI.

The costs of treatment with LEN+PEM and treatment with NIV+IPI are functions of the price of the drugs and the duration of treatment. The MSD/AG model results are potentially sensitive to the TTD data chosen to reflect the duration of treatment with each drug. LEN+PEM TTD data are available from the CLEAR trial; however, the AG does not have access to NIV+IPI TTD data. In the absence of NIV+IPI TTD data, the AG does not consider that it is unreasonable to use either lenvatinib or pembrolizumab TTD data from the CLEAR trial as a proxy. In the AG base case analysis, NIV+IPI TTD was modelled using CLEAR trial lenvatinib TTD data. A scenario analysis was carried out to explore the impact of using CLEAR trial pembrolizumab TTD data to model TTD for patients treated with NIV+IPI. For completeness, the AG has run an analysis using CLEAR trial pembrolizumab TTD data to reflect the experience of patients treated with NIV+IPI and no OS difference between patients treated with LEN+PEM and those treated with NIV+IPI.

The AG has not considered treatment waning for patients treated with LEN+PEM. Whilst pembrolizumab has a 2-year-stopping rule, there is no treatment stopping associated with lenvatinib. The AG therefore considered that it was inappropriate to apply a waning of treatment effect based solely on the stopping rule for pembrolizumab when the other active treatment (lenvatinib) continued. The AG considers that this is analogous to there being no waning of treatment effect for NIV+IPI despite ipilimumab having a four-cycle-stopping rule.

3.1 AG deterministic base case cost effectiveness results: intermediate/poor risk subgroup

The AG base case has been amended to reflect the changes to the PFS and OS HRs for the comparison of LEN+PEM versus NIV+IPI generated by the AG updated NMAs. The HR for LEN+PEM versus cabozantinib (CABO) did not change. The AG updated base case cost effectiveness results do not include oral chemotherapy costs; this amendment was made in response to company comments made during the consultation period prior to ACM1.

Table 1 and Table 2 show the AG original base case results and

Table 3 and Table 4 show revised base case generated using results from the updated NMAs.

Table 1 AG pairwise deterministic results, intermediate/poor risk subgroup: LEN+PEM versus CABO and versus NIV+IPI (list prices) (not including oral chemotherapy costs)

Drug	Total			Incremental: LEN+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	4.933	[redacted]	-	-	-	-
CABO	[redacted]	4.080	[redacted]	[redacted]	0.852	[redacted]	£161,714
NIV+IPI	[redacted]	4.707	[redacted]	[redacted]	0.226	[redacted]	£132,969

AG=Assessment Group; ICER=incremental cost effectiveness ratio; LYs=life years gained; QALYs=quality adjusted life years

Table 2 AG fully incremental analysis, intermediate/poor risk subgroup LEN+PEM versus CABO and versus NIV+IPI (list prices) (not including oral chemotherapy costs)

Drug	Total		Incremental		ICER/QALY gained
	Costs	QALYs	Costs	QALYs	
CABO	[redacted]	[redacted]	-	-	-
NIV+IPI	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated by LEN+PEM
LEN+PEM	[redacted]	[redacted]	[redacted]	[redacted]	£161,714

AG=Assessment Group; ICER=incremental cost effectiveness ratio; QALYs=quality adjusted life years

Table 3 AG pairwise deterministic results, intermediate/poor risk subgroup: LEN+PEM versus cabozantinib and versus NIV+IPI (list prices) (not including oral chemotherapy costs)

Drug	Total			Incremental: LEN+PEM vs comparator			
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER/QALY gained
LEN+PEM	[redacted]	4.933	[redacted]	-	-	-	-
CABO	[redacted]	4.080	[redacted]	[redacted]	0.852	[redacted]	£161,714
NIV+IPI	[redacted]	4.592	[redacted]	[redacted]	0.341	[redacted]	£89,524

AG=Assessment Group; ICER=incremental cost effectiveness ratio; LYs=life years gained; QALYs=quality adjusted life years

Table 4 AG fully incremental analysis, intermediate/poor risk subgroup LEN+PEM versus cabozantinib and versus NIV+IPI (list prices) (not including oral chemotherapy costs)

Drug	Total		Incremental		ICER/QALY gained
	Costs	QALYs	Costs	QALYs	
CABO	[redacted]	[redacted]	-	-	-
NIV+IPI	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated by LEN+PEM
LEN+PEM	[redacted]	[redacted]	[redacted]	[redacted]	£161,714

AG=Assessment Group; ICER=incremental cost effectiveness ratio; QALYs=quality adjusted life years

3.2 AG deterministic scenario analysis results: intermediate/poor risk subgroup

The AG has run a scenario in which there is no OS difference between treatment with LEN+PEM and treatment with NIV+IPI. Results are presented in Table 5.

Table 5 AG scenario analyses: intermediate/poor risk subgroup LEN+PEM versus NIV+IPI (list prices) (not including oral chemotherapy costs)

AG scenarios Intermediate/poor risk subgroup	Lenvatinib plus pembrolizumab		Nivolumab plus ipilimumab		Incremental		*ICER £/QALY*
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
AG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£132,969
S1: NIV+IPI=Eisai PEM TTD (Weibull)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM dominates
S2: OS NIV+IPI=OS LEN+PEM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM is dominated
S1+S2:	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	LEN+PEM dominates

AG=Assessment Group; ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

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