NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [ID3761]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [ID3761]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document** from Merck Serono
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   b. Appendix 1
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3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Roy Castle Lung Cancer Foundation

There were no comments on the Appraisal Consultation Document from the experts or submitted through the NICE website.

4. **Evidence Review Group critique of company comments on the ACD**

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations

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

Definitions:

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 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 determination (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, 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.

Comments received from consultees

Consultee	Comment [sic]	Response
Merck Serono Ltd	**ACD Section 3.2, page 5-6: *Untreated and treated subgroups should be considered separately*** In the original company submission (CS), the line-agnostic group was the base case population, however full subgroup analyses were provided for untreated and previously-treated subgroups separately. For all of the updated comparisons, line of therapy subgroups have been considered separately, for both tepotinib and the comparators, including for the most relevant comparison of chemo-immunotherapy in the untreated population. Furthermore, the relevant PD-L1 expression groups have been noted and accounted for in each comparison where appropriate.	Thank you for your comment. The FAD notes the new company analyses in section 3.2.

Merck Serono Ltd	**ACD Section 3.3, page 6-7: *The appraisal should focus on untreated non-squamous NSCLC with METex14 skipping alterations*** **Summary** • **Merck agree that the appraisal should focus on untreated non-squamous NSCLC with METex14 skipping alterations, as this is the most relevant population who will receive tepotinib.** • **However clinical experts have highlighted the importance of including previously-treated patients, as in some cases tepotinib could be used in the previously-treated setting. Furthermore, even though squamous histology is rare in METex14 skipping NSCLC and not routinely tested, all clinical experts interviewed have stated that access to tepotinib in squamous patients is still preferable, as there is a high unmet need even in this very small population. Squamous patients were included in the VISION study as well.** • **This is consistent with all NICE appraisals in NSCLC with other oncogenic driver mutations reviewed by the company (e.g. ALK, ROS-1, RET NSCLC) where squamous histology also is rare, but the final NICE recommendation did not restrict to non-squamous patients only.** **Line of therapy** Merck agree with the committee that the most relevant population in this appraisal with regards to line of therapy is the untreated NSCLC population with METex14 skipping alterations. As discussed in the ACD and from clinical expert feedback, if reimbursed, tepotinib would mostly be offered to patients in the untreated (treatment naïve) setting. However, in some cases, tepotinib could be used in previously-treated patients, for example in case of a delay to a genomic test result, or for patients who have already started treatment before tepotinib is reimbursed. Therefore, clinical expert feedback sought by Merck has reinforced that it is important for previously-treated patients to be included in the appraisal population. To support this, Merck have provided supplementary analysis in the previously-treated group (discussed in Comments **6** and **10-11**). **Histology** Merck agree with the committee that the most relevant population in this appraisal with regards to histology is the non-squamous NSCLC population with METex14 skipping alterations. The majority of patients with METex14 skipping NSCLC are non-squamous histology. For example, in VISION, [redacted]% of patients were adenocarcinoma histology (including non-squamous), and [redacted]% were squamous histology (based on Cohort A), and this is similar to proportions reported in the literature for METex14 skipping NSCLC (see Section B.3.2.2 of the company submission). The ACD also stated that squamous patients will not be routinely tested for in NSCLC. Therefore, as covered later in the ACD response, Merck have updated the ITC to reflect the more relevant non-squamous comparators (for example, KEYNOTE-189, for pembrolizumab + pemetrexed + platinum, which is in non-squamous	Thank you for your comments. Section 3.3 of the FAD notes that the majority of the available evidence is for untreated non-squamous NSCLC with METex14 skipping alterations, but makes clear that tepotinib is appraised within its full marketing authorisation.

patients only). Please see Comment **12** for how else the model has been updated to reflect these changes.

However, Merck have received consistent clinical expert feedback (from a previous advisory board with four UK clinicians; and three further interviews with separate clinicians as part of this ACD response) that clinicians would still prefer access to tepotinib in squamous advanced NSCLC patients, even if rarer than non-squamous and not routinely tested for, as there is still a high unmet need for a targeted treatment in this very small group of patients. The VISION trial results demonstrated that tepotinib was effective in the ITT population including a small sub-set of squamous patients, and the marketing authorisation for tepotinib does not restrict on the basis of histology to exclude squamous patients.[2] For all of the above reasons, patients with squamous NSCLC harbouring METex14 skipping alterations were included in the overall analysis in the original company submission (CS), and the company's position remains the appraisal recommendation should not be restricted to non-squamous patients only. Furthermore, it is important to remember that squamous METex14 skipping patients represent an incredibly small population within the UK. Squamous histology is present in roughly 3-9% of METex14 skipping tumours (from a SLR conducted by NICE, B.1.3.2.2), which is itself only in 3% of NSCLC cases.

Precedent in previous comparable appraisals

This approach is consistent with other appraisals in NSCLC with other oncogenic driver mutations. In these other oncogenic driver mutations in NSCLC (e.g. ALK, ROS-1, RET) squamous histology also tends to be rare, and often the Final Appraisal Document (FAD) acknowledged that non-squamous patients were the most relevant cohort. However, in all of these appraisals, the final NICE recommendation did not restrict to non-squamous patients, even if squamous patients were not included in the relevant clinical trial or analysis. Therefore, the consideration of subgroups in the tepotinib appraisal should be consistent with these previous comparable appraisals in NSCLC with other oncogenic driver mutations (described in Table 1 below) to ensure equity of care to all eligible patients.

Table 1. Review of previous NICE appraisals in advanced NSCLC with other oncogenic driver mutations since 2018, and if the recommendation mentions histology

TA and date of publication	Treatment	Driver mutation	Squamous patients excluded from recommendation?	Discussion of squamous histology in FAD
TA760[3] 12 Jan 2022	Selpercatinib	RET	No	• The company did not present evidence on selpercatinib for squamous disease because of the rarity of RET in squamous NSCLC, clinical advice, and the very small number of people with squamous NSCLC in the trial

Consultee	Comment [sic]					Response
					• The committee agreed that the recommendations in this technology appraisal would apply to both squamous and non-squamous advanced NSCLC, because of the wording of the marketing authorisation and because the squamous population is so small	
	TA670[4] 27 January 2021	Brigatinib	ALK	No	None	
	TA643[5]	Entrectinib	ROS-1	No	None	
	TA628[7] 13 May 2020	Lorlatinib	ALK	No	None	
	TA571[8] 20 March 2019	Brigatinib	ALK	No	None	
	TA529[9] 04 July 2018	Crizotinib	ROS1	No	• The marketing authorisation for crizotinib did not specify non-squamous disease, but ROS1-positive NSCLC is almost exclusively seen in non-squamous tumours • The summary of product characteristic states that there is limited information available in patients with ROS1-positive NSCLC with non adenocarcinoma histology, including squamous. • Testing for the ALK mutation is routinely done in the non-squamous population only.	
	In conclusion, Merck reiterate that the appraisal population (and any potential recommendation of tepotinib) should still include previously-treated patients, as well as squamous patients, due to clinical feedback that there are unmet clinical needs for tepotinib in both these groups, although they do not represent the group most likely to receive tepotinib. This approach is in line with the tepotinib marketing authorisation, and also consistent with previous comparable appraisals in NSCLC which did not restrict recommendations by histology subgroups.					

Consultee	Comment [sic]	Response
Merck Serono Ltd	**ACD Section 3.4: *Chemo-immunotherapy is the most relevant comparator for tepotinib*** Merck agree with the ACD that the appraisal should focus on untreated non-squamous METex14 skipping NSCLC, and that the most relevant comparator is chemo-immunotherapy (specifically pembrolizumab with pemetrexed and platinum chemotherapy). This is in line with the latest clinical feedback given to Merck, which stated that most untreated, non-squamous patients receive chemo-immunotherapy in UK practice. Furthermore, clinical experts highlighted that as patients with METex14 skipping NSCLC are known to respond poorly to immunotherapy monotherapy, even if a patient had PD-L1≥50%, they would mostly be given chemo-immunotherapy over immunotherapy monotherapy in the absence of a targeted therapy. Therefore, we align with the committee's view that chemo-immunotherapy is the most relevant comparator. As part of this ACD response, Merck have provided an updated ITC comparing tepotinib to pembrolizumab with pemetrexed and platinum, using clinical trial data from NSCLC without specific oncogenic biomarkers (wildtype NSCLC), as well as an updated economic model to reflect this comparison. Additional comparisons have also been conducted, however the chemo-immunotherapy comparison remains the most relevant and important comparison. As such the chemo-immunotherapy comparison will be the base-case comparison in this appraisal for tepotinib in METex14 skipping NSCLC.	Thank you for your comments. Section 3.4 of the FAD makes clear that chemo-immunotherapy is the most relevant comparator for untreated non-squamous METex14 skipping NSCLC. It also states that the company has provided the most relevant analyses for this and other populations in the appraisal.

Merck Serono Ltd	**ACD Section 3.5, page 7–8: *The clinical evidence for tepotinib is uncertain because it is based on 1 single-arm study that may not be generalisable to NHS practice*** **Summary** • **Merck disagree that the VISION trial is not generalisable to NHS practice or the UK population. The VISION trial was reflective of the METex14 skipping NSCLC population for age, histology and other characteristics typical of the specific population.** • **In addition, a recent publication of METex14 skipping patients treated with tepotinib in the UK through an Early Access to Medicines Scheme (EAMS) showed these UK patients had similar characteristics (e.g. in age, histology etc) to those from VISION, further supporting the generalisability of VISION to UK METex14 skipping patients. Furthermore, over half of patients in VISION were European patients.** • **For most patients, VISION was also reflective of subsequent treatments that would be given after tepotinib in NHS practice, with most patients receiving chemotherapy or immunotherapy, which is in line with clinical expert expectations. Only a minority of patients received treatments outside of NHS practice, primarily crizotinib.** In the ACD, clinical experts noted that the response rate in VISION was higher than would be expected with current standard treatments, and the committee agreed that VISION shows that tepotinib is clinically effective. However, it noted that the distribution of subsequent treatments in VISION meant that the results may not be generalisable to NHS clinical practice. **Use of a single-arm trial in METex14 skipping NSCLC** The company acknowledges the uncertainty provided by a single-arm trial, in what is a rare mutation and small population. However, despite the inherent uncertainty due to lack of a trial comparator arm and the challenges associated with this type of trial, there is precedent for single arm studies being used in NICE decision-making and informing UK clinical practice in NSCLC, e.g. TA643 and TA529.[5,9] Furthermore, certain circumstances exist where randomised controlled trials (RCTs) can be considered ethically questionable or unfeasible due to a disease's rarity impacting only a small population. In this instance a Phase 2 study provides sufficient information on efficacy in this very rare cancer, with high unmet medical need where no approved treatments are currently available in the UK. There is a precedent for single-arm trials providing a strong alternative to RCTs as long as the patient population is well-defined and the drug produces a substantial Objective Response Rate (ORR) that exceeds that of existing treatments. The VISION trial builds on strong scientific evidence and pre-clinical data, and so the single-arm study design was the most feasible and appropriate method for VISION. Furthermore, Merck disagrees with the suggestion that VISION is not generalisable to NHS practice, for reasons outlined below. **Generalisability of VISION to the METex14 skipping NSCLC population in the UK** Firstly, the most important argument supporting the generalisability of VISION is that patient characteristics are reflective of advanced NSCLC harbouring METex14 skipping alterations. As presented in Section B.3.2.2 of the CS, METex14 skipping NSCLC patients have a specific set of	Thank you for your comments. Section 3.5 of the FAD discusses the committee's concerns about the quality of the evidence for tepotinib from the single-arm VISION trial. It refers to the trial study locations and also briefly that there are differences in subsequent treatments compared with NHS practice (discussed in more detail in section 3.14). More broadly, the section states that the committee had concerns about the extent of the uncertainty caused by the use of a single arm trial and that a RCT should have been conducted to reduce uncertainty in the comparative analysis.

	characteristics, including older age (median age ~73 years), with predominately non-squamous histology, poor fitness (i.e. mostly ECOG 1 over ECOG 0) and poor responses to immunotherapy. Also in the CS (Section B.2.3.1.3), it was demonstrated that the VISION trial was reflective of these characteristics, and so remains generalisable to the METex14 skipping population, including for UK patients in NHS practice. Four clinical experts interviewed by Merck previously as part of an advisory board all agreed that the VISION population was reflective and generalisable to the UK METex14 skipping population, as did the three clinical experts interviewed separately as part of this ACD response. Secondly, a recent publication at the British Thoracic Oncology Group (BTOG) conference is presented in Appendix **1** to this ACD response, reporting outcomes from UK patients treated with tepotinib through the Early Access to Medicines Scheme (EAMS) (n=15). Although low in patient numbers, the patient characteristics were reflective of what is expected for the METex14 skipping population, and what is observed in the VISION trial, specifically older age and predominantly non-squamous histology.[10] Tepotinib was also observed to be clinically effective in this UK-specific population. This further supports the generalisability of VISION to METex14 skipping patients in the UK population. In addition, 51% of the VISION trial was from Europe (Section B.2.3.1.3 and Appendix R.1.2.21 of the CS), and nearly all Western Europe specifically, which represents a broadly similar population to the UK, further highlighting the generalisability of VISION to the UK and NHS practice. **Generalisability of subsequent treatments to NHS practice** Merck disagrees with the ACD statement that the distribution of subsequent treatments in VISION meant that the results may not be generalisable to NHS clinical practice. As part of this ACD response, Merck has elicited feedback from three clinical experts, and they have been asked specifically about expected subsequent treatments after tepotinib in NHS practice (Comment **8** and Appendix **1**). This was also discussed by the clinical experts in the first ACM. The feedback from the three clinical experts on subsequent treatments is consistent: in NHS practice, patients will be able to receive either chemotherapy (platinum-doublet chemotherapy or docetaxel +/- nintedanib) or immunotherapy monotherapy after tepotinib. The specific regimens will depend on tepotinib line of therapy, and in the case of previously-treated patients, will depend on treatment prior to tepotinib. Please see Comment **8** and Appendix **1** for more detailed feedback on subsequent treatments after tepotinib. In summary: • **Tepotinib in previously-untreated patients:** o All clinical experts consulted as part of ACD response agreed that patients will receive either immunotherapy monotherapy or platinum-based chemotherapy as a second-line treatment after tepotinib. Patients could then receive docetaxel +/- nintedanib as a third-line treatment. o Based on the three interviews conducted by Merck, the split between those receiving immunotherapy and those receiving platinum-based chemotherapy after tepotinib is expected to range from 50:50 to 90:10 (in favour of subsequent immunotherapy over	

	chemotherapy), although all experts highlighted that this split between immunotherapy and chemotherapy is not completely known at the moment. They also agreed that the vast majority of immunotherapy-treated patients would go onto pembrolizumab, and chemotherapy would be mostly pemetrexed (with carboplatin). ○ In the untreated population in VISION (Cohort A+C), of patients who received subsequent treatment, most received subsequent immunotherapy ([redacted]) and/or chemotherapy ([redacted]), in line with expected NHS practice and clinical expert feedback. The most common immunotherapy was pembrolizumab, and the most common chemotherapy was pemetrexed, with/without carboplatin, again in line with expectations of NHS practice. ○ A smaller proportion of patients received subsequent treatments outside of NHS practice: primarily subsequent crizotinib ([redacted]), or a different subsequent MET inhibitor ([redacted]), or another investigational treatment ([redacted]) across a number of lines of therapy. • **Tepotinib in previously-treated patients**: ○ The clinical experts stated that if a patient receives chemo-immunotherapy before tepotinib, then docetaxel +/- nintedanib will be given as a third-line treatment, or in some specific cases, another single agent chemotherapy such as paclitaxel (off label use). Most patients get chemo-immunotherapy up front, so after tepotinib, most patients will receive subsequent docetaxel +/- nintedanib. ○ If immunotherapy monotherapy is given in first line (in patients with PD-L1 expression ≥50%), then after tepotinib, platinum-based chemotherapy will be given. This will mostly be carboplatin + pemetrexed, but some could receive other options (such as gemcitabine/vinorelbine) in combination with carboplatin. ○ If a patient has not had any immunotherapy first-line, they could receive immunotherapy third-line after tepotinib, but this is unlikely and will be rare according to clinical experts (although possible within NHS practice). ○ This distribution of treatments was mostly aligned with the previously treated population in VISION Cohort A+C, where [redacted] received chemotherapy and [redacted] received immunotherapy, again aligned to what is possible and expected within NHS practice. ○ Again the main difference was the subsequent crizotinib ([redacted]), other MET inhibitors ([redacted]) or investigational treatment ([redacted]) which are not offered in UK, albeit in even lower proportions to untreated patients. In the ACD response Appendix **1**, the full subsequent treatments received by patients in VISION is reported, by line of therapy. Furthermore, the full clinical feedback on subsequent treatments is reported in the Appendix **1** as well as in Comment **8** of this document. • Finally, clinical experts interviewed by Merck as part of this ACD response highlighted that the use of subsequent treatments outside of NHS practice is typical for global clinical trials, and	

Consultee	Comment [sic]	Response
	similar to trials that NICE would have appraised in the past. However, it is important to note that these subsequent treatments outside of NHS practice in VISION are the minority, and most patients who received subsequent treatments were aligned with NHS practice, highlighting that VISION is largely generalisable to NHS practice for subsequent treatments.	
Merck Serono Ltd	**Section 3.6 page 8: *Using the data from cohort A plus cohort C has little effect on the results, but would be preferable*** As per the committee's stated preference in the ACD, Merck have used the larger Cohort A+C (n=290) from VISION in the updated ITC, comparing to using clinical trials in wildtype NSCLC as well as the updated immunotherapy monotherapy comparison using METex14 skipping NSCLC observational data. The full dataset of Cohort A+C (n=290) is marginally larger than from the 275 patients with at least 3 months of follow up, described previously in Technical Engagement and in the original submission. Although the additional 15 patients add little for long-term extrapolation, they do further increase confidence in the short term results of tepotinib, and there is no statistical reason for their exclusion when analysis is performed. Therefore, the full 290 patients have been included. As previously discussed, using Cohort A+C has minimal impact on the results, but provides further certainty with the larger patient cohort, and this is further explored in Appendix 2.	Thank you for your comments. Section 3.6 of the FAD states the committee's preference for using data from cohorts A + C in the analysis, and that the company agreed to provide this at consultation.

Merck Serono Ltd	**ACD Section 3.7 page 9–11: *The indirect treatment comparisons results are highly uncertain***	Thank you for your comments. Section 3.7 of the FAD describes what the company did in its original indirect treatment comparisons. Section 3.8 of the FAD discusses why the committee felt that these were not sufficiently robust, whilst also acknowledging that the company had made every effort to provide appropriate analyses in the METex14 skipping NSCLC population. Sections 3.9 and 3.10 of the FAD discuss the new analyses provided by the company at consultation where data from VISION is compared to data from trials in wild-type NSCLC. These sections conclude that each approach to the indirect treatment comparison contain different sources of uncertainty, and that both were considered in the committee's decision making.

Summary

- **The company initially used observational data specific to the METex14 skipping NSCLC population to inform the comparator arm of the ITC, as METex14 skipping is a distinct population within NSCLC, with different patient characteristics (including older age and worse ECOG) and a poorer response to immunotherapy versus wildtype NSCLC. In appraisals for other oncogenic driver mutations in NSCLC, companies have previously been criticised by NICE for using comparator data outside of the specific mutation.**
- **The company undertook extensive validation of the observational comparator data compared to published studies in the METex14 skipping population, as well as against clinical trials in wildtype NSCLC.**
- **The immunotherapy monotherapy outcomes of the Merck real-world cohort analysis, particularly for the relevant untreated METex14 skipping NSCLC population, are aligned to the outcomes from other published studies in METex14 skipping NSCLC with immunotherapy (e.g. Sabari et al, Guisier et al.), as well as in expectations compared to clinical trials in wildtype NSCLC for immunotherapy. The treatment mix is also aligned to NHS practice.**
- **Merck acknowledge the chemotherapy outcomes from the observational data are less aligned to clinical expectations, likely driven by the high proportions of subsequent treatments and treatments not fully reflective of NHS practice (as the data was primarily from US and Canada). There is also limited real-world data for METex14 skipping patients treated with chemo-immunotherapy, which is the main comparator for tepotinib, as highlighted in the ACD.**
- **Nonetheless, tepotinib demonstrated greater PFS that was statistically significant compared to immunotherapy and chemotherapy in the real-world cohort comparisons, and numerically greater OS, despite the overstated chemotherapy efficacy. It is clinically implausible that tepotinib does not have greater survival compared to chemotherapy, across lines of therapy, based on extensive external validation, interviews with clinical experts and the targeted mechanism of tepotinib. The survival benefit for tepotinib is expected to be substantially greater than estimated from the observational data.**

Merck acknowledge there is inherent uncertainty in using real-world data in what is a rare population with limited patient numbers. However, we wanted to provide our rationale and context for use of observational comparator data in the specific METex14 skipping population, and then highlight where it is still relevant and appropriate for use in this appraisal. The updated ITC using clinical trial data in wildtype NSCLC, and the comparisons where this revised ITC is most relevant, is then described and reported.

Rationale for use of observational data in METex14 skipping NSCLC for the original indirect treatment comparison

As noted in the ACD, there are no clinical trials for the key comparators to tepotinib (immunotherapy and/or chemotherapy) in METex14 skipping NSCLC specifically. As described in Section B.2.9.1 of the

	CS, it was important to ensure comparator data came from the METex14 skipping population, if possible in this appraisal, for the following reasons: • Firstly, the population has prognostic characteristics substantially different to that of other types of NSCLC, notably being substantially older (median age 73 years) and therefore less fit (higher ECOG 1 over ECOG 0), as well as with high proportions of non-squamous histology (Section B.1.3.2.2 of CS). • Secondly and most importantly, it has been shown that patients with METex14 skipping NSCLC have a poorer prognosis compared to patients without this mutation (Section B.1.3.2.3 of the CS) and are known to respond poorly to immunotherapy in particular (Section B.1.3.3.2 of the CS). Studies consistently show low response rates and PFS for immunotherapy in the METex14 skipping population, and although OS varies, it is still observed to be lower than what is expected in wildtype NSCLC.[11-13] Clinical expert feedback sought by the company as part of this ACD response confirmed this poor response to immunotherapy. This was either from clinician's direct experience in METex14 skipping NSCLC, or clinician's expectations that this poor response would be similar to other oncogenic driver mutations in NSCLC (e.g. ALK and EGFR), where poorer immunotherapy outcomes are also observed.[13,14] • Finally, a further rationale for using data from a METex14 skipping population specifically was to avoid the critique raised in previous NICE appraisals in NSCLC with other oncogenic driver mutations, regarding the use of comparator data that was not specific to the driver mutation. Examples of appraisals where this critique was raised include: TA529, TA643 (ROS-1 NSCLC) and TA760 (RET NSCLC).[3,5,9] For the reasons stated above, the company identified observational data in the METex14 skipping population, and used this data to inform the ITC and economic model. A systematic search of all possible data sources in METex14 skipping NSCLC was undertaken (as described in Appendix L and Technical Engagement response to Key Issue 4), and the dataset constructed by Merck (partly through non-interventional studies run by Merck), is the largest patient-level dataset in the METex14 skipping NSCLC population the company are aware of, with access to patient characteristics and outcomes for most of the key comparator classes. Furthermore, there were sufficient patient numbers for robust statistical analysis, in what is a rare mutation. The access to patient level data allowed for a tight match of patient characteristics to VISION based on inclusion and exclusion criteria and using propensity score weighting. As a result, the company were able to generate comparisons which were statistically robust and as unbiased as possible. All of these comparisons were validated against a wide range of external data sources (discussed below). The rare nature of the disease and the relatively low patient numbers (compared to clinical trial data) mean that the wide confidence intervals are to be expected, and likely to be observed in any comparison using observational data in a rare disease. Therefore, despite a number of limitations related to the rare nature of the mutation and lack of UK-specific data, Merck still believe the observational data represents a reliable data source for NICE's decision-making	

in a METex14 skipping NSCLC population, but particularly for immunotherapy where there is known to be a poor prognosis in this specific population versus wildtype NSCLC.

Validation of observational data ITC outcomes against published data in METex14 skipping NSCLC and clinical trials in wildtype NSCLC: immunotherapy monotherapy

The outcomes from the observational data used in the ITC (after weighting) were validated against published data in the METex14 skipping population, as well as clinical trials in wildtype NSCLC, as reported in Section B.3.2 of the CS. The studies used for external validation of the ITC results are summarised in Table 2 below, with median OS and median PFS reported. Furthermore, the long-term survival curves selected in the economic model were also validated against these same studies in Section B.3.8.7 of the CS.

All studies used in the validation were also reported in Section B.3.2. of the CS, with the exception of the Standing Cohort data. This data source is from real-world outcomes provided by Public Health England (PHE) for advanced (Stage IIIB/C and IV) NSCLC, for patients treated with the specific treatments listed in the NICE scope for tepotinib. More details have been provided as a separate reference.[6] This represents another useful source to validate outcomes for NSCLC in the UK specifically.

Please also note that the ITC has been updated to be weighed against VISION Cohort A+C (given the committee's preference for Cohort A+C as in Section 3.6 of the ACD), as well as to include another observational dataset in the METex14 skipping population for the comparators that the company recently received access to (referred to as the French/GFPC dataset). This new analysis is described in detail in the ACD response Appendix **2**. The ITC outcomes remain consistent with the initial analysis as also shown in Appendix **2**.

Table 2. Median OS and PSF by trial for immunotherapy

Study	Population	N	Line of therapy	Treatment	Median OS (95% CI)	Median PFS (95% CI)
Line agnostic						
Real-world cohort data (original Merck analysis)	METex14 skipping NSCLC	51*	Line agnostic	Mostly pembrolizumab (65%)	[redacted]	[redacted]
Real-world cohort data (updated Merck analysis†)	METex14 skipping NSCLC	99	Line agnostic	Mostly pembrolizumab (75%)	[redacted]	[redacted]
Sabari et al. 2018[12]	METex14 skipping NSCLC	24	A mixture of 1L and 2L+	Immunotherapy monotherapy (22/24); immunotherapy +	18.2 months (12.9-NR)	1.9 months (1.7-2.7)

				chemotherapy (2/24)		
Mazieres et al. 2019[13]	METex14 skipping NSCLC	36	A mixture of 1L and 2L+	Mostly pembrolizumab and nivolumab	18.6 (7.0-NR)	3.4 (1.7-6.2)
Untreated patients						
Real-world cohort data (original Merck analysis)	METex14 skipping NSCLC	20	1L	Mostly pembrolizumab	[redacted]	[redacted]
Real-world cohort data (original Merck analysis†)	METex14 skipping NSCLC	32	1L	Mostly pembrolizumab	[redacted]	[redacted]
Guisier et al. 2020[11]	METex14 skipping NSCLC	30	1L	Mostly nivolumab (80%) and pembrolizumab (17%) and	13.4 months (9.4-NR)	4.9 months (2.0-11.4)
KEYNOTE-024[15]	Wildtype advanced NSCLC with PD-L1 >50%	154	1L	Pembrolizumab monotherapy	26.3 months (18.3-40.4)	7.7 months (6.1-10.2)
KEYNOTE-042[16]	Wildtype advanced with PD-L1 >1%	637	1L	Pembrolizumab monotherapy	PD-L1 >50%: 20.0 months; PD-L1>1%: 16.7 months	PD-L1 >50%: 7.1 months; PD-L1>1%: 5.4 months
UK Standing Cohort data[6]	Wildtype advanced with PD-L1 >50%	3,425	1L	Pembrolizumab	[redacted]	[redacted]
Previously-treated patients						
Real-world cohort data (original Merck analysis)	METex14 skipping NSCLC	32	2L+	Mostly pembrolizumab and nivolumab	[redacted]	[redacted]
Real-world cohort data (original Merck analysis†)	METex14 skipping NSCLC	67	2L+	Mostly pembrolizumab and nivolumab	[redacted]	[redacted]
KEYNOTE-010[17]	Wildtype advanced with PD-L1 >1%	691	2L	Pembrolizumab monotherapy	11.8 months (10.4-13.1)	4.0 months (3.1-4.1)

CheckMate 017/057[18]	Wildtype advanced NSCLC	427	2L	Nivolumab	11.1 months (9.2-13.1)	2.5 months (2.2-3.5)
UK Standing Cohort data[6]	Wildtype advanced NSCLC	2,707	2L	Pembrolizumab, nivolumab, atezolizumab	[redacted]	[redacted]

*There is one fewer patient in the line-agnostic group than the untreated and previously treated patients combined. This is because one patient received two lines of immunotherapy, and so is in both the untreated and previously treated group. However to avoid double counting in the line-agnostic, a random sampling approach was taken for the line agnostic group, where the patient was only included once in this group.
†The immunotherapy ITC has been updated to be weighed against VISION Cohort A+C, as well as to include another comparator data source in the METex14 skipping population that the company recently received access to (data source known as GFPC, and was obtained from an academic centre in France). Please see Appendix 2 for details. Outcomes are shown after weighting to VISION Cohort A+C, although n numbers are shown pre-weighting for transparency.

Based on validation using the above studies, the median OS and median PFS from the immunotherapy observational data in the METex14 skipping NSCLC population are aligned to the external studies and clinical expectations, for the line-agnostic immunotherapy group, as well as the separate untreated and previously treated groups. These are all in a similar population (METex14 skipping NSCLC) and were matched to VISION using propensity score weighting. The untreated subgroup is the primary focus in this response, as it was highlighted by clinical experts and in the ACD as being the group who are most likely to receive immunotherapy monotherapy.

The median PFS for immunotherapy seen in the real-world cohort (line agnostic, after weighting to VISION) is mostly aligned to that seen in other studies in the METex14 skipping population ([redacted] months versus 1.9, 3.4 and 4.9 months in Sabari et al.,[12] Mazieres et al.[13] and Guisier et al.[11]). For the untreated group specifically, the PFS was close to what is seen in the relevant clinical trial ([redacted] and [redacted] months versus 7.7 months in KEYNOTE-024)[15] and aligned to expectations by being slightly lower in the METex14 skipping group, expected due to the poor response of these patients to immunotherapy.

Similarly to PFS, the Merck real-world cohort OS for immunotherapy is more in line with the other studies in METex14 skipping NSCLC and is lower than wildtype clinical trials, as expected by clinical experts. This is what is observed for the line agnostic population ([redacted] and [redacted] months), which was similar to the relevant METex14 skipping studies (13.4, 18.2, and 18.6 months in Guisier et al.,[11] Sabari et al.,[12] and Mazieres et al.[13]). The untreated population results for the real-world cohort were also slightly lower than the relevant clinical trials ([redacted] and [redacted] months versus 26.3 months for KEYNOTE 024),[15] in line with clinical expectations. These immunotherapy outcomes were deemed to be clinically plausible when presented to four UK clinicians at an advisory board previously,[14] and in recent interviews with three clinical experts as part of the ACD response. Similar trends are seen in the comparison of the survival curves against Kaplan-Meier curves from the external validation sources (Section B.3.8.7 of the CS, and Appendix N.1.1.8 of the CS).

The ACD stated in Section 3.7 that the observational data outcomes "*could be partially explained by a lack of generalisability to the UK population, because of the mix of comparator treatments and because people in VISION and from the matched comparator cohort were fitter than would be seen in UK clinical practice*".

For the immunotherapy real-world cohort, the treatment mix was mostly aligned to NHS practice, with most patients receiving pembrolizumab at first-line, and a mixture of pembrolizumab and nivolumab at subsequent-lines. There were only two patients who received treatments not in line with UK practice in the untreated group: ipilimumab & nivolumab ([redacted]) and nivolumab ([redacted]).

In summary, Merck believe the immunotherapy monotherapy outcomes from the observational data are aligned to published studies in the METex14 skipping population, as well as aligned with clinical expert expectations compared to wildtype clinical trials. This included the relevant untreated population, which was further supported by clinical expert opinion. Furthermore, the treatment mix is also reflective of NHS practice.

Validation of real-world cohort data against published data in METex14 skipping NSCLC and clinical trials in wildtype NSCLC: chemotherapy

Merck are aware that there was more uncertainty in the ITC from the comparator chemotherapy outcomes (after weighting to VISION), which were less aligned to expectations in clinical practice. Table 3 reports the external validation conducted against chemotherapy outcomes in the METex14 skipping NSCLC population and wildtype NSCLC clinical trials. The publications used are the same as described in Section B.3.8.7 of the CS, alongside the UK Standing Cohort data and updated ITC analysis. In this part of the CS, validation of the curve extrapolations against the published Kaplan Meier curves was also presented. The previously-treated group is focused on here, as this is the population most likely to receive chemotherapy alone in NHS practice, in line with clinical feedback and from the ACD.

Table 3. Median OS and PSF by trial for chemotherapy

Study	Population	N	Line of therapy	Treatment	Median OS (95% CI)	Median PFS (95% CI)
Line agnostic						
Real-world cohort data (original Merck analysis)	METex14 skipping NSCLC	66*	Line agnostic	Mixture of chemotherapy regimens	[redacted]	[redacted]
Real-world cohort data (updated Merck analysis†)	METex14 skipping NSCLC	148	Line agnostic	Mixture of chemotherapy regimens	[redacted]	[redacted]

Awad et al 2019[19]	METex14 skipping NSCLC	34	1L, 2L+	Platinum based regimens (64%) and/or pemetrexed based regimens (61%)	8.1 months (5.3, NR)	Not reported
Untreated patients						
Real-world cohort data (original Merck analysis)	METex14 skipping NSCLC	49	1L	Mixture of chemotherapy regimens	[redacted]	[redacted]
Real-world cohort data (updated Merck analysis†)	METex14 skipping NSCLC	117	1L	Mixture of chemotherapy regimens	[redacted]	[redacted]
Hur et al[20]	METex14 skipping NSCLC	20	1L	Mixture of chemotherapy regimens	9.5 months (6.5, 23.1)	4.0 months (2.8-14.1)
Gajra et al, 2018[21]	Advanced NSCLC	< 70 years: 736 ≥70 years: 270	1L	Platinum-based chemotherapy regimens	< 70 years: 9.9 (9.0-11.0) ≥ 70 years: 7.7 (6.0 – 8.9)	Not reported
KEYNOTE-024[15]	Advanced NSCLC with PD-L1 >50%	151	1L	Platinum-based chemotherapy regimens	13.4 months (9.4, 18.3)	5.5 months (4.2-6.2)
KEYNOTE-189[22]	Advanced NSCLC	206	1L	Pemetrexed and platinum	10.6 months (8.7, 13.6)	4.9 (4.7-5.5)
KEYNOTE-042[23]	Advanced NSCLC with PD-L1 >1%	615	1L	Platinum-based chemotherapy regimens	12.1 months (11.3, 13.3)	6.5 months
UK Standing Cohort data[6]	Advanced NSCLC	23,919	1L	Any platinum-based chemotherapy regimen	[redacted]	[redacted]
Previously treated patients						
Real-world cohort data	METex14 skipping NSCLC	34	2L+	Mixture of chemotherapy regimens	[redacted]	[redacted]

(original Merck analysis)						
Real-world cohort data (updated Merck analysis†)	METex14 skipping NSCLC	56	2L+	Mixture of chemotherapy regimens	[redacted]	[redacted]
KEYNOTE-010[17]	Advanced NSCLC with PD-L1 >1%	309	2L	Docetaxel	8.4 months (7.6, 9.5)	4.1 (3.8-4.5)
CheckMate 017/057[18]	Advanced NSCLC	427	2L	Docetaxel	8.1 months (7.2, 9.2)	3.5 (3.1-4.2)
UK Standing Cohort data[6]	Advanced NSCLC	3,323	2L	Any chemotherapy regimen, primarily docetaxel +/- nintedanib	[redacted]	[redacted]

*There are fewer patients in the line-agnostic group than the untreated and previously treated patients combined. This is because some patients received two lines of chemotherapy, and so are in both the untreated and previously treated group. However to avoid double counting in the line agnostic group, a random sampling approach was taken for the line agnostic group, where such patients are only included once in this group. This is also why the outcomes for the line agnostic group do not completely align with the outcomes from each subgroup.

†The chemotherapy ITC has been updated to be weighed against VISION Cohort A+C, as well as to include another comparator data source in the METex14 skipping population that the company recently received access to (data source known as GFPC, and was obtained from an academic centre in France). Please see Appendix 2 for details.

The median PFS of the real-world cohort treated with chemotherapy was aligned with other studies in METex14 skipping NSCLC, and was also slightly lower than published clinical trials in wildtype NSCLC, as expected. The median PFS in the line-agnostic group was [redacted] months, and [redacted] months in the previously-treated group, compared to 4.0 months in the only other METex14 skipping study to report chemotherapy outcomes.

However, the median OS of the chemotherapy real-world cohort appears to be overstated compared to the METex14 skipping studies, as well as the wildtype clinical trials. This discrepancy is likely due to the fact that a higher proportion of patients in the chemotherapy cohort received a least one subsequent treatment compared to the other treatment cohorts ([redacted]% for chemotherapy versus [redacted]% for tepotinib in VISION for the line-agnostic group, with similar proportions in the previously treated group, see Table 58 of the CS, and 54 of the Appendix), and this included crizotinib, which is not available in the UK for METex14 skipping patients ([redacted]% for chemotherapy versus [redacted]% for tepotinib in VISION) which is known to improve survival in patients with METex14 skipping NSCLC.[24] When patients with subsequent treatments are removed from the analysis in exploratory analysis, the OS is indeed much lower (Figure 1), and as expected, the PFS does not change substantially (

	Figure 2). This difference in subsequent treatments was accounted for in the subsequent treatment costs applied in the model in the original CS, and was expected to be a conservative comparison for tepotinib, as the comparator survival would be overstated compared to tepotinib. The impact of subsequent treatments in the chemotherapy cohort is explored further in the Appendix **2**, with also an explanation of the limitations of this analysis. **Figure 1. OS for patients in previously-treated chemotherapy group, for patients who had a subsequent treatment versus those who did not**	

	 **Figure 2. PFS for patients in the previously-treated chemotherapy group, for patients who had a subsequent treatment versus those who did not**	

	[redacted]  **Discussion of the survival benefit for tepotinib over immunotherapy and chemotherapy** The ACD (Section 3.7) suggested that there might not be a survival benefit for tepotinib over chemotherapy or immunotherapy, possibly due to the lack of statistical significance in the OS outcomes. Firstly, it is worth highlighting that tepotinib showed numerically greater OS compared to both chemotherapy and immunotherapy, in both the line agnostic and previously treated groups. Tepotinib also had statistically greater PFS compared to both immunotherapy and chemotherapy across all groups. **Chemotherapy**: The rare nature of the disease and the low patient numbers mean that the wide confidence intervals for OS are to be expected, and likely to be observed in any comparison using observational data in a rare disease with few patients. It has already been shown that the outcomes for the chemotherapy real-world cohort specifically are likely to be overstated compared to previous studies in the METex14 population and clinical trials in wildtype NSCLC, and in reality, the survival	

	difference between tepotinib and chemotherapy is expected to be greater. This was confirmed by four clinical experts interviewed at a UK advisory board, who expected the chemotherapy outcomes to be lower, and therefore a larger survival benefit for tepotinib was expected (as a targeted MET inhibitor treatment for the specific METex14 skipping mutation) over chemotherapy, across lines of therapy. Therefore, the suggestion in the ACD that there might not be a survival benefit for tepotinib over chemotherapy is clinically implausible. **Immunotherapy:** With immunotherapy, the patients in the real-world cohort also received high rates of subsequent treatments, and it is known that METex14 skipping NSCLC patients treated with immunotherapy tend to respond poorly (particularly in PFS and response rates, but observed for OS too). Therefore, the OS benefit observed for tepotinib over immunotherapy is expected to be the minimum observed, and in reality could be expected to be greater. This expectation of at least similar OS, and likely greater, for tepotinib compared to immunotherapy in clinical practice was also confirmed with three clinical experts at recent interviews conducted to inform this ACD response. Tepotinib also had a statistically significant PFS compared to immunotherapy. Finally, the ACD also compared the OS curves of the real-world cohort treated with immunotherapy vs. those treated with chemotherapy. Due to the low patient numbers and rare nature of the mutation, as well as the differences seen between the immunotherapy and chemotherapy cohorts (e.g. in subsequent treatments, discussed above) the outcomes from these two comparisons should not be compared directly. Instead they are both used to inform separate comparisons versus tepotinib, where propensity score weighting was used to generate unbiased comparisons between tepotinib and the specific comparator arm. This was not performed between the chemotherapy and immunotherapy groups, and so naïve comparisons between these two comparator arms are not statistically robust or validated. In conclusion, Merck acknowledge there is uncertainty in the use of the observational data, particularly in the chemotherapy data where outcomes were higher than expected and not aligned to NHS practice. Therefore, an alternative ITC has been explored, using clinical trial data in wildtype NSCLC, as discussed in the ACD and confirmed with NICE. **<u>Comparison of VISION to clinical trial data in wildtype NSCLC</u>** **Summary** • **In Section 3.7 of the ACD, it was suggested that the company could consider basing the indirect treatment comparisons on data from comparator trials in people without specific oncogenic biomarkers (wildtype NSCLC).** • **Merck acknowledge the limitations associated with the lack of METex14 skipping data for chemo-immunotherapy in the untreated setting (the most relevant comparator in this appraisal), as well as for chemotherapy in the previously-treated setting, where the OS observed in the METex14 skipping real-world cohort was longer than expected. However, the immunotherapy monotherapy comparison using the real-world cohort data is still appropriate and in line with clinical expectations.**	

	• **Although it remains best practice to compare within the METex14 skipping population where possible, Merck have updated the ITC using matching-adjusted indirect comparison (MAIC) methodology, to compare tepotinib to clinical trials in wildtype NSCLC, for the key comparator (chemo-immunotherapy: pembrolizumab + pemetrexed + platinum, untreated patients, PD-L1<50% and ≥50%) as well as supplementary analyses for pembrolizumab monotherapy (untreated, PD-L1≥50%), and docetaxel +/- nintedanib in the previously treated setting (PD-L1<50% and ≥50%).** • **In the MAIC, tepotinib demonstrated numerically greater median OS and PFS to chemo-immunotherapy, as well as greater OS for up to 24 months and consistently greater PFS for the whole time period, with similar results when compared to immunotherapy monotherapy. Tepotinib also shows substantially greater OS and PFS compared to docetaxel +/- nintedanib in the previously-treated setting. All MAIC results are in line with clinical expert expectations as well.** • **Nonetheless, this remains a challenging comparison due to the large differences in patient characteristics between VISION and comparator clinical trials in wildtype NSCLC, where patients in VISION are much older and with fewer ECOG 0 patients. This is why population adjustment methodology was required over a naïve comparison. Furthermore, immunotherapy (including chemo-immunotherapy) is expected to perform worse in patients with METEx14 skipping NSCLC compared to the wildtype data used, based on previously published studies and clinical expert opinion.** • **In conclusion, tepotinib has shown strong clinical benefit compared to the main comparator chemo-immunotherapy, as well as in all supplementary comparisons to other comparators. In addition to the clinical benefit seen, tepotinib will provide an oral option which can be taken at home, instead of frequent infusions in hospital associated with immunotherapy +/- chemotherapy, which provide a resource and capacity burden on the NHS. Finally, tepotinib provides a safe and tolerable option for these elderly patients, instead of the high toxicity burden associated with chemo-immunotherapy and chemotherapy.** • **For the base-case chemo-immunotherapy comparison and the supplementary previously treated comparisons to docetaxel +/- nintedanib, Merck believe the comparisons to wildtype clinical trial data provides the best data source for the committee's decision making. However for the supplementary immunotherapy comparison, Merck believe the real-world cohort data remains a more robust comparison in the METex14 skipping population compared to the MAIC analysis, specifically.** In this section, Merck discuss the ITC updates that were conducted based on feedback from the ACD, as well as the company's position on the most relevant and clinically plausible data to inform each of chemo-immunotherapy, chemotherapy and immunotherapy comparisons versus tepotinib. Then the methodology of the updated ITC is described, and finally results reported. More detail on the updated ITC can be found in the Appendix also provided. **Company position on use of real-world data and updated analysis using clinical trial data in wildtype NSCLC for comparator data in ITC** The ACD noted that:	

	• "*The clinical experts considered that the overall survival results from the indirect treatment comparisons did not reflect what would be expected in clinical practice, particularly for chemotherapy. The committee agreed that the results of the indirect treatment comparisons were inconsistent and counter to expectations…*" (Section 3.7) • "*The clinical experts and Cancer Drugs Fund clinical lead suggested that the company could consider basing the indirect treatment comparisons on data from comparator trials in people without specific oncogenic biomarkers. This may be more robust as it would allow larger comparator patient numbers. The committee agreed that these analyses may have value, but acknowledged that there would be uncertainty because the comparator trial populations would be different to that of tepotinib*." (Section 3.7) • "*Because chemo-immunotherapy was the most relevant comparator (see section 3.4), the committee would also have liked to have seen a more robust indirect treatment comparison of tepotinib with chemo-immunotherapy*." (Section 3.7) <u>Chemo-immunotherapy</u> The ACD conclusion that chemo-immunotherapy is the most relevant comparator is consistent with clinical feedback given to Merck, where in this setting, most patients are given chemo-immunotherapy (specifically pembrolizumab plus pemetrexed plus platinum chemotherapy). The previous approach taken by the company for this comparison was to use a hazard ratio from KEYNOTE-189, and apply it to the METex14 skipping chemotherapy data, as there was extremely limited data available in the METex14 skipping NSCLC population from the real-world cohorts and in every possible data source explored by Merck. However because of the unexpectedly high OS outcomes in the chemotherapy data, this also overestimated the chemo-immunotherapy outcomes, as discussed in the ACD. Tepotinib was still cost-effective in this comparison, nonetheless, Merck agrees with the suggestion that a comparison to wildtype NSCLC data for this treatment would allow for an alternative and more robust comparison to the main comparator, in the absence of specific METex14 skipping data. This comparison has been provided below, however it is worth highlighting that METex14 skipping patients are still expected to perform poorer to compared to published chemo-immunotherapy results in wildtype NSCLC, based on clinical expert feedback, and there are very different patient characteristics between VISION and the relevant chemo-immunotherapy trial. Nonetheless, in the absence of specific data, Merck believe this remains the most appropriate data source for the committee's decision making given the feedback in the ACD. <u>Chemotherapy</u> In the previous section, the company presented extensive validation of the real-world data outcomes versus published studies, and agree with the clinical experts that OS in the chemotherapy group is	

	higher than expected in NHS clinical practice as noted in the original submission. The uncertainty does not work in the favour of tepotinib (as the comparator outcomes are likely overstated, due to more aggressive treatments mixes and higher proportions of subsequent treatments) and so the company's original position was that this is conservative for tepotinib, and updating this analysis would only work more in tepotinib's favour. However, Merck appreciates the limitations associated with the clinically implausible chemotherapy OS curves from the observational studies, which are unlikely to be seen in NHS practice (without extensive use of MET inhibitors as per the real-world cohort). Based on clinical feedback stating that the vast majority of patients receive docetaxel + nintedanib with a few receiving docetaxel monotherapy, Merck have conducted additional comparisons to clinical trial data in wildtype NSCLC for docetaxel +/- nintedanib in the previously-treated setting. Very few patients are expected to receive chemotherapy at first-line according to clinical feedback, so these comparisons have not been updated using clinical trial data, which was agreed with NICE. As this is not the main comparison (most patients are expected to receive tepotinib at first line, and so first-line comparisons are the most relevant, as discussed in the ACD and in Comment **1** and **4** above), the comparisons are considered supplementary and have been provided in Appendix **2**. <u>Immunotherapy monotherapy</u> As highlighted in the above section, the real-world immunotherapy monotherapy outcomes, particularly for the relevant untreated METex14 skipping NSCLC population, are closely aligned to outcomes in previous studies in METex14 skipping NSCLC, as well as in expectations compared to clinical trials in wildtype NSCLC. Furthermore, the treatment mix was reflective of NHS practice. As part of the ACD response, Merck discussed this data source and outcomes with clinical experts, who all stated that using this METex14 skipping data was appropriate for immunotherapy monotherapy specifically. Therefore, Merck still consider this comparator data source and ITC to be relevant and appropriate for any comparison to immunotherapy monotherapy within the appraisal. Merck have now updated this comparison using the VISION A+C cohort and incorporating the French/GFPC data set within the real-world data set, described in detail in Appendix **2**. Nonetheless, as NICE have suggested the exploration of wildtype NSCLC comparisons, Merck has also conducted a comparison to pembrolizumab monotherapy specifically (PD-L1≥50%). Again, this is not the main comparison, as highlighted in the ACD. Most patients are expected to receive chemo-immunotherapy at first line, with only a small percentage of patients receiving immunotherapy monotherapy, based on PD-L1 expression above 50%. This was confirmed with clinical experts as well, who also stated that specifically in METex14 skipping NSCLC, clinicians would be very reluctant to use immunotherapy monotherapy. Furthermore, this comparison is not as relevant in the METex14 skipping population, as METex14 skipping specific data for immunotherapy monotherapy is available and aligned to clinical expectations. Nonetheless, the supplementary wildtype clinical comparison has been provided in the Appendix as well. Clinical expert opinion highlighted that very few patients receive immunotherapy at second-line, so these comparisons have not been updated using clinical trial data.	

These four comparators described above (pembrolizumab + pemetrexed + platinum; pembrolizumab monotherapy; docetaxel; docetaxel + nintedanib) were presented to NICE ahead of the ACD response, and confirmed as the relevant comparators for the ITC update.

Selection of comparators and clinical trials for comparisons of VISION to clinical trial data in wildtype NSCLC

To identify the relevant clinical trials for each of these comparisons, the company used the previous literature review conducted as part of the CS, and presented in Appendix G of the CS. Specifically this was the review of previous NICE appraisals in NSCLC (G.1.2). For each of the four comparators, the relevant NICE appraisal was identified, and the pivotal trial used within that appraisal was extracted (presented in Table 4 below).

Each clinical trial identified was presented to three clinical experts, to be confirmed as the relevant clinical trial in wildtype NSCLC for use within the ITC. For pembrolizumab + pemetrexed + platinum, pembrolizumab monotherapy and docetaxel + nintedanib, the pivotal trial identified was aligned to the clinical expert opinion. However, for docetaxel monotherapy, 5 clinical trials were identified which could be used within the ITC, as docetaxel is often the comparator in RCTs for previously-treated NSCLC. The clinical experts were asked which trial should be selected for use within the ITC as the most relevant compared to tepotinib, and the rationale for this. The details of this, and the final selection, are summarised in Appendix **2**.

Table 4 presents the final comparators, clinical trials used within the ITC, and relevant associated subgroups.

Table 4. Comparator treatments, relevant clinical trials and subgroups, for use within the updated ITC in wildtype NSCLC

Comparator treatment	Relevant Technology Appraisal	Clinical trial used within updated ITC	Clinical trial reference used	Line of therapy	PD-L1 subgroups	Histology subgroups†
Base case, main comparison						
Pembrolizumab + pemetrexed + platinum	TA683[25]	KEYNOTE-189	Rodríguez-Abreu et al. 2021[16]	Untreated patients	All (>50%, <50%)	Non-squamous
Supplementary comparisons						
Pembrolizumab	TA531[26]	KEYNOTE-24	Reck et al. 2021[15]	Untreated patients	≥50%	Non-squamous or squamous
Docetaxel + nintedanib	TA347[27]	LUME-Lung 1	Reck et al. 2014[28]	Previously treated	All (>50%, <50%)	Adenocarcinoma

Docetaxel monotherapy	N/A*	TAX 320	Fossella et al. 2000[29]	Previously treated	All (>50%, <50%)	Non-squamous or squamous

*Docetaxel monotherapy was not identified with a relevant TA on the NICE website. Instead it was identified as a comparator treatment in a number of TAs in previously treated wildtype NSCLC (TA124, TA428, TA347, TA484, TA520, TA655).
†As per the ACD, non-squamous NSCLC is the key population for this appraisal. However not all clinical trials identified were in solely non-squamous NSCLC, although the clinical trial for the key comparator, pembrolizumab + pemetrexed + platinum, was in non-squamous patients only. For the other clinical trials, the MAIC was conducted using histology as a characteristic to match on, so the high prevalence of non-squamous patients in VISION was adjusted and accounted for within the MAIC where appropriate. Therefore, any small differences in histology have been accounted for across all comparisons.

Other comparisons

There were several comparisons that were initially presented in the CS that are not included in the revised ITC, for example first-line chemotherapy, and second-line immunotherapy. Due to time limitations and importantly, due to the fact that these comparisons do not reflect routine NHS practice, according to clinical expert feedback, they were not included in the new ITC and therefore not presented in this ACD response.

Methodology of updated indirect treatment comparison: Matching adjusted indirect comparison (MAIC)

Appendix **2** reports the full methodology and results of the MAICs conducted as part of the ACD response. A short summary of the methodology and results are given below, with a focus on the chemo-immunotherapy comparison, as the most relevant comparator to tepotinib, as detailed in the ACD.

In order to compare to the published studies, MAIC methodology was performed. MAIC was selected as the preferred methodology, as it works by weighting all patients in the individual patient data (VISION), such that the (selected) aggregate characteristics (from the clinical trials) match between groups. The assumption implicit being that should patients be identical in observed characteristics, the outcomes should be comparable, provided all important characteristics are matched on. The large differences in patient characteristics between VISION and the comparator clinical trials meant that this adjustment was required over a naïve comparison. This approach also is similar to the comparisons made previously using patient level data in the original submission (propensity score weighting). The treatment groups were balanced on all characteristics available from the list of important prognostic factors provided by clinicians for the original submission (for use in propensity scoring), which is reproduced below:

- Percentage of patients previously untreated
- ECOG
- Age (in published studies this is given variously as mean, median, % over 65)
- Sex

- Adenocarcinoma
- Smoking
- Metastatic vs advanced

MAICs were implemented matching on all characteristics available in each comparison.

For each comparison, patient characteristics were collected from each study (from Table 4 above), compared to the VISION (A+C) data and used to weight the VISION patients to match the reported patients of the comparator study.

Results of the MAIC

Chemo-immunotherapy

When comparing patient characteristics from VISION to the KEYNOTE-189 study, large differences in the populations were noted (see separate Appendix **2** for details), including for age (median 74 years for VISION versus 65 for KEYNOTE-189) and ECOG (ECOG 0, 28% versus 45%). Therefore as mentioned, MAIC was required to ensure like-for-like comparisons were performed between the different patient populations. As a result of the differences between populations, a large quantity of the sample size was lost when re-weighting VISION patients: from 148 untreated patients to an effective sample size (ESS) of 38.7. Despite this, the matching was successful, with matching on all reported variables achieved, creating a comparison which removes as much difference possible between the groups in prognostic characteristics.

The outcomes of this comparison are presented below in Table 5.

Table 5. MAIC outcomes comparing VISION A+C to KEYNOTE-189

	VISION A+C (weighted) (n=148; ESS = 38.7)	KEYNOTE-189 (pembrolizumab + pemetrexed + platinum (n=410)
Progression-free survival		
Median, months (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
p-value	[redacted]	
Overall survival		
Median, months (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	

p-value	[redacted]

Key: CI, confidence interval; ESS, effective sample size; NA, not available

Compared to pembrolizumab + pemetrexed + platinum, tepotinib is shown to have a numerically greater median PFS, with an improvement of [redacted] months, nearly at the 5% significance level. On the Kaplan-Meier graph in Appendix **2** (Figure 13) tepotinib showed consistently greater PFS for the whole time duration. Tepotinib is also shown to have a numerically greater median OS ([redacted] months improvement), and on the Kaplan-Meier graph in Appendix **2** (Figure 13), tepotinib shows greater OS for the first 24 months, with similar OS after that time point.

Limitations

The main limitation of this comparison is that the comparison is between wildtype NSCLC and METex14 skipping NSCLC. Therefore, the matching conducted does not account for the presence of the METex14 skipping mutation. METex14 skipping was not collected or reported in KEYNOTE-189, and is only present in ~3% of NSCLC cases, and so the trial is expected to only contain a small number of METex14 skipping patients (if any at all). Therefore, the poorer performing patients in KEYNOTE-189 are expected to be closer to the METex14 population. For example, in KEYNOTE-189 patients over 65 years had an OS hazard ratio (comparing pembrolizumab + pemetrexed+ platinum versus pemetrexed + platinum) of 0.72 compared to 0.49 in the below 65 years group. As discussed previously, METex14 skipping is a known independent prognostic factor that predicts poorer survival in NSCLC,[30] particularly for immunotherapy-treated patients,[12] and so when even adjusting for age and other characteristics, the results of this comparison are likely to underestimate the OS and PFS benefit for tepotinib, which could be expected to be even greater.

The other main limitation of this MAIC is that although the key prognostic factors were successfully matched (outside of METex14 skipping status), the differences between populations should be noted, and this results in a largely reduced sample size. There are some other differences which also cannot be adjusted such as PD-L1 status (which was not captured in the VISION trial).

Discussion

Base case comparison

As noted in the ACD, chemo-immunotherapy in the untreated setting was considered the most relevant comparison for tepotinib in this appraisal. Given the limited data in the METex14 skipping real-world cohort for chemo-immunotherapy, an alternative method using wildtype NSCLC data was used to inform this comparison, with VISION data re-weighted to match KEYNOTE-189 for key prognostic factors including age, ECOG and sex. The results show that tepotinib has at least a comparable OS and a consistently greater PFS when patient characteristics are matched. This is in line with feedback from three clinical experts interviewed who all expected tepotinib to have greater PFS and OS compared to chemo-immunotherapy in a matched population, based on the tepotinib clinical data and

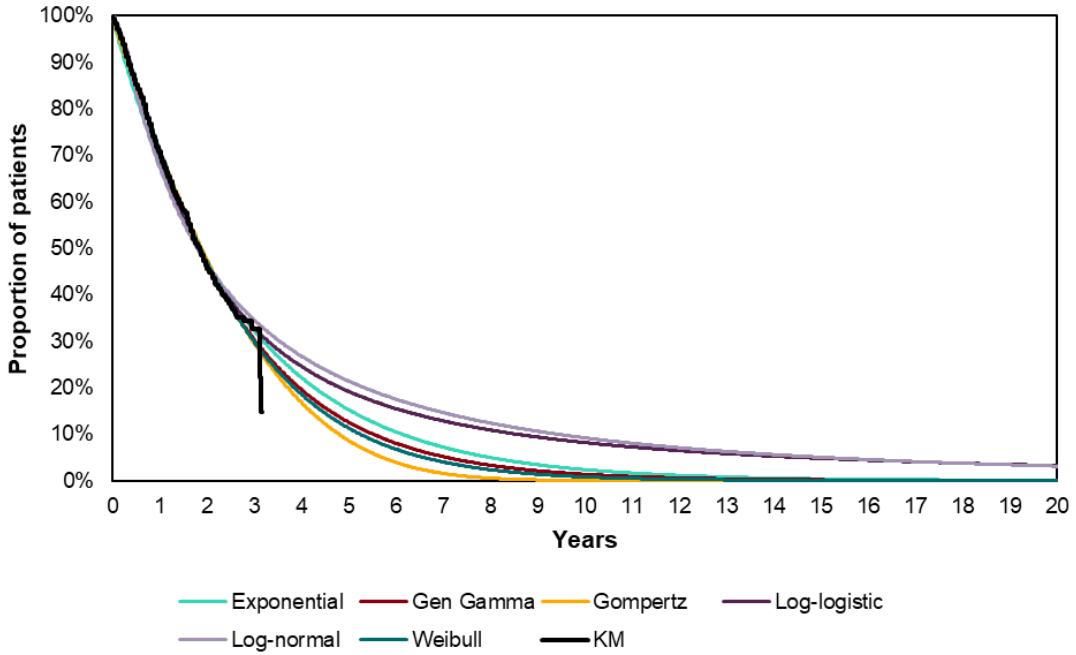
Consultee	Comment [sic]	Response
	targeted mechanism of action. Therefore, this provides a more robust comparison than the previous approach for chemo-immunotherapy presented in the original CS, with increased certainty in the comparator outcomes using the best available source for chemo-immunotherapy (clinical trial data), whilst also ensuring as close a match as possible in prognostic patient characterises between the different patient cohorts. Despite the limitations noted, the results demonstrate that tepotinib provides an important alternative to chemo-immunotherapy, based on better PFS and at least similar OS, whilst also targeted to the patient's specific mutation. Furthermore, tepotinib has a number of important patient-friendly benefits, including oral administration, allowing tepotinib to be taken at home, whereas chemo-immunotherapy requires patients to come into hospital for frequent, burdensome infusions. Furthermore, tepotinib has a much improved side-effect profile compared to chemo-immunotherapy, highlighted by clinical experts and in the ACD. Therefore, as well as the demonstrated PFS and OS compared to chemo-immunotherapy, tepotinib offers an important patient-friendly alterative in this elderly population. ***Supplementary comparisons*** The supplementary comparisons conducted by Merck are described in Appendix **2**. Although not the most relevant comparators to tepotinib, as per the ACD, they are included for completeness to further demonstrate tepotinib clinical effectiveness and address uncertainties discussed at the ACM. A number of comparisons to immunotherapy monotherapy are presented in Appendix **2**. However the ACD highlighted that this is not the main comparator for tepotinib, and this has been confirmed by three clinical experts interviewed by the company. They highlighted that most patients received chemo-immunotherapy anyway in wildtype NSCLC, and within the METex14 skipping population specifically, the poor response of patients to immunotherapy monotherapy means that clinicians would prefer to treat with chemo-immunotherapy in the absence of a targeted therapy. Nonetheless, in summary, tepotinib shows numerically greater PFS and similar OS compared to pembrolizumab monotherapy, using wildtype NSCLC clinical trial data (PD-L1≥50%). However the real-world cohort analysis in the METex14 skipping population has also been updated, which presents OS estimates that are aligned with the METex14 skipping population, and therefore, a much more appropriate comparison for immunotherapy monotherapy, where tepotinib shows statistically greater median PFS and similar OS. • Finally, comparisons to docetaxel +/- nintedanib in the previously treated setting are also presented in Appendix **2**. Tepotinib shows substantially greater OS and PFS to both, highlighting the large and important benefit tepotinib can offer patients in the previously-treated setting, where currently only poorly tolerated chemotherapy options are available, with limited clinical benefit and a high unmet need.	

Merck Serono Ltd	**ACD Section 3.9, page 12–23: *The comparator overall survival extrapolations are implausible, particularly for chemotherapy and chemo-immunotherapy*** As discussed in response to Comment **6**, new indirect treatment comparisons have been conducted to compare tepotinib to specific comparators in wildtype NSCLC to alleviate the uncertainty associated with the real-world data. Parametric survival models (PSMs) have been fit to the pseudo-patient level data derived from digitising the latest published OS and PFS Kaplan-Meier data for each comparison (see Table 4). For tepotinib, parametric survival curves were fit to the Kaplan-Meier data from VISION (Cohort A + C) after re-weighting to each of the published studies, and all options validated extensively with three clinical experts. Given that the untreated population in comparison to pembrolizumab + pemetrexed + platinum is considered the most relevant comparison, the curve selections presented here are focused on this comparison. Details of the curve selections for the other comparisons are presented within Appendix **1**. **Pembrolizumab + pemetrexed + platinum** To inform the efficacy of pembrolizumab + pemetrexed + platinum, three-year trial data was digitised from the latest KEYNOTE-189 publication.[16] Pseudo patient-level data was then created using the Guyot algorithm. PSMs were fitted to OS and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate over a life-time horizon. Visual fit, along with AIC/BIC score and clinical opinion of long-term estimates were then used to inform the most appropriate curve to take forward for the base case. ***Overall survival*** The statistical goodness of fit scores are presented in Table 6. Based on AIC and BIC scores, the Weibull distribution is the best fitting, however all models except log-normal provide reasonably similar fits (within five points) and so were visually compared in Figure 3. **Table 6: Statistical goodness-of-fit scores – KEYNOTE 189 – OS** Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival All curves appeared to fit the data well apart from the last few events of the Kaplan Meier data from year 3, which is likely driven by censoring at data cut off. Clinical expects consulted as part of the response to the ACD expected that survival of patients with wildtype NSCLC treated with chemo-immunotherapy would be around 15-20% at five-years and around 5-10% at 10 years. Both log-logistic and log-normal sat within this plausible range, although estimated 10-year OS at the higher end of this	Thank you for your comments. Section 3.12 of the FAD discusses the company's original survival analyses, and why the committee considered some comparator survival extrapolations to be clinically implausible. Section 3.13 of the FAD discusses the company's new survival analyses provided at consultation, and concludes that while these are also uncertain, committee felt that they were appropriate for decision making.

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	2260.89	2264.91	5	2
Weibull	2256.10	2264.13	1	1
Gompertz	2258.74	2266.77	3	3
Log-logistic	2259.04	2267.07	4	4
Log-normal	2271.88	2279.91	6	6
Generalised gamma	2257.84	2269.89	2	5

clinical estimate range (8.2% and 9.2%, respectively). Clinical experts agreed that these curves were the most plausible for wildtype NSCLC. As such, based on goodness of fit, visual fit and long-term plausibility, log-logistic was selected to inform the base case OS, as this provided a better statistical and visual fit over log-normal.

Figure 3: Parametric curve fits – KEYNOTE-189 – OS



Key: KM, Kaplan-Meier; OS, overall survival

Progression-free survival

The statistical goodness of fit scores are presented in Table 7. Based on AIC and BIC scores, the log-normal distribution is the best fitting, closely followed by generalised gamma and log-normal which had reasonably similar fits (within five points). Therefore, the curves were visually compared in Figure 4.

Table 7: Statistical goodness-of-fit scores – KEYNOTE 189 – PFS

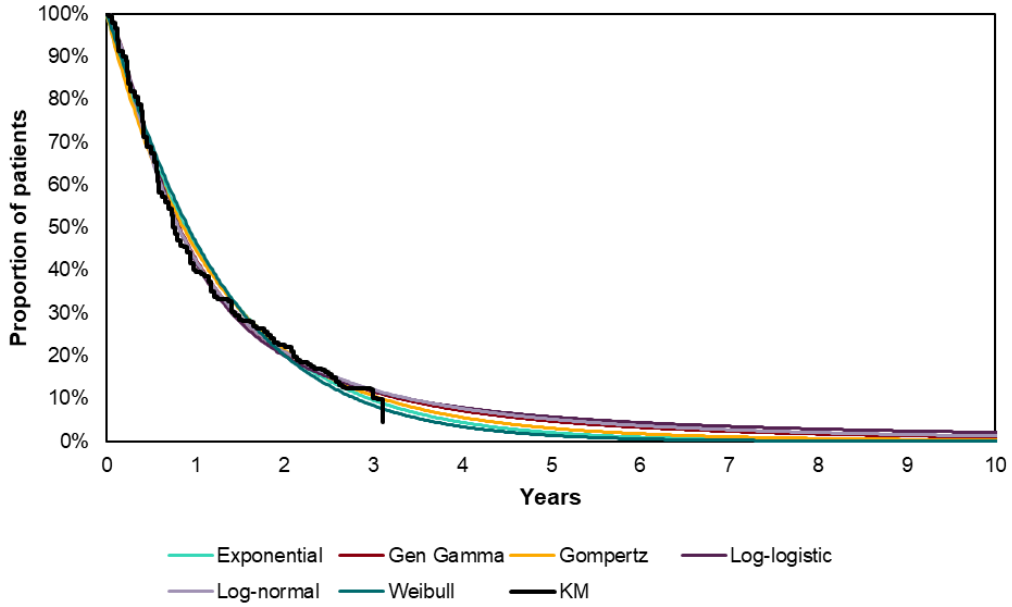
Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	2488.27	2492.28	5	4

Weibull	2487.46	2495.49	4	5
Gompertz	2489.51	2497.55	6	6
Log-logistic	2462.87	2470.90	3	2
Log-normal	2461.03	2469.06	1	1
Generalised gamma	2462.75	2474.80	2	3

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

All curves appeared to fit the data well throughout the observed period. Clinical expects consulted as part of the response to ACD expected that the PFS of patients with wildtype NSCLC treated with chemo-immunotherapy would be around 7.5-10% at five-years and around 2.5% at 10 years. Both log-logistic and log-normal were the closest to this plausible range, and clinical exerts thought that both of these curves were plausible. Given that log-logistic provided the higher of the two estimates and, based on goodness of fit, visual fit and long-term plausibility, log-logistic was selected to inform the base case PFS.

Figure 4: Parametric curve fits – KEYNOTE-189 – PFS



Key: KM, Kaplan-Meier; PFS, progression-free survival

Tepotinib

To inform the efficacy of tepotinib in comparison to pembrolizumab + pemetrexed + platinum, untreated VISION data (Cohort A+C) was matched to the KEYNOTE-189 clinical trial population.[16] PSMs were fitted to weighted OS and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate over a life-time horizon. Visual fit, along with AIC/BIC score and plausibility of long-term estimates were then used to inform the most appropriate curve to take forward for the base case.

Overall survival

The statistical goodness of fit scores are presented in Table 8. Based on AIC and BIC scores, the Weibull and exponential distributions are the best fitting, respectively, however all models provide reasonably similar fits (within five points) and so were visually compared in Figure 5.

Table 8: Statistical goodness-of-fit scores – VISION (weighted to KEYNOTE-189) – OS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	210.74	213.74	3	1
Weibull	210.68	216.67	1	2
Gompertz	211.57	217.56	4	4
Log-logistic	210.69	216.68	2	3
Log-normal	212.45	218.45	5	5
Generalized gamma	212.64	221.63	6	6

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

All curves appeared to fit the data reasonably well until year 2 where the curves struggle to capture the large step in the KM which is likely driven by weighting of the VISION data and low ESS.

The three clinicians interviewed expected that survival of tepotinib would be least similar to that of patients treated with chemo-immunotherapy in a matched population, and likely greater for tepotinib, especially in the short term. As such, based on goodness of fit, visual fit and long-term plausibility, log-logistic was selected to inform the base case OS as this closely aligned with the pembrolizumab + pemetrexed + platinum estimates in the long term.

Figure 5: Parametric curve fits – VISION (weighted to KEYNOTE-189) – OS

Key: KM, Kaplan-Meier; OS, overall survival

Progression-free survival

The statistical goodness of fit scores are presented in Table 9. Based on AIC and BIC scores, the log-logistic and exponential distribution are the best fitting, respectively, however all models provide reasonably similar fits (within five points) and so were visually compared in Figure 6.

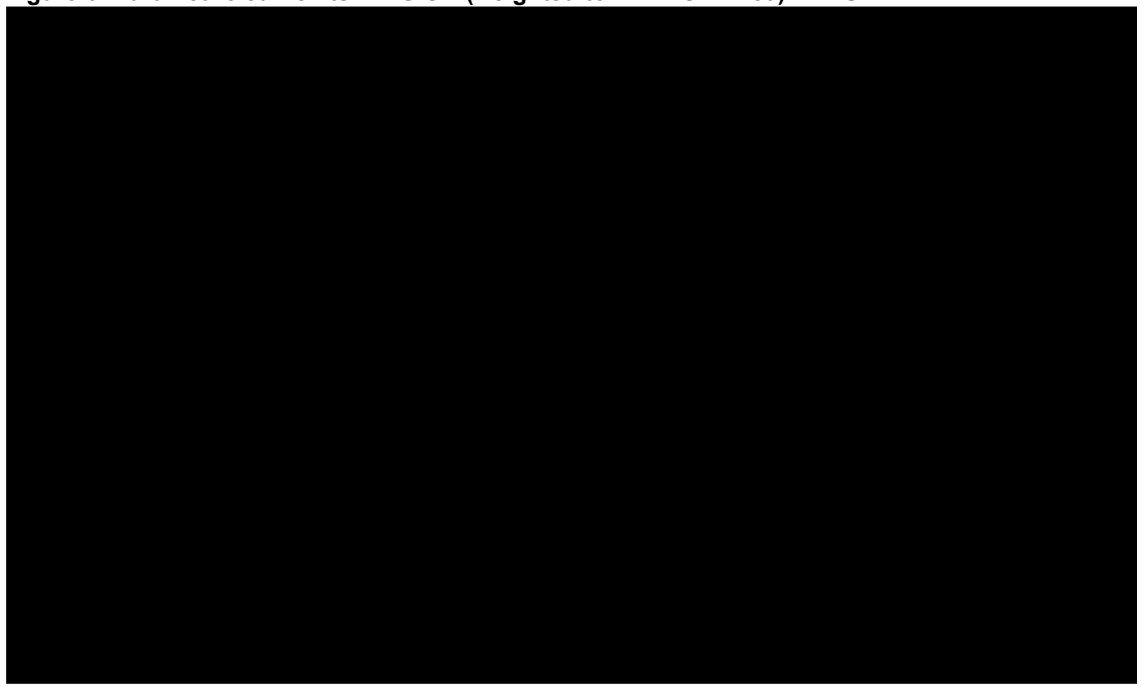
Table 9: Statistical goodness-of-fit scores – VISION (weighted to KEYNOTE 189) – PFS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	256.86	259.85	4	1
Weibull	257.54	263.54	5	4
Gompertz	258.85	264.85	6	5
Log-logistic	254.41	260.40	1	2
Log-normal	254.78	260.78	2	3
Generalized gamma	256.74	265.73	3	6

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

All curves appeared to fit the data well until around 1 year where the curves struggle to capture the large steps in the Kaplan Meier data, likely caused by the weighting of the tepotinib data and low ESS. Given that log-logistic had the best AIC and visually fits the data best towards the end of the KM, log-logistic was selected to inform the base case PFS. This also provides reasonable estimates when comparing against pembrolizumab + pemetrexed + platinum PFS, where clinicians expected tepotinib to have a greater PFS, as per the MAIC results.

Figure 6: Parametric curve fits – VISION (weighted to KEYNOTE-189) – PFS

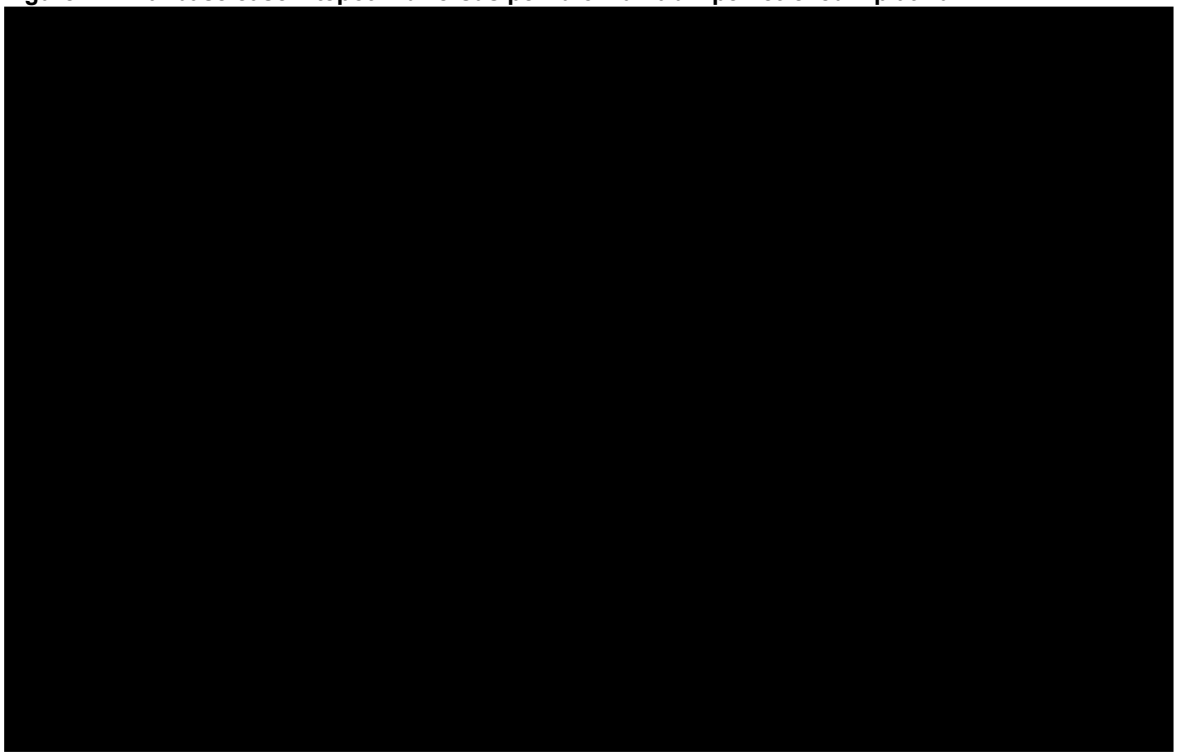


Key: KM, Kaplan-Meier; PFS, progression-free survival

Final base case

Figure 7 presents the final curves selected to inform the base case of tepotinib versus pembrolizumab + pemetrexed + platinum.

It is important to note that these curves reflect a wildtype NSCLC population. Patients with METex14 skipping mutations are expected to have poorer outcomes with immunotherapy, including chemo-immunotherapy. Furthermore, clinical experts highlighted that there is no evidence to suggest patients

Consultee	Comment [sic]	Response
	with METex14 skipping mutations treated with immunotherapy would respond any better when treated with chemo-immunotherapy, despite the difference in PD-L1 expression. As such, clinical experts interviewed expected METex14 patients to perform worse with chemo-immunotherapy compared to wildtype NSCLC, therefore the estimated differences between tepotinib and pembrolizumab + pemetrexed + platinum are conservative using the wildtype data, even after adjusting for patient characteristics. **Figure 7: Final base case – tepotinib versus pembrolizumab + pemetrexed + platinum**  Key: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival •	

Merck Serono Ltd	**ACD Section 3.10, page 13–14: *Separate subsequent treatment distributions based on prior treatment status, and for people having chemo-immunotherapy, are needed*** **Summary** • **The VISION trial and real-world cohort data were reflective of the subsequent treatment distributions that patients would receive in NHS practice for the most part, with the main exception being use of subsequent crizotinib or other MET inhibitors.** • **The company have elicited feedback from three clinical experts who advised on the expectations of subsequent treatments in NHS practice after tepotinib (untreated or previously treated groups) as well as the key comparators in the updated economic model.** • **The economic model has been updated to reflect NHS practice for subsequent treatment distributions, with a number of scenarios run to explore different possibilities in the subsequent treatment distributions.** As described in Comment **3,** VISION was mostly reflective of the subsequent treatments that patients would expect to receive in NHS practice after treatment with tepotinib, primarily immunotherapy or chemotherapy (platinum-based chemotherapy, or docetaxel +/- nintedanib) depending on line of therapy, prior treatment and PD-L1 expression. This was confirmed by clinical experts interviewed as part of the ACD response. The main exception was the minority of patients who received a subsequent MET inhibitor or another investigational treatment which are not used in the UK to treat METex14 skipping patients. This clinical feedback was similar for the real-world cohorts, where the majority of patients received chemotherapy or immunotherapy in the chemotherapy cohort, or chemotherapy alone in the immunotherapy cohort (Table 58 of CS Document B, Tables 36 and 54 of CS Appendix). Again, the main exception was the minority of patients who received a subsequent MET inhibitor. Nonetheless, the company have updated the subsequent treatment distributions in the base case analysis for all comparators and tepotinib, in line with clinical feedback on standard NHS practice, based on interviews with three clinical experts. The details of the clinical expert feedback is presented in the ACD response Appendix **1**. In the updated analysis, all patients are assumed to go onto subsequent treatments for simplicity (except for docetaxel +/- nintedanib). Where relevant, the subsequent treatment distributions accounted for prior treatment and PD-L1 expression. However, clinicians consulted as part of the ACD response said that not all patients would go onto subsequent therapy, and that it is more likely to be between 20% and 70% depending on subsequent therapy. Two of three experts said that under half of patients would go into subsequent therapy at all. Therefore, scenarios are considered assuming that only 50% patients go onto subsequent treatment in all treatment arms. Otherwise, subsequent treatments are calculated in the same way as described in B.3.5.4.1 of the CS and applied as a one-off cost.	Thank you for your comments. Section 3.14 of the FAD discusses the issue of subsequent treatment distributions used in the economic model. This section states that there were some differences to NHS clinical practice, but reiterates the company's view that these differences are minor. This section further discusses the sensitivity of the economic model to changes in the proportion of people having subsequent treatments, and that fewer people would progress to second-line treatment than anticipated by the company.

The subsequent treatment distributions and assumptions used in the updated economic model are detailed in Table 10 below.

Table 10. Subsequent treatment distributions used in the updated economic model, to reflect NHS practice following treatment with tepotinib and each key comparator

Treatment	Subsequent treatment distributions	Assumptions
Untreated patients		
Pembrolizumab + pemetrexed + platinum (untreated, PD-L1 <50%, ≥50%)	100%: Docetaxel +/- nintedanib (90% with nintedanib)	• All patients go on to docetaxel +/- nintedanib, with 90% for docetaxel + nintedanib and 10% with just docetaxel. However a scenario is included in the model where the split is 50/50 with/without nintedanib. • The subsequent treatments do not vary by PD-L1 according to the clinical experts.
Pembrolizumab monotherapy (untreated, PD-L1≥50%)	Second-line treatment: 100%: Platinum-based chemotherapy, specifically carboplatin + pemetrexed, Last-line treatment: 100%: Docetaxel +/- nintedanib (90% with nintedanib)	• All patients are assumed to go onto platinum-based chemotherapy, and then all go onto docetaxel +/- nintedanib • It is assumed that all patients received carboplatin + pemetrexed specifically, and a 90/10 split between with/without nintedanib. Scenarios have also been included with a different split with/without nintedanib (50/50). • The subsequent treatments do not vary by PD-L1 as this is only in the PD-L1≥50% group anyway.
Tepotinib (untreated, PD-L1 <50%, ≥50%)	Second-line treatment: 75%: Immunotherapy monotherapy (all pembrolizumab) 25%: Platinum-based chemotherapy (all carboplatin + pemetrexed) Last-line treatment: 100%: docetaxel +/- nintedanib (90% with nintedanib)	• Patients will either go on to immunotherapy monotherapy or platinum-based chemotherapy after tepotinib at first line, according to clinical expert feedback. • Based on clinical feedback, some clinicians will not prescribe immunotherapy monotherapy in the METex14 skipping population at all, due to the poorer associated outcomes. Therefore, the clinical feedback was that the split between subsequent immunotherapy and chemotherapy after tepotinib would range between 50% and 90% in favour of immunotherapy. The base case assumes 75%, however different splits are explored in scenarios. • All immunotherapy is assumed to be pembrolizumab, however scenarios are run where there is also a split between pembrolizumab,

		nivolumab and atezolizumab after tepotinib at first line. • All patients eventually go onto docetaxel +/- nintedanib as a last-line treatment.
Previously treated		
Docetaxel monotherapy (previously treated, PD-L1 <50%, ≥50%)	No subsequent treatment	• Clinical expert feedback states this is the last line of treatment available to patients, so they just move onto best supportive care afterwards.
Docetaxel + nintedanib (previously treated, PD-L1 <50%, ≥50%)	No subsequent treatment	• Clinical expert feedback states this is the last line of treatment available to patients, so they just move onto best supportive care afterwards.
Tepotinib (previously treated, PD-L1 <50%, ≥50%)	<u>For those with 1L chemo-IO (80% of total):</u> Docetaxel +/- nintedanib (90% with nintedanib) as last line after tepotinib <u>For those with 1L IO (20% of total):</u> Platinum-based chemotherapy, specifically carboplatin + pemetrexed, then docetaxel +/- nintedanib (90% of these patients with nintedanib) as last line after tepotinib	• In line with clinical expert feedback, patients who have tepotinib at second-line will have had chemo-immunotherapy or immunotherapy monotherapy at first line, based on PD-L1 expression. • Patients who had chemo-immunotherapy at first line will go onto docetaxel +/- nintedanib after tepotinib. • Patients who had immunotherapy monotherapy will go onto platinum-based chemotherapy after tepotinib. They will then go onto docetaxel +/- nintedanib afterwards. • An estimated 30% of NSCLC patients are PD-L1≥50%,[31] but clinical feedback is that roughly a third of these patients will go onto chemo-immunotherapy anyway. So 80% are assumed to have chemo-immunotherapy and 20% immunotherapy monotherapy at first line.

A number of scenarios were developed to explore the ranges of subsequent treatment distributions given by the three recently interviewed clinical experts. Scenarios included in the updated economic model are:

- The split between docetaxel + / - nintedanib is 50% for docetaxel + nintedanib and 50% with just docetaxel rather than 90% versus 10%. The feedback from clinical experts is that the use of docetaxel can vary by NHS Trust and region.
- After tepotinib as a first-line treatment, 50% or 90% of patients go onto immunotherapy monotherapy, not 75%, in line with range given by clinical experts interviewed.

Consultee	Comment [sic]	Response
	• After tepotinib as a first-line treatment, the immunotherapy split is a third pembrolizumab, nivolumab and atezolizumab, rather than all pembrolizumab. • After tepotinib second-line treatment, 50% of patients go on to platinum-based chemotherapy, assuming a higher proportion of patients had pembrolizumab treatment up front, as clinical experts said this could also vary by NHS Trust and clinician preference. • Only 50% of patients go onto subsequent treatment, in line with feedback from clinical experts that not all patients receive subsequent treatments in NHS practice. •	
Merck Serono Ltd	**ACD Section 3.11, page 14: *There is uncertainty about the most appropriate time-on-treatment model for tepotinib, but the company's base case is likely appropriate*** **Summary** • **Based on clinical feedback, the two most clinically plausible time-on-treatment (ToT) curves for tepotinib were the exponential model and generalised gamma** • **In the interest of being conservative for tepotinib, the company selected the ToT curve with higher estimates for tepotinib (generalised gamma). Scenario analyses using the other plausible curve, exponential, results in a decrease to the tepotinib ICER.** Based on the UK advisory board, previously reported in the CS (Section B.3.3.3) and Technical Engagement response (Key Issue 12), clinical opinion indicated the majority of patients would be off tepotinib treatment at 5 years, with only small numbers of patients remaining on treatment at this time. This was confirmed by the three recent clinical expert interviews. • The log-logistic curve provides one of the best fitting parametric statistical fit according to AIC and BIC (AIC rank 1, BIC rank 2) but predicts 4.3% of patients on tepotinib treatment at 5 years, which was considered too high by clinical experts. The exponential model provides the next best parametric statistical fit (AIC rank 3, BIC rank 1) and predicts 0.6% of patients on treatment at 5 years. The generalised gamma predicts 1.4% of patients on treatment at 5 years. The clinical experts thought that these lower estimates of long-term treatment were the most plausible (generalised gamma or exponential). In the interests of being conservative for tepotinib, of the two options, the company selected the curve which estimated a higher proportion of patients still on treatment at later time points, i.e., generalised gamma. However the company provided a scenario analysis which uses the exponential model for ToT in CS scenario analysis section (Table 64 and 65, Section B.3.8.3), which results in a decrease to the ICER.	Thank you for your comments. Section 3.15 of the FAD concludes that there is some uncertainty in the selection of the most appropriate time-on-treatment for tepotinib, but concludes that the company's selection is likely appropriate.

<table>
<tr>
<td>Merck Serono Ltd</td>
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<u>ACD Section 3.12, page 14–15: Life expectancy for people with METex14 skipping NSCLC is likely to be less than 2 years in the overall population</u>

Summary
• Merck agree that agree that the life expectancy of patients with advanced NSCLC harbouring METex14 skipping alterations is expected to be below 2 years, regardless of treatment.
• However Merck also previously provided evidence that tepotinib meets end-of-life criteria in the previously-treated setting specifically. This has now also been presented for the updated wildtype clinical trial comparison as well.
• Regardless of data source used, tepotinib meets end-of-life criteria in the previously-treated setting.

The ACD stated that “Because it would prefer to consider the cost-effectiveness results for previously treated and untreated disease separately (see section 3.2), the committee concluded that although life expectancy for people with METex14 skipping NSCLC is likely to be less than 2 years in the company’s base case population, this would not be used to inform its decision-making on the end-of-life criteria.

Merck agree that the life expectancy of patients with advanced NSCLC harbouring METex14 skipping alterations is expected to be below 2 years, regardless of treatment. Extensive evidence of this was provided in the CS (Section B.2.13.1) and the Technical Engagement response, and was confirmed by clinical experts interviewed.

However, Merck did also provide analysis of end-of-life criteria by untreated and previously treated disease separately, as detailed in the Table 9 of the Technical Engagement response. This analysis demonstrated that tepotinib qualifies for end-of-life criteria in the previously-treated setting, regardless of treatment. The updated ITC and model results, using clinical trial wildtype data for docetaxel +/- nintedanib in the previously treated setting, as well as previously presented real-world cohort comparisons, are presented in Table 11 to Table 13 below. The ITC was not updated using previously treated immunotherapy data, as this was determined by clinical experts and in the ACD to not be a relevant treatment in the second-line setting, and also due to limited time for this response. However, the observational data outcomes for previously-treated immunotherapy is presented in the table below for completeness.

This shows that regardless of data source used, tepotinib meets end-of-life criteria in the previously-treated setting. This is especially important for the clinical trial comparisons, which are now deemed to be more reflective of NHS practice.

Table 11. Mean and median survival for VISION versus docetaxel in the previously-treated group (PD-L1<50%, ≥50%)
<table>
<tr><th colspan="2">Evidence, months</th><th>Tepotinib (weighted)</th><th>Docetaxel</th></tr>
<tr><td>MAIC results (Clinical trial /VISION)</td><td>Median</td><td>[redacted]</td><td>6.0</td></tr>
<tr><td>CE model</td><td>Mean</td><td>[redacted]</td><td>12.0</td></tr>
</table>
</td>
<td>Thank you for your comments. Section 3.16 of the FAD concludes that for people who have had treatment for METex14 skipping NSCLC, life expectancy is likely to be less than 2 years.</td>
</tr>
</table>

Consultee	Comment [sic]	Response
	Table 12. Mean and median survival for VISION versus docetaxel + nintedanib in the previously-treated group (PD-L1<50%, ≥50%) **Evidence, months** | **Tepotinib (weighted)** | **Docetaxel + nintedanib** MAIC results (Clinical trial /VISION) | Median | [redacted] | 12.9 CE model | Mean | [redacted] | 17.6 **Table 13. Mean and median survival from real-world cohort comparisons in the previously-treated group (PD-L1<50%, ≥50%)** **Evidence, months** | **Tepotinib** | **Immunotherapy†** | **Chemotherapy** Observed data (ITC/VISION) | Median | [redacted] | [redacted] | [redacted] CE model | Mean | [redacted] | [redacted] | [redacted] *As highlighted in Key Issue 10 and Section B.3.2 of the company submission, the modelled mean OS and the median OS from the real-world cohorts is considered to be overstated for chemotherapy, likely due to the high number of subsequent treatments, and inclusion of subsequent treatments not seen in UK clinical practice (e.g. crizotinib for wildtype NSCLC or METex14 skipping NSCLC patients). Therefore, the modelled mean OS is considered to be the absolute maximum expected, and likely will be lower in practice. †Immunotherapy was determined by clinical experts to not be a relevant treatment in the second-line setting, however has been included here for completeness, as this was presented in the Technical Engagement response. •	

Merck Serono Ltd	**ACD Section 3.13, page 15–16: *It is uncertain whether tepotinib extends life by more than 3 months, so it does not meet the end-of-life criteria*** **Summary** • **Merck have presented evidence that tepotinib provides a 3-month survival gain compared to all comparators in the real-world cohort, and the key comparators of docetaxel +/- nintedanib in the wildtype clinical trial comparisons for the previously treated population. This was confirmed with clinical experts, who all expected tepotinib to have at least a 3 month survival gain compared to docetaxel +/- nintedanib.** • **Regardless of data source used, tepotinib meets end-of-life criteria in the previously treated setting.** In Section 3.13 of the ACD, it stated: "*The committee agreed that because of the uncertainty in the data and the lack of a statistically significant overall survival benefit for tepotinib from the indirect treatment comparisons, the estimates of the extension to life for tepotinib were not sufficiently robust*" However the survival gain from the modelled mean (using curves for both chemotherapy and immunotherapy comparators which were deemed in the ACD to be optimistic) were all greater than 3 months. Statistical significance is not highlighted in the NICE Guide to the Methods of Technology Appraisal 2013 (wording below) as being a requirement for end-of-life criteria. Nonetheless, in the updated comparison to the relevant previously treated comparators (docetaxel +/- nintedanib), tepotinib has also shown a median OS benefit of substantially greater than 3 months ([redacted] and [redacted] months, respectively), and the modelled means show a benefit for tepotinib substantially greater than 3 months as well ([redacted] months and [redacted] months, respectively). **"*Section 6.2.10:*** *In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met:* • *the treatment is indicated for patients with a short life expectancy, normally less than 24 months and* • *There is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.* • As such, Merck has now provided comparisons in the previously-treated population using all possible data sources, i.e. in observational data in the METex14 skipping population, as well as clinical trial data in wildtype NSCLC. Taken together with evidence presented in Comment **10**, we demonstrate here that the 3-month OS gain is achieved in all comparisons in the previously treated-setting, using the modelled means. Therefore, for all of these comparisons,	Thank you for your comments. Section 3.17 of the FAD concludes that tepotinib meets the end of life criteria in the previously treated subgroup.

Consultee	Comment [sic]	Response
	tepotinib is shown to meet end-of-life criteria, and this collectively represents the most robust and plausible analysis possible.	

Merck Serono Ltd	**ACD Section 3.14, page 16: A plausible ICER could not be determined because of problems with the company's modelling approach and uncertainty in the model parameters, so tepotinib is not recommended for routine use** The economic model has been updated to address the committee's concerns noted in Section 3.14 of the ACD, around the indirect comparison, survival extrapolations and subsequent treatment distributions. In summary: • New indirect treatment comparisons have been conducted comparing VISION to published wildtype NSCLC clinical trial data for the key comparators (see response to Comment **6**), including the main comparator chemo-immunotherapy. Where the real-world cohort data in the METex14 skipping population is still most appropriate (immunotherapy monotherapy comparison using RWD), this ITC has also been updated to include VISION Cohort A+C and an additional METex14 skipping dataset, to increase certainty • The survival extrapolations have also been updated to reflect the new and updated ITCs, which has been validated with three clinical exerts and deemed to be clinically plausible (please see Comment **7** and Appendix **1**) • Subsequent treatments have been updated to reflect NHS practice and expectations after tepotinib, based on clinical expert opinion (please see Comment **8**) Other updates to the economic model are covered in Appendix **1**, and include: • Updated patient characteristics to reflect the source clinical trial • Updated utility and adverse event data to reflect Cohort A+C for tepotinib • Removal of testing costs for squamous patients to reflect the relevant non-squamous population highlighted in the ACD response • A larger PAS for tepotinib has been submitted to PASLU (now [redacted]% off the list price). The model and all results have been updated to reflect this new PAS The updates and comparisons have been incorporated into the economic model to assess the cost-effectiveness of tepotinib to each comparator within both the untreated and previously treated populations. **Base case results for chemo-immunotherapy** As per feedback from the ACD, the most relevant comparator is chemo-immunotherapy (i.e., pembrolizumab + pemetrexed + platinum). Therefore, full cost-effectiveness results are presented for this comparison below. Supplementary deterministic results for the other comparisons are also presented in Appendix **1**. Table 14 presents the base case results for tepotinib compared to pembrolizumab + pemetrexed + platinum. The results show that tepotinib is projected to be less costly and more effective than pembrolizumab + pemetrexed + platinum (dominant) using the wildtype clinical trial data. Given the expectations of a worse response to chemo-immunotherapy in METex14 skipping NSCLC, tepotinib	Thank you for your comments. Section 3.18 of the FAD briefly recalls the new analyses provided by the company at consultation and agrees that this is suitable for decision making. It concludes that when the committee's preferred assumptions for subsequent treatments are included in the economic model, tepotinib is cost effective for both untreated and previously treated METex14 skipping NSCLC.

could be expected to be even more cost-effective if data were available for chemo-immunotherapy in this population.

Table 14: Base case results – tepotinib versus pembrolizumab + pemetrexed + platinum

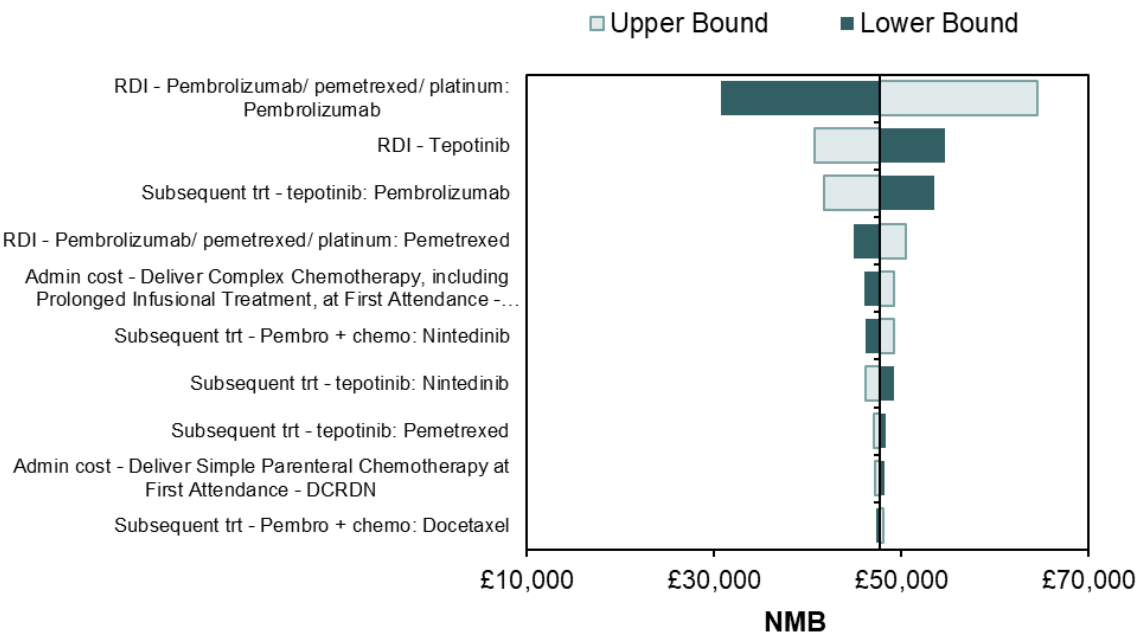
Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Tepotinib	[redacted]	4.26	[redacted]				
Pembrolizumab + pemetrexed + platinum	[redacted]	3.65	[redacted]	[redacted]	0.62	[redacted]	Dominant

Key: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years

One-way sensitivity analysis

Figure 8 present the tornado diagram showing the parameters with the greatest impact on the net-monetary benefit (NMB) after varying each parameter individually within their 95% confidence intervals. The inputs which had the most impact are the relative dose intensity (RDI) and proportion receiving subsequent treatments. However, all results demonstrated that tepotinib is cost-effective within the £30,000 willingness-to-pay (WTP) threshold.

Figure 8: Tornado plot – tepotinib versus pembrolizumab + pemetrexed + platinum (WTP = £30,000)



Key: DCRDN, day case regular day and night; NMB, net-monetary benefit; RDI, relative dose intensity; WTP, willingness-to-pay

Probabilistic sensitivity analysis

The mean results from the probabilistic sensitivity analysis (PSA) are presented in Table 15 with visual results presented in Figure 9. The probabilistic results are consistent with the deterministic results with all iterations showing tepotinib is cost-effective at the £30,000 threshold.

Table 15: PSA results – tepotinib versus pembrolizumab + pemetrexed + platinum

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Tepotinib	[redacted]	4.33	[redacted]				
Pembrolizumab + pemetrexed + platinum	[redacted]	3.64	[redacted]	[redacted]	0.69	[redacted]	Dominant

Key: ICER, incremental cost-effectiveness ratio; LYs, life-years; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years

	Figure 9: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus pembrolizumab + pemetrexed + platinum  Key: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years Figure 10 present the cost-effectiveness acceptability curve at different WTP thresholds. At the £30,000 threshold, the probability of tepotinib being cost-effective is 100%. **Figure 10: Cost-effectiveness acceptability curve – tepotinib versus pembrolizumab + pemetrexed + platinum**	

[redacted]

Scenario analysis

To address the key uncertainties regarding long-term survival estimates and subsequent treatments, a number of scenarios were included, comprising:

- Each parametric curve selected for tepotinib and pembrolizumab + pemetrexed + platinum is varied in turn for OS and PFS
- A scenario assuming tepotinib has equal OS to pembrolizumab plus chemotherapy for the whole time period
- A number of scenarios for subsequent treatments described in Comment **8**.

Table 16: Scenario results – tepotinib versus pembrolizumab + pemetrexed + platinum

Parameter	Base case	Scenario	Incremental		ICERs
			Costs	QALYs	
OS - tepotinib	Log-logistic	Exponential	[redacted]	[redacted]	**Dominant**
		Gen Gamma	[redacted]	[redacted]	£255,979 (SW)
		Gompertz	[redacted]	[redacted]	£122,191 (SW)
		Log-logistic	[redacted]	[redacted]	**Dominant***
		Log-normal	[redacted]	[redacted]	**Dominant**

		Weibull	[redacted]	[redacted]	£183,747 (SW)
		Assume same as pembro + chemo	[redacted]	[redacted]	Dominant
PFS - tepotinib	Log-logistic	Exponential	[redacted]	[redacted]	Dominant
		Gen Gamma			**Dominant**
		Gompertz			Dominant
		Log-logistic			**Dominant***
		Log-normal			**Dominant**
		Weibull			Dominant
OS – pembro + chemo	Log-logistic	Exponential			Dominant
		Gen Gamma			Dominant
		Gompertz			Dominant
		Log-logistic			**Dominant***
		Log-normal			**Dominant**
		Weibull			Dominant
PFS – pembro + chemo	Log-logistic	Exponential			Dominant
		Gen Gamma			Dominant
		Gompertz			Dominant
		Log-logistic			**Dominant***
		Log-normal			**Dominant**
		Weibull			Dominant
Subsequent treatments – after tepotinib (untreated)	75% pembrolizumab; 25% platinum-based chemotherapy	50% pembrolizumab vs platinum chemotherapy	[redacted]	[redacted]	Dominant
		90% pembrolizumab vs platinum chemotherapy	[redacted]	[redacted]	Dominant
		75% immunotherapy split between pembrolizumab/ atezolizumab/nivolumab	[redacted]	[redacted]	Dominant
Subsequent treatments	90% docetaxel + nintedanib; 10% docetaxel monotherapy	50% docetaxel + nintedanib; 50% docetaxel monotherapy	[redacted]	[redacted]	Dominant
Proportion receiving subsequent treatment	100%	Assuming 50% receive subsequent treatment after progressing	[redacted]	[redacted]	Dominant

Key: ICERs, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life-years; SW, South-West quadrant, showing tepotinib is cost-effective by being cheaper with lower QALYs.
Bold: Clinically plausible curves based on the clinical expert estimates of OS and PFS
*Selected curve used in the base case model

Tepotinib remains cost-effective across all scenarios analysed.

When looking at chemo-immunotherapy OS, the ICER remains dominant when the other clinically plausible curve (log-normal) is selected. This remains true when the other clinically plausible PFS curve (log-normal) is selected. Similarly for the tepotinib OS curve, the three plausible curves based on clinical expert expectations of at least similar OS to chemo-immunotherapy (in line with MAIC results too) were log-logistic, exponential and log-normal. For the two curves not chosen (log-normal and

Consultee	Comment [sic]	Response
	exponential), tepotinib remains dominant. Similarly for the three plausible tepotinib PFS curves based on clinical expert feedback and MAIC results (log-logistic, log-normal, generalised gamma), tepotinib remains dominant. Even with the very conservative assumption that the OS for tepotinib and pembrolizumab + pemetrexed + platinum are equal throughout the time period, tepotinib remains dominant and therefore cost-effective. **Supplementary results** Supplementary economic results for the other comparators are presented in Appendix **1**. For all remaining comparisons, tepotinib remains cost-effective at the relevant £30,000 and £50,000 thresholds. **Conclusions** Tepotinib is clinically and cost-effective compared to the main comparator pembrolizumab + pemetrexed + platinum in the untreated setting, as well as in the supplementary comparisons that Merck have conducted to other treatments (Appendix **2**). Given that patients with METex14 skipping mutations have a poorer prognosis than in wildtype NSCLC, especially when on immunotherapy, the clinical and economic benefits are likely to be even greater for tepotinib compared to what is estimated from the MAICs based on a wildtype NSCLC population. These results support the conclusions presented in the initial submission and real-world METex14 skipping cohort comparisons, where tepotinib was shown to be cost effective to chemo-immunotherapy. Although data sources are limited, Merck have provided comparisons for both METex14 skipping data and clinical trial data in wildtype NSCLC, covering every possible data source available for this appraisal. For each one, we demonstrate the clinical and economic benefits associated with tepotinib. A number of scenarios have been analysed to address the uncertainty in the population and associated long term survival. In nearly all of these scenarios, and in all the clinically plausible scenarios based on expert feedback, tepotinib remains cost-effective, projecting lower costs than chemo-immunotherapy and greater QALYs. Furthermore, tepotinib was demonstrated to be budget saving for the NHS, by replacing more expensive chemo-immunotherapy, which was confirmed by NICE Budget Impact Analysis. • Given the very limited timeframe we had to update the model with the new data and analyses, the focus of the results is on the untreated population from VISION versus pembrolizumab + pemetrexed + platinum, as this was confirmed as the most relevant comparison by the committee and clinical experts. However results for the other comparisons are presented for completeness in Appendix **2**, and demonstrates that tepotinib remains clinically and cost-effective against all comparators, again consistent with the previous analysis conducted in the METex14 skipping population comparing to the real-world cohort data.	

Consultee	Comment [sic]	Response
Roy Castle Lung Cancer Foundation	We are disappointed that the Appraisal Committee Decision is not to recommend this therapy in this indication. As acknowledged in the ACD, this is a small segmented group of lung cancer patients, with poorer prognosis and obvious unmet need. Whilst other target therapy options are available, this would be the first for patients with MET gene alterations. We would urge re-consideration that Tepotinib be available through the Cancer Drugs Fund at this time, as data matures. Or that, on discussion with the manufacturer, review is considered earlier than the three years, as suggested in paragraph 4.1.	Thank you for your comments. The FAD now recommends tepotinib as cost effective for both untreated and previously treated METex14 skipping NSCLC.

Comments received from clinical experts and patient experts

None received

Comments received from commentators

None received

Comments received from members of the public

None received

Summary of comments received from members of the public

Not applicable

NICE National Institute for Health and Care Excellence

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [ID3761]

Consultation on the appraisal consultation document – deadline for comments 5pm on 23 February 2022. Please submit via NICE Docs.

Dear Appraisal Committee members,

Merck Serono Ltd welcome the opportunity to comment on the Appraisal Consultation Document (ACD) of tepotinib for treating advanced non-small-cell lung cancer (NSCLC) with MET gene alterations [ID3761]. Merck are disappointed with the draft decision; however, we remain committed to working with NICE to achieve access to tepotinib for patients with advanced NSCLC with METex14 skipping alterations in England and Wales, given the high unmet need in this elderly and frail population who do not have access to a targeted treatment. In a survey published at the British Thoracic Oncology Group (BTOG) Annual Conference in January 2022, UK clinicians (n=57) highlighted METex14 as the mutation with most clinical value that does not currently have a treatment routinely available in UK. All of the clinicians preferred to use targeted therapy over immunotherapy in the first-line setting for NSCLC with a driver mutation.[1] This highlights the importance of access to tepotinib, the first targeted treatment for patients with METex14 skipping NSCLC in the UK. We have summarised below our comments on the ACD, and revised analyses in response to the ACD:

- Merck agree that untreated, non-squamous METex14 skipping NSCLC is the most relevant subgroup, although access for previously-treated patients and squamous patients is important and in line with clinical expert feedback and the tepotinib marketing authorisation.
- Merck agree with the feedback in the ACD that chemo-immunotherapy is the most relevant comparator for tepotinib. As such, the chemo-immunotherapy comparison (specifically pembrolizumab with pemetrexed and platinum), in the untreated non-squamous population, will be the main focus and new base case analysis presented in this ACD response.
- Merck disagree that VISION is not generalisable to the UK, as the patient characteristics in VISION align closely with patient characteristics of the METex14 skipping population in UK clinical practice and clinical experts confirmed that subsequent treatment mix from VISION is largely reflective of NHS practice.
- METex14 skipping is a rare mutation, and so any analysis using data in this small population will include some inherent uncertainty. Observational data specific to METex14 skipping NSCLC for comparator efficacy was initially used within this appraisal, as the population has substantially different patient characteristics to the wider NSCLC population, as well as poorer responses to immunotherapy.
- While chemotherapy outcomes using observational data were higher than expected in UK practice, the real-world immunotherapy monotherapy outcomes in METex14 skipping NSCLC were aligned to external validation and clinical expert expectations in this population.
- Based on committee feedback, Merck have provided a new indirect treatment comparison (ITC) using clinical trial data in NSCLC without specific oncogenic biomarkers (wildtype NSCLC). Matching adjusted indirect comparison (MAIC) was used to account for the large differences in patient populations between trials.
- The key output from the new ITC was the comparison between tepotinib and pembrolizumab with pemetrexed and platinum in the untreated setting. As this is the most relevant comparison, representative of UK clinical practice and the setting where tepotinib will be mostly used (confirmed by clinical experts and in the ACD), this forms the revised base case comparison presented in the below ACD response.
- Supplementary comparisons to pembrolizumab monotherapy in the untreated setting (PD-L1≥50%), and docetaxel with or without nintedanib in the previously-treated setting were also performed using new clinical trial data. These comparisons are also representative of current NHS practice but are not considered the most relevant comparison for tepotinib by clinical experts and in the ACD, and therefore have been included in the Appendices. Other comparisons were not included in the revised ITC, for example first-line chemotherapy, and second-line immunotherapy as they do not reflect current routine NHS practice, according to clinical experts.
- The economic model has been updated to reflect the new comparisons. Survival extrapolations have been validated with three additional clinical experts (on top of the four experts consulted during the development of the company's submission dossier), and all subsequent treatments are now aligned to expected NHS practice.

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NICE National Institute for Health and Care Excellence

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [ID3761]

Consultation on the appraisal consultation document – deadline for comments 5pm on **23 February 2022**. Please submit via NICE Docs.

Based on the updated analyses, we have demonstrated that tepotinib is clinically effective against the main comparator chemo-immunotherapy, despite differences in clinical characteristics between the trials in the wildtype NSCLC analysis, which introduces uncertainty. In the updated economic model, the base-case analysis demonstrates that tepotinib is dominant (higher QALYs with lower costs) compared to chemo-immunotherapy.

The supplementary analyses also show tepotinib to be clinically and cost-effective against pembrolizumab monotherapy in the untreated PD-L1≥50% setting, as well as in the previously-treated setting compared to docetaxel +/- nintedanib, where tepotinib meets end of life criteria. Having now conducted analyses using all possible data sources (real-world data vs. trial data) and approaches (METex14 skipping data vs. wildtype NSCLC), tepotinib has been shown to be clinically effective and cost-effective, across a wide range of scenarios. Furthermore, in the budget impact analysis conducted by NICE, tepotinib was also shown to be budget saving for the NHS. Finally, Merck have also submitted a further PAS offer as part of the ACD response. We look forward to the opportunity to discuss these new analyses on 10th March 2022 at the second Appraisal Committee Meeting.

Yours sincerely,

Thomas McLean

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NICE National Institute for Health and Care Excellence

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [ID3761]

Consultation on the appraisal consultation document – deadline for comments 5pm on **23 February 2022**. Please submit via NICE Docs.

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

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NICE National Institute for Health and Care Excellence

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [ID3761]

Consultation on the appraisal consultation document – deadline for comments 5pm on **23 February 2022**. Please submit via NICE Docs.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1 Line of therapy subgroups	**ACD Section 3.2, page 5-6: *Untreated and treated subgroups should be considered separately*** In the original company submission (CS), the line-agnostic group was the base case population, however full subgroup analyses were provided for untreated and previously-treated subgroups separately. For all of the updated comparisons (described in Comments **6-12** and Appendix **2**), line of therapy subgroups have been considered separately, for both tepotinib and the comparators, including for the most relevant comparison of chemo-immunotherapy in the untreated population. Furthermore, the relevant PD-L1 expression groups have been noted and accounted for in each comparison where appropriate.
2 Relevant subgroups	**ACD Section 3.3, page 6-7: *The appraisal should focus on untreated non-squamous NSCLC with METex14 skipping alterations*** **Summary** • **Merck agree that the appraisal should focus on untreated non-squamous NSCLC with METex14 skipping alterations, as this is the most relevant population who will receive tepotinib.** • **However clinical experts have highlighted the importance of including previously-treated patients, as in some cases tepotinib could be used in the previously-treated setting. Furthermore, even though squamous histology is rare in METex14 skipping NSCLC and not routinely tested, all clinical experts interviewed have stated that access to tepotinib in squamous patients is still preferable, as there is a high unmet need even in this very small population. Squamous patients were included in the VISION study as well.** • **This is consistent with all NICE appraisals in NSCLC with other oncogenic driver mutations reviewed by the company (e.g. ALK, ROS-1, RET NSCLC) where squamous histology also is rare, but the final NICE recommendation did not restrict to non-squamous patients only.** **Line of therapy** Merck agree with the committee that the most relevant population in this appraisal with regards to line of therapy is the untreated NSCLC population with METex14 skipping alterations. As discussed in the ACD and from clinical expert feedback, if reimbursed, tepotinib would mostly be offered to patients in the untreated (treatment naïve) setting. However, in some cases, tepotinib could be used in previously-treated patients, for example in case of a delay to a genomic test result, or for patients who have already started treatment before tepotinib is reimbursed. Therefore, clinical expert feedback sought by Merck has reinforced that it is important for previously-treated patients to be included in the appraisal population. To support this, Merck have provided supplementary analysis in the previously-treated group (discussed in Comments **6** and **10-11**). **Histology** Merck agree with the committee that the most relevant population in this appraisal with regards to histology is the non-squamous NSCLC population with METex14 skipping alterations. The majority of patients with METex14 skipping NSCLC are non-squamous histology. For example, in VISION, [redacted]% of patients were adenocarcinoma histology (including non-squamous), and [redacted]% were squamous histology (based on Cohort A), and this is similar to proportions reported in the literature for METex14 skipping NSCLC (see Section B.3.2.2 of the company submission). The ACD also stated that squamous patients will not be routinely tested for in NSCLC. Therefore, as covered later in the ACD response, Merck have updated the ITC to reflect the more relevant non-squamous comparators (for

example, KEYNOTE-189, for pembrolizumab + pemetrexed + platinum, which is in non-squamous patients only). Please see Comment **12** for how else the model has been updated to reflect these changes.

However, Merck have received consistent clinical expert feedback (from a previous advisory board with four UK clinicians; and three further interviews with separate clinicians as part of this ACD response) that clinicians would still prefer access to tepotinib in squamous advanced NSCLC patients, even if rarer than non-squamous and not routinely tested for, as there is still a high unmet need for a targeted treatment in this very small group of patients. The VISION trial results demonstrated that tepotinib was effective in the ITT population including a small sub-set of squamous patients, and the marketing authorisation for tepotinib does not restrict on the basis of histology to exclude squamous patients.[2] For all of the above reasons, patients with squamous NSCLC harbouring METex14 skipping alterations were included in the overall analysis in the original company submission (CS), and the company's position remains the appraisal recommendation should not be restricted to non-squamous patients only. Furthermore, it is important to remember that squamous METex14 skipping patients represent an incredibly small population within the UK. Squamous histology is present in roughly 3-9% of METex14 skipping tumours (from a SLR conducted by NICE, B.1.3.2.2), which is itself only in 3% of NSCLC cases.

Precedent in previous comparable appraisals

This approach is consistent with other appraisals in NSCLC with other oncogenic driver mutations. In these other oncogenic driver mutations in NSCLC (e.g. ALK, ROS-1, RET) squamous histology also tends to be rare, and often the Final Appraisal Document (FAD) acknowledged that non-squamous patients were the most relevant cohort. However, in all of these appraisals, the final NICE recommendation did not restrict to non-squamous patients, even if squamous patients were not included in the relevant clinical trial or analysis. Therefore, the consideration of subgroups in the tepotinib appraisal should be consistent with these previous comparable appraisals in NSCLC with other oncogenic driver mutations (described in Table 1 below) to ensure equity of care to all eligible patients.

Table 1. Review of previous NICE appraisals in advanced NSCLC with other oncogenic driver mutations since 2018, and if the recommendation mentions histology

TA and date of publication	Treatment	Driver mutation	Squamous patients excluded from recommendation ?	Discussion of squamous histology in FAD
TA760[3] 12 Jan 2022	Selpercatinib	RET	No	• The company did not present evidence on selpercatinib for squamous disease because of the rarity of RET in squamous NSCLC, clinical advice, and the very small number of people with squamous NSCLC in the trial • The committee agreed that the recommendations in this technology appraisal would apply to both squamous and non-squamous advanced NSCLC, because of the wording of the marketing authorisation and because the squamous population is so small
TA670[4] 27 January 2021	Brigatinib	ALK	No	None
TA643[5]	Entrectinib	ROS-1	No	None
TA628[7] 13 May 2020	Lorlatinib	ALK	No	None

	TA571[8] 20 March 2019	Brigatinib	ALK	No	None
	TA529[9] 04 July 2018	Crizotinib	ROS1	No	• The marketing authorisation for crizotinib did not specify non-squamous disease, but ROS1-positive NSCLC is almost exclusively seen in non-squamous tumours • The summary of product characteristic states that there is limited information available in patients with ROS1-positive NSCLC with non adenocarcinoma histology, including squamous. • Testing for the ALK mutation is routinely done in the non-squamous population only.

In conclusion, Merck reiterate that the appraisal population (and any potential recommendation of tepotinib) should still include previously-treated patients, as well as squamous patients, due to clinical feedback that there are unmet clinical needs for tepotinib in both these groups, although they do not represent the group most likely to receive tepotinib. This approach is in line with the tepotinib marketing authorisation, and also consistent with previous comparable appraisals in NSCLC which did not restrict recommendations by histology subgroups.

3 Chemo-immunotherapy comparisons	**ACD Section 3.4: *Chemo-immunotherapy is the most relevant comparator for tepotinib*** Merck agree with the ACD that the appraisal should focus on untreated non-squamous METex14 skipping NSCLC, and that the most relevant comparator is chemo-immunotherapy (specifically pembrolizumab with pemetrexed and platinum chemotherapy). This is in line with the latest clinical feedback given to Merck, which stated that most untreated, non-squamous patients receive chemo-immunotherapy in UK practice. Furthermore, clinical experts highlighted that as patients with METex14 skipping NSCLC are known to respond poorly to immunotherapy monotherapy, even if a patient had PD-L1≥50%, they would mostly be given chemo-immunotherapy over immunotherapy monotherapy in the absence of a targeted therapy. Therefore, we align with the committee's view that chemo-immunotherapy is the most relevant comparator. As part of this ACD response, Merck have provided an updated ITC comparing tepotinib to pembrolizumab with pemetrexed and platinum, using clinical trial data from NSCLC without specific oncogenic biomarkers (wildtype NSCLC), as well as an updated economic model to reflect this comparison. Additional comparisons have also been conducted (discussed in Comment **6**) however the chemo-immunotherapy comparison remains the most relevant and important comparison. As such the chemo-immunotherapy comparison will be the base-case comparison in this appraisal for tepotinib in METex14 skipping NSCLC.
4 VISION generalisability	**ACD Section 3.5, page 7–8: *The clinical evidence for tepotinib is uncertain because it is based on 1 single-arm study that may not be generalisable to NHS practice*** **Summary** • **Merck disagree that the VISION trial is not generalisable to NHS practice or the UK population. The VISION trial was reflective of the METex14 skipping NSCLC population for age, histology and other characteristics typical of the specific population.** • **In addition, a recent publication of METex14 skipping patients treated with tepotinib in the UK through an Early Access to Medicines Scheme (EAMS) showed these UK patients had similar characteristics (e.g. in age, histology etc) to those from VISION, further supporting the generalisability of VISION to UK METex14 skipping patients. Furthermore, over half of patients in VISION were European patients.** • **For most patients, VISION was also reflective of subsequent treatments that would be given after**

tepotinib in NHS practice, with most patients receiving chemotherapy or immunotherapy, which is in line with clinical expert expectations. Only a minority of patients received treatments outside of NHS practice, primarily crizotinib.

In the ACD, clinical experts noted that the response rate in VISION was higher than would be expected with current standard treatments, and the committee agreed that VISION shows that tepotinib is clinically effective. However, it noted that the distribution of subsequent treatments in VISION meant that the results may not be generalisable to NHS clinical practice.

Use of a single-arm trial in METex14 skipping NSCLC

The company acknowledges the uncertainty provided by a single-arm trial, in what is a rare mutation and small population. However, despite the inherent uncertainty due to lack of a trial comparator arm and the challenges associated with this type of trial, there is precedent for single arm studies being used in NICE decision-making and informing UK clinical practice in NSCLC, e.g. TA643 and TA529.[5,9] Furthermore, certain circumstances exist where randomised controlled trials (RCTs) can be considered ethically questionable or unfeasible due to a disease's rarity impacting only a small population. In this instance a Phase 2 study provides sufficient information on efficacy in this very rare cancer, with high unmet medical need where no approved treatments are currently available in the UK. There is a precedent for single-arm trials providing a strong alternative to RCTs as long as the patient population is well-defined and the drug produces a substantial Objective Response Rate (ORR) that exceeds that of existing treatments. The VISION trial builds on strong scientific evidence and pre-clinical data, and so the single-arm study design was the most feasible and appropriate method for VISION.

Furthermore, Merck disagrees with the suggestion that VISION is not generalisable to NHS practice, for reasons outlined below.

Generalisability of VISION to the METex14 skipping NSCLC population in the UK

Firstly, the most important argument supporting the generalisability of VISION is that patient characteristics are reflective of advanced NSCLC harbouring METex14 skipping alterations. As presented in Section B.3.2.2 of the CS, METex14 skipping NSCLC patients have a specific set of characteristics, including older age (median age ~73 years), with predominately non-squamous histology, poor fitness (i.e. mostly ECOG 1 over ECOG 0) and poor responses to immunotherapy. Also in the CS (Section B.2.3.1.3), it was demonstrated that the VISION trial was reflective of these characteristics, and so remains generalisable to the METex14 skipping population, including for UK patients in NHS practice. Four clinical experts interviewed by Merck previously as part of an advisory board all agreed that the VISION population was reflective and generalisable to the UK METex14 skipping population, as did the three clinical experts interviewed separately as part of this ACD response.

Secondly, a recent publication at the British Thoracic Oncology Group (BTOG) conference is presented in Appendix **1** to this ACD response, reporting outcomes from UK patients treated with tepotinib through the Early Access to Medicines Scheme (EAMS) (n=15). Although low in patient numbers, the patient characteristics were reflective of what is expected for the METex14 skipping population, and what is observed in the VISION trial, specifically older age and predominantly non-squamous histology.[10] Tepotinib was also observed to be clinically effective in this UK-specific population. This further supports the generalisability of VISION to METex14 skipping patients in the UK population. In addition, 51% of the VISION trial was from Europe (Section B.2.3.1.3 and Appendix R.1.2.21 of the CS), and nearly all Western Europe specifically, which represents a broadly similar population to the UK, further highlighting the generalisability of VISION to the UK and NHS practice.

Generalisability of subsequent treatments to NHS practice

Merck disagrees with the ACD statement that the distribution of subsequent treatments in VISION meant that the results may not be generalisable to NHS clinical practice. As part of this ACD response, Merck has elicited feedback from three clinical experts, and they have been asked specifically about expected subsequent treatments after tepotinib in NHS practice (Comment **8** and Appendix **1**). This

was also discussed by the clinical experts in the first ACM. The feedback from the three clinical experts on subsequent treatments is consistent: in NHS practice, patients will be able to receive either chemotherapy (platinum-doublet chemotherapy or docetaxel +/- nintedanib) or immunotherapy monotherapy after tepotinib. The specific regimens will depend on tepotinib line of therapy, and in the case of previously-treated patients, will depend on treatment prior to tepotinib. Please see Comment **8** and Appendix **1** for more detailed feedback on subsequent treatments after tepotinib. In summary:

- **Tepotinib in previously-untreated patients:**
    - All clinical experts consulted as part of ACD response agreed that patients will receive either immunotherapy monotherapy or platinum-based chemotherapy as a second-line treatment after tepotinib. Patients could then receive docetaxel +/- nintedanib as a third-line treatment.
    - Based on the three interviews conducted by Merck, the split between those receiving immunotherapy and those receiving platinum-based chemotherapy after tepotinib is expected to range from 50:50 to 90:10 (in favour of subsequent immunotherapy over chemotherapy), although all experts highlighted that this split between immunotherapy and chemotherapy is not completely known at the moment. They also agreed that the vast majority of immunotherapy-treated patients would go onto pembrolizumab, and chemotherapy would be mostly pemetrexed (with carboplatin).
    - In the untreated population in VISION (Cohort A+C), of patients who received subsequent treatment, most received subsequent immunotherapy ([redacted]) and/or chemotherapy ([redacted]), in line with expected NHS practice and clinical expert feedback. The most common immunotherapy was pembrolizumab, and the most common chemotherapy was pemetrexed, with/without carboplatin, again in line with expectations of NHS practice.
    - A smaller proportion of patients received subsequent treatments outside of NHS practice: primarily subsequent crizotinib ([redacted]), or a different subsequent MET inhibitor ([redacted]), or another investigational treatment ([redacted]) across a number of lines of therapy.
- **Tepotinib in previously-treated patients**:
    - The clinical experts stated that if a patient receives chemo-immunotherapy before tepotinib, then docetaxel +/- nintedanib will be given as a third-line treatment, or in some specific cases, another single agent chemotherapy such as paclitaxel (off label use). Most patients get chemo-immunotherapy up front, so after tepotinib, most patients will receive subsequent docetaxel +/- nintedanib.
    - If immunotherapy monotherapy is given in first line (in patients with PD-L1 expression ≥50%), then after tepotinib, platinum-based chemotherapy will be given. This will mostly be carboplatin + pemetrexed, but some could receive other options (such as gemcitabine/vinorelbine) in combination with carboplatin.
    - If a patient has not had any immunotherapy first-line, they could receive immunotherapy third-line after tepotinib, but this is unlikely and will be rare according to clinical experts (although possible within NHS practice).
    - This distribution of treatments was mostly aligned with the previously treated population in VISION Cohort A+C, where [redacted] received chemotherapy and [redacted] received immunotherapy, again aligned to what is possible and expected within NHS practice.
    - Again the main difference was the subsequent crizotinib ([redacted]), other MET inhibitors ([redacted]) or investigational treatment ([redacted]) which are not offered in UK, albeit in even lower proportions to untreated patients.

In the ACD response Appendix **1**, the full subsequent treatments received by patients in VISION is reported, by line of therapy. Furthermore, the full clinical feedback on subsequent treatments is reported in the Appendix **1** as well as in Comment **8** of this document.

Finally, clinical experts interviewed by Merck as part of this ACD response highlighted that the use of

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	subsequent treatments outside of NHS practice is typical for global clinical trials, and similar to trials that NICE would have appraised in the past. However, it is important to note that these subsequent treatments outside of NHS practice in VISION are the minority, and most patients who received subsequent treatments were aligned with NHS practice, highlighting that VISION is largely generalisable to NHS practice for subsequent treatments.
5 Cohort A+C	**Section 3.6 page 8: *Using the data from cohort A plus cohort C has little effect on the results, but would be preferable*** As per the committee's stated preference in the ACD, Merck have used the larger Cohort A+C (n=290) from VISION in the updated ITC, comparing to using clinical trials in wildtype NSCLC as well as the updated immunotherapy monotherapy comparison using METex14 skipping NSCLC observational data. The full dataset of Cohort A+C (n=290) is marginally larger than from the 275 patients with at least 3 months of follow up, described previously in Technical Engagement and in the original submission. Although the additional 15 patients add little for long-term extrapolation, they do further increase confidence in the short term results of tepotinib, and there is no statistical reason for their exclusion when analysis is performed. Therefore, the full 290 patients have been included. As previously discussed, using Cohort A+C has minimal impact on the results, but provides further certainty with the larger patient cohort, and this is further explored in Appendix 2.
6 Indirect treatment comparison	**ACD Section 3.7 page 9–11: *The indirect treatment comparisons results are highly uncertain*** **Summary** • **The company initially used observational data specific to the METex14 skipping NSCLC population to inform the comparator arm of the ITC, as METex14 skipping is a distinct population within NSCLC, with different patient characteristics (including older age and worse ECOG) and a poorer response to immunotherapy versus wildtype NSCLC. In appraisals for other oncogenic driver mutations in NSCLC, companies have previously been criticised by NICE for using comparator data outside of the specific mutation.** • **The company undertook extensive validation of the observational comparator data compared to published studies in the METex14 skipping population, as well as against clinical trials in wildtype NSCLC.** • **The immunotherapy monotherapy outcomes of the Merck real-world cohort analysis, particularly for the relevant untreated METex14 skipping NSCLC population, are aligned to the outcomes from other published studies in METex14 skipping NSCLC with immunotherapy (e.g. Sabari et al, Guisier et al.), as well as in expectations compared to clinical trials in wildtype NSCLC for immunotherapy. The treatment mix is also aligned to NHS practice.** • **Merck acknowledge the chemotherapy outcomes from the observational data are less aligned to clinical expectations, likely driven by the high proportions of subsequent treatments and treatments not fully reflective of NHS practice (as the data was primarily from US and Canada). There is also limited real-world data for METex14 skipping patients treated with chemo-immunotherapy, which is the main comparator for tepotinib, as highlighted in the ACD.** • **Nonetheless, tepotinib demonstrated greater PFS that was statistically significant compared to immunotherapy and chemotherapy in the real-world cohort comparisons, and numerically greater OS, despite the overstated chemotherapy efficacy. It is clinically implausible that tepotinib does not have greater survival compared to chemotherapy, across lines of therapy, based on extensive external validation, interviews with clinical experts and the targeted mechanism of tepotinib. The survival benefit for tepotinib is expected to be substantially greater than estimated from the observational data.** Merck acknowledge there is inherent uncertainty in using real-world data in what is a rare population with limited patient numbers. However, we wanted to provide our rationale and context for use of observational comparator data in the specific METex14 skipping population, and then highlight where it is still relevant and appropriate for use in this appraisal. The updated ITC using clinical trial data in wildtype NSCLC, and the comparisons where this revised ITC is most relevant, is then described and reported.

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Rationale for use of observational data in METex14 skipping NSCLC for the original indirect treatment comparison

As noted in the ACD, there are no clinical trials for the key comparators to tepotinib (immunotherapy and/or chemotherapy) in METex14 skipping NSCLC specifically. As described in Section B.2.9.1 of the CS, it was important to ensure comparator data came from the METex14 skipping population, if possible in this appraisal, for the following reasons:

- Firstly, the population has prognostic characteristics substantially different to that of other types of NSCLC, notably being substantially older (median age 73 years) and therefore less fit (higher ECOG 1 over ECOG 0), as well as with high proportions of non-squamous histology (Section B.1.3.2.2 of CS).

- Secondly and most importantly, it has been shown that patients with METex14 skipping NSCLC have a poorer prognosis compared to patients without this mutation (Section B.1.3.2.3 of the CS) and are known to respond poorly to immunotherapy in particular (Section B.1.3.3.2 of the CS). Studies consistently show low response rates and PFS for immunotherapy in the METex14 skipping population, and although OS varies, it is still observed to be lower than what is expected in wildtype NSCLC.[11-13] Clinical expert feedback sought by the company as part of this ACD response confirmed this poor response to immunotherapy. This was either from clinician's direct experience in METex14 skipping NSCLC, or clinician's expectations that this poor response would be similar to other oncogenic driver mutations in NSCLC (e.g. ALK and EGFR), where poorer immunotherapy outcomes are also observed.[13,14]

- Finally, a further rationale for using data from a METex14 skipping population specifically was to avoid the critique raised in previous NICE appraisals in NSCLC with other oncogenic driver mutations, regarding the use of comparator data that was not specific to the driver mutation. Examples of appraisals where this critique was raised include: TA529, TA643 (ROS-1 NSCLC) and TA760 (RET NSCLC).[3,5,9]

For the reasons stated above, the company identified observational data in the METex14 skipping population, and used this data to inform the ITC and economic model. A systematic search of all possible data sources in METex14 skipping NSCLC was undertaken (as described in Appendix L and Technical Engagement response to Key Issue 4), and the dataset constructed by Merck (partly through non-interventional studies run by Merck), is the largest patient-level dataset in the METex14 skipping NSCLC population the company are aware of, with access to patient characteristics and outcomes for most of the key comparator classes. Furthermore, there were sufficient patient numbers for robust statistical analysis, in what is a rare mutation. The access to patient level data allowed for a tight match of patient characteristics to VISION based on inclusion and exclusion criteria and using propensity score weighting. As a result, the company were able to generate comparisons which were statistically robust and as unbiased as possible. All of these comparisons were validated against a wide range of external data sources (discussed below). The rare nature of the disease and the relatively low patient numbers (compared to clinical trial data) mean that the wide confidence intervals are to be expected, and likely to be observed in any comparison using observational data in a rare disease. Therefore, despite a number of limitations related to the rare nature of the mutation and lack of UK-specific data, Merck still believe the observational data represents a reliable data source for NICE's decision-making in a METex14 skipping NSCLC population, but particularly for immunotherapy where there is known to be a poor prognosis in this specific population versus wildtype NSCLC.

Validation of observational data ITC outcomes against published data in METex14 skipping NSCLC and clinical trials in wildtype NSCLC: immunotherapy monotherapy

The outcomes from the observational data used in the ITC (after weighting) were validated against published data in the METex14 skipping population, as well as clinical trials in wildtype NSCLC, as reported in Section B.3.2 of the CS. The studies used for external validation of the ITC results are summarised in Table 2 below, with median OS and median PFS reported. Furthermore, the long-term

survival curves selected in the economic model were also validated against these same studies in Section B.3.8.7 of the CS.

All studies used in the validation were also reported in Section B.3.2. of the CS, with the exception of the Standing Cohort data. This data source is from real-world outcomes provided by Public Health England (PHE) for advanced (Stage IIIB/C and IV) NSCLC, for patients treated with the specific treatments listed in the NICE scope for tepotinib. More details have been provided as a separate reference.[6] This represents another useful source to validate outcomes for NSCLC in the UK specifically.

Please also note that the ITC has been updated to be weighed against VISION Cohort A+C (given the committee's preference for Cohort A+C as in Section 3.6 of the ACD), as well as to include another observational dataset in the METex14 skipping population for the comparators that the company recently received access to (referred to as the French/GFPC dataset). This new analysis is described in detail in the ACD response Appendix **2**. The ITC outcomes remain consistent with the initial analysis as also shown in Appendix **2**.

Table 2. Median OS and PSF by trial for immunotherapy

Study	Population	N	Line of therapy	Treatment	Median OS (95% CI)	Median PFS (95% CI)
Line agnostic						
Real-world cohort data (original Merck analysis)	METex14 skipping NSCLC	51*	Line agnostic	Mostly pembrolizumab (65%)	[redacted]	[redacted]
Real-world cohort data (updated Merck analysis†)	METex14 skipping NSCLC	99	Line agnostic	Mostly pembrolizumab (75%)	[redacted]	[redacted]
Sabari et al. 2018[12]	METex14 skipping NSCLC	24	A mixture of 1L and 2L+	Immunotherapy monotherapy (22/24); immunotherapy + chemotherapy (2/24)	18.2 months (12.9-NR)	1.9 months (1.7-2.7)
Mazieres et al. 2019[13]	METex14 skipping NSCLC	36	A mixture of 1L and 2L+	Mostly pembrolizumab and nivolumab	18.6 (7.0-NR)	3.4 (1.7-6.2)
Untreated patients						
Real-world cohort data (original Merck analysis)	METex14 skipping NSCLC	20	1L	Mostly pembrolizumab	[redacted]	[redacted]
Real-world cohort data (original Merck analysis†)	METex14 skipping NSCLC	32	1L	Mostly pembrolizumab	[redacted]	[redacted]
Guisier et al. 2020[11]	METex14 skipping NSCLC	30	1L	Mostly nivolumab (80%) and pembrolizumab (17%) and	13.4 months (9.4-NR)	4.9 months (2.0-11.4)
KEYNOTE-024[15]	Wildtype advanced NSCLC with PD-L1 >50%	154	1L	Pembrolizumab monotherapy	26.3 months (18.3-40.4)	7.7 months (6.1-10.2)
KEYNOTE-042[16]	Wildtype advanced with PD-L1 >1%	637	1L	Pembrolizumab monotherapy	PD-L1 >50%: 20.0 months; PD-L1>1%: 16.7 months	PD-L1 >50%: 7.1 months; PD-L1>1%: 5.4 months

UK Standing Cohort data[6]	Wildtype advanced with PD-L1 >50%	3,425	1L	Pembrolizumab	[redacted]	[redacted]
Previously-treated patients						
Real-world cohort data (original Merck analysis)	METex14 skipping NSCLC	32	2L+	Mostly pembrolizumab and nivolumab	[redacted]	[redacted]
Real-world cohort data (original Merck analysis†)	METex14 skipping NSCLC	67	2L+	Mostly pembrolizumab and nivolumab	[redacted]	[redacted]
KEYNOTE-010[17]	Wildtype advanced with PD-L1 >1%	691	2L	Pembrolizumab monotherapy	11.8 months (10.4-13.1)	4.0 months (3.1-4.1)
CheckMate 017/057[18]	Wildtype advanced NSCLC	427	2L	Nivolumab	11.1 months (9.2-13.1)	2.5 months (2.2-3.5)
UK Standing Cohort data[6]	Wildtype advanced NSCLC	2,707	2L	Pembrolizumab, nivolumab, atezolizumab	[redacted]	[redacted]

*There is one fewer patient in the line-agnostic group than the untreated and previously treated patients combined. This is because one patient received two lines of immunotherapy, and so is in both the untreated and previously treated group. However to avoid double counting in the line-agnostic, a random sampling approach was taken for the line agnostic group, where the patient was only included once in this group.

†The immunotherapy ITC has been updated to be weighed against VISION Cohort A+C, as well as to include another comparator data source in the METex14 skipping population that the company recently received access to (data source known as GFPC, and was obtained from an academic centre in France). Please see Appendix 2 for details. Outcomes are shown after weighting to VISION Cohort A+C, although n numbers are shown pre-weighting for transparency.

Based on validation using the above studies, the median OS and median PFS from the immunotherapy observational data in the METex14 skipping NSCLC population are aligned to the external studies and clinical expectations, for the line-agnostic immunotherapy group, as well as the separate untreated and previously treated groups. These are all in a similar population (METex14 skipping NSCLC) and were matched to VISION using propensity score weighting. The untreated subgroup is the primary focus in this response, as it was highlighted by clinical experts and in the ACD as being the group who are most likely to receive immunotherapy monotherapy.

The median PFS for immunotherapy seen in the real-world cohort (line agnostic, after weighting to VISION) is mostly aligned to that seen in other studies in the METex14 skipping population ([redacted] months versus 1.9, 3.4 and 4.9 months in Sabari et al.,[12] Mazieres et al.[13] and Guisier et al.[11]). For the untreated group specifically, the PFS was close to what is seen in the relevant clinical trial ([redacted] and [redacted] months versus 7.7 months in KEYNOTE-024)[15] and aligned to expectations by being slightly lower in the METex14 skipping group, expected due to the poor response of these patients to immunotherapy.

Similarly to PFS, the Merck real-world cohort OS for immunotherapy is more in line with the other studies in METex14 skipping NSCLC and is lower than wildtype clinical trials, as expected by clinical experts. This is what is observed for the line agnostic population ([redacted] and [redacted] months), which was similar to the relevant METex14 skipping studies (13.4, 18.2, and 18.6 months in Guisier et al.,[11] Sabari et al.,[12] and Mazieres et al.[13]). The untreated population results for the real-world cohort were also slightly lower than the relevant clinical trials ([redacted] and [redacted] months versus 26.3 months for KEYNOTE 024),[15] in line with clinical expectations. These immunotherapy outcomes were deemed to be clinically plausible when presented to four UK clinicians at an advisory board previously,[14] and in recent interviews with three clinical experts as part of the ACD response. Similar trends are seen in the comparison of the survival curves against Kaplan-Meier curves from the external validation sources (Section B.3.8.7 of the CS, and Appendix N.1.1.8 of the CS).

The ACD stated in Section 3.7 that the observational data outcomes "*could be partially explained by a*

lack of generalisability to the UK population, because of the mix of comparator treatments and because people in VISION and from the matched comparator cohort were fitter than would be seen in UK clinical practice".

For the immunotherapy real-world cohort, the treatment mix was mostly aligned to NHS practice, with most patients receiving pembrolizumab at first-line, and a mixture of pembrolizumab and nivolumab at subsequent-lines. There were only two patients who received treatments not in line with UK practice in the untreated group: ipilimumab & nivolumab ([redacted]) and nivolumab ([redacted]).

In summary, Merck believe the immunotherapy monotherapy outcomes from the observational data are aligned to published studies in the METex14 skipping population, as well as aligned with clinical expert expectations compared to wildtype clinical trials. This included the relevant untreated population, which was further supported by clinical expert opinion. Furthermore, the treatment mix is also reflective of NHS practice.

Validation of real-world cohort data against published data in METex14 skipping NSCLC and clinical trials in wildtype NSCLC: chemotherapy

Merck are aware that there was more uncertainty in the ITC from the comparator chemotherapy outcomes (after weighting to VISION), which were less aligned to expectations in clinical practice. Table 3 reports the external validation conducted against chemotherapy outcomes in the METex14 skipping NSCLC population and wildtype NSCLC clinical trials. The publications used are the same as described in Section B.3.8.7 of the CS, alongside the UK Standing Cohort data and updated ITC analysis. In this part of the CS, validation of the curve extrapolations against the published Kaplan Meier curves was also presented. The previously-treated group is focused on here, as this is the population most likely to receive chemotherapy alone in NHS practice, in line with clinical feedback and from the ACD.

Table 3. Median OS and PSF by trial for chemotherapy

Study	Population	N	Line of therapy	Treatment	Median OS (95% CI)	Median PFS (95% CI)
Line agnostic						
Real-world cohort data (original Merck analysis)	METex14 skipping NSCLC	66*	Line agnostic	Mixture of chemotherapy regimens	[redacted]	[redacted]
Real-world cohort data (updated Merck analysis†)	METex14 skipping NSCLC	148	Line agnostic	Mixture of chemotherapy regimens	[redacted]	[redacted]
Awad et al 2019[19]	METex14 skipping NSCLC	34	1L, 2L+	Platinum based regimens (64%) and/or pemetrexed based regimens (61%)	8.1 months (5.3, NR)	Not reported
Untreated patients						
Real-world cohort data (original Merck analysis)	METex14 skipping NSCLC	49	1L	Mixture of chemotherapy regimens	[redacted]	[redacted]
Real-world cohort data (updated Merck analysis†)	METex14 skipping NSCLC	117	1L	Mixture of chemotherapy regimens	[redacted]	[redacted]
Hur et al[20]	METex14 skipping	20	1L	Mixture of chemotherapy	9.5 months	4.0 months

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	NSCLC			regimens	(6.5, 23.1)	(2.8-14.1)
Gajra et al, 2018[21]	Advanced NSCLC	< 70 years: 736 ≥70 years: 270	1L	Platinum-based chemotherapy regimens	< 70 years: 9.9 (9.0-11.0) ≥ 70 years: 7.7 (6.0 – 8.9)	Not reported
KEYNOTE-024[15]	Advanced NSCLC with PD-L1 >50%	151	1L	Platinum-based chemotherapy regimens	13.4 months (9.4, 18.3)	5.5 months (4.2-6.2)
KEYNOTE-189[22]	Advanced NSCLC	206	1L	Pemetrexed and platinum	10.6 months (8.7, 13.6)	4.9 (4.7-5.5)
KEYNOTE-042[23]	Advanced NSCLC with PD-L1 >1%	615	1L	Platinum-based chemotherapy regimens	12.1 months (11.3, 13.3)	6.5 months
UK Standing Cohort data[6]	Advanced NSCLC	23,919	1L	Any platinum-based chemotherapy regimen	[redacted]	[redacted]
Previously treated patients						
Real-world cohort data (original Merck analysis)	METex14 skipping NSCLC	34	2L+	Mixture of chemotherapy regimens	[redacted]	[redacted]
Real-world cohort data (updated Merck analysis†)	METex14 skipping NSCLC	56	2L+	Mixture of chemotherapy regimens	[redacted]	[redacted]
KEYNOTE-010[17]	Advanced NSCLC with PD-L1 >1%	309	2L	Docetaxel	8.4 months (7.6, 9.5)	4.1 (3.8-4.5)
CheckMate 017/057[18]	Advanced NSCLC	427	2L	Docetaxel	8.1 months (7.2, 9.2)	3.5 (3.1-4.2)
UK Standing Cohort data[6]	Advanced NSCLC	3,323	2L	Any chemotherapy regimen, primarily docetaxel +/- nintedanib	[redacted]	[redacted]

*There are fewer patients in the line-agnostic group than the untreated and previously treated patients combined. This is because some patients received two lines of chemotherapy, and so are in both the untreated and previously treated group. However to avoid double counting in the line agnostic group, a random sampling approach was taken for the line agnostic group, where such patients are only included once in this group. This is also why the outcomes for the line agnostic group do not completely align with the outcomes from each subgroup.

†The chemotherapy ITC has been updated to be weighed against VISION Cohort A+C, as well as to include another comparator data source in the METex14 skipping population that the company recently received access to (data source known as GFPC, and was obtained from an academic centre in France). Please see Appendix 2 for details.

The median PFS of the real-world cohort treated with chemotherapy was aligned with other studies in METex14 skipping NSCLC, and was also slightly lower than published clinical trials in wildtype NSCLC, as expected. The median PFS in the line-agnostic group was [redacted] months, and [redacted] months in the previously-treated group, compared to 4.0 months in the only other METex14 skipping study to report chemotherapy outcomes.

However, the median OS of the chemotherapy real-world cohort appears to be overstated compared to the METex14 skipping studies, as well as the wildtype clinical trials. This discrepancy is likely due to the fact that a higher proportion of patients in the chemotherapy cohort received a least one subsequent treatment compared to the other treatment cohorts ([redacted]% for chemotherapy versus

	[redacted]% for tepotinib in VISION for the line-agnostic group, with similar proportions in the previously treated group, see Table 58 of the CS, and 54 of the Appendix), and this included crizotinib, which is not available in the UK for METex14 skipping patients ([redacted]% for chemotherapy versus [redacted]% for tepotinib in VISION) which is known to improve survival in patients with METex14 skipping NSCLC.[24] When patients with subsequent treatments are removed from the analysis in exploratory analysis, the OS is indeed much lower (Figure 1), and as expected, the PFS does not change substantially (Figure 2). This difference in subsequent treatments was accounted for in the subsequent treatment costs applied in the model in the original CS, and was expected to be a conservative comparison for tepotinib, as the comparator survival would be overstated compared to tepotinib. The impact of subsequent treatments in the chemotherapy cohort is explored further in the Appendix **2**, with also an explanation of the limitations of this analysis. **Figure 1. OS for patients in previously-treated chemotherapy group, for patients who had a subsequent treatment versus those who did not**

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Figure 2. PFS for patients in the previously-treated chemotherapy group, for patients who had a subsequent treatment versus those who did not

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Discussion of the survival benefit for tepotinib over immunotherapy and chemotherapy

The ACD (Section 3.7) suggested that there might not be a survival benefit for tepotinib over chemotherapy or immunotherapy, possibly due to the lack of statistical significance in the OS outcomes. Firstly, it is worth highlighting that tepotinib showed numerically greater OS compared to both chemotherapy and immunotherapy, in both the line agnostic and previously treated groups. Tepotinib also had statistically greater PFS compared to both immunotherapy and chemotherapy across all groups.

Chemotherapy: The rare nature of the disease and the low patient numbers mean that the wide confidence intervals for OS are to be expected, and likely to be observed in any comparison using observational data in a rare disease with few patients. It has already been shown that the outcomes for the chemotherapy real-world cohort specifically are likely to be overstated compared to previous studies in the METex14 population and clinical trials in wildtype NSCLC, and in reality, the survival difference between tepotinib and chemotherapy is expected to be greater. This was confirmed by four clinical experts interviewed at a UK advisory board, who expected the chemotherapy outcomes to be lower, and therefore a larger survival benefit for tepotinib was expected (as a targeted MET inhibitor treatment for the specific METex14 skipping mutation) over chemotherapy, across lines of therapy. Therefore, the suggestion in the ACD that there might not be a survival benefit for tepotinib over chemotherapy is clinically implausible.

Immunotherapy: With immunotherapy, the patients in the real-world cohort also received high rates of subsequent treatments, and it is known that METex14 skipping NSCLC patients treated with immunotherapy tend to respond poorly (particularly in PFS and response rates, but observed for OS too). Therefore, the OS benefit observed for tepotinib over immunotherapy is expected to be the minimum observed, and in reality could be expected to be greater. This expectation of at least similar OS, and likely greater, for tepotinib compared to immunotherapy in clinical practice was also confirmed with three clinical experts at recent interviews conducted to inform this ACD response. Tepotinib also had a statistically significant PFS compared to immunotherapy.

Finally, the ACD also compared the OS curves of the real-world cohort treated with immunotherapy vs. those treated with chemotherapy. Due to the low patient numbers and rare nature of the mutation, as

well as the differences seen between the immunotherapy and chemotherapy cohorts (e.g. in subsequent treatments, discussed above) the outcomes from these two comparisons should not be compared directly. Instead they are both used to inform separate comparisons versus tepotinib, where propensity score weighting was used to generate unbiased comparisons between tepotinib and the specific comparator arm. This was not performed between the chemotherapy and immunotherapy groups, and so naïve comparisons between these two comparator arms are not statistically robust or validated.

In conclusion, Merck acknowledge there is uncertainty in the use of the observational data, particularly in the chemotherapy data where outcomes were higher than expected and not aligned to NHS practice. Therefore, an alternative ITC has been explored, using clinical trial data in wildtype NSCLC, as discussed in the ACD and confirmed with NICE.

Comparison of VISION to clinical trial data in wildtype NSCLC

Summary

- **In Section 3.7 of the ACD, it was suggested that the company could consider basing the indirect treatment comparisons on data from comparator trials in people without specific oncogenic biomarkers (wildtype NSCLC).**
- **Merck acknowledge the limitations associated with the lack of METex14 skipping data for chemo-immunotherapy in the untreated setting (the most relevant comparator in this appraisal), as well as for chemotherapy in the previously-treated setting, where the OS observed in the METex14 skipping real-world cohort was longer than expected. However, the immunotherapy monotherapy comparison using the real-world cohort data is still appropriate and in line with clinical expectations.**
- **Although it remains best practice to compare within the METex14 skipping population where possible, Merck have updated the ITC using matching-adjusted indirect comparison (MAIC) methodology, to compare tepotinib to clinical trials in wildtype NSCLC, for the key comparator (chemo-immunotherapy: pembrolizumab + pemetrexed + platinum, untreated patients, PD-L1<50% and ≥50%) as well as supplementary analyses for pembrolizumab monotherapy (untreated, PD-L1≥50%), and docetaxel +/- nintedanib in the previously treated setting (PD-L1<50% and ≥50%).**
- **In the MAIC, tepotinib demonstrated numerically greater median OS and PFS to chemo-immunotherapy, as well as greater OS for up to 24 months and consistently greater PFS for the whole time period, with similar results when compared to immunotherapy monotherapy. Tepotinib also shows substantially greater OS and PFS compared to docetaxel +/- nintedanib in the previously-treated setting. All MAIC results are in line with clinical expert expectations as well.**
- **Nonetheless, this remains a challenging comparison due to the large differences in patient characteristics between VISION and comparator clinical trials in wildtype NSCLC, where patients in VISION are much older and with fewer ECOG 0 patients. This is why population adjustment methodology was required over a naïve comparison. Furthermore, immunotherapy (including chemo-immunotherapy) is expected to perform worse in patients with METEx14 skipping NSCLC compared to the wildtype data used, based on previously published studies and clinical expert opinion.**
- **In conclusion, tepotinib has shown strong clinical benefit compared to the main comparator chemo-immunotherapy, as well as in all supplementary comparisons to other comparators. In addition to the clinical benefit seen, tepotinib will provide an oral option which can be taken at home, instead of frequent infusions in hospital associated with immunotherapy +/- chemotherapy, which provide a resource and capacity burden on the NHS. Finally, tepotinib provides a safe and tolerable option for these elderly patients, instead of the high toxicity burden associated with chemo-immunotherapy and chemotherapy.**
- **For the base-case chemo-immunotherapy comparison and the supplementary previously treated comparisons to docetaxel +/- nintedanib, Merck believe the comparisons to wildtype clinical trial data provides the best data source for the committee's decision making. However for the supplementary immunotherapy comparison, Merck believe the real-world cohort data remains a more robust comparison in the METex14 skipping population compared to the MAIC analysis, specifically.**

In this section, Merck discuss the ITC updates that were conducted based on feedback from the ACD, as well as the company's position on the most relevant and clinically plausible data to inform each of

chemo-immunotherapy, chemotherapy and immunotherapy comparisons versus tepotinib. Then the methodology of the updated ITC is described, and finally results reported. More detail on the updated ITC can be found in the Appendix also provided.

Company position on use of real-world data and updated analysis using clinical trial data in wildtype NSCLC for comparator data in ITC

The ACD noted that:

- "*The clinical experts considered that the overall survival results from the indirect treatment comparisons did not reflect what would be expected in clinical practice, particularly for chemotherapy. The committee agreed that the results of the indirect treatment comparisons were inconsistent and counter to expectations…*" (Section 3.7)
- "*The clinical experts and Cancer Drugs Fund clinical lead suggested that the company could consider basing the indirect treatment comparisons on data from comparator trials in people without specific oncogenic biomarkers. This may be more robust as it would allow larger comparator patient numbers. The committee agreed that these analyses may have value, but acknowledged that there would be uncertainty because the comparator trial populations would be different to that of tepotinib*." (Section 3.7)
- "*Because chemo-immunotherapy was the most relevant comparator (see section 3.4), the committee would also have liked to have seen a more robust indirect treatment comparison of tepotinib with chemo-immunotherapy*." (Section 3.7)

<u>Chemo-immunotherapy</u>

The ACD conclusion that chemo-immunotherapy is the most relevant comparator is consistent with clinical feedback given to Merck, where in this setting, most patients are given chemo-immunotherapy (specifically pembrolizumab plus pemetrexed plus platinum chemotherapy).

The previous approach taken by the company for this comparison was to use a hazard ratio from KEYNOTE-189, and apply it to the METex14 skipping chemotherapy data, as there was extremely limited data available in the METex14 skipping NSCLC population from the real-world cohorts and in every possible data source explored by Merck. However because of the unexpectedly high OS outcomes in the chemotherapy data, this also overestimated the chemo-immunotherapy outcomes, as discussed in the ACD. Tepotinib was still cost-effective in this comparison, nonetheless, Merck agrees with the suggestion that a comparison to wildtype NSCLC data for this treatment would allow for an alternative and more robust comparison to the main comparator, in the absence of specific METex14 skipping data.

This comparison has been provided below, however it is worth highlighting that METex14 skipping patients are still expected to perform poorer to compared to published chemo-immunotherapy results in wildtype NSCLC, based on clinical expert feedback, and there are very different patient characteristics between VISION and the relevant chemo-immunotherapy trial. Nonetheless, in the absence of specific data, Merck believe this remains the most appropriate data source for the committee's decision making given the feedback in the ACD.

<u>Chemotherapy</u>

In the previous section, the company presented extensive validation of the real-world data outcomes versus published studies, and agree with the clinical experts that OS in the chemotherapy group is higher than expected in NHS clinical practice as noted in the original submission. The uncertainty does not work in the favour of tepotinib (as the comparator outcomes are likely overstated, due to more aggressive treatments mixes and higher proportions of subsequent treatments) and so the company's original position was that this is conservative for tepotinib, and updating this analysis would only work more in tepotinib's favour. However, Merck appreciates the limitations associated with the clinically implausible chemotherapy OS curves from the observational studies, which are unlikely to be seen in

	NHS practice (without extensive use of MET inhibitors as per the real-world cohort). Based on clinical feedback stating that the vast majority of patients receive docetaxel + nintedanib with a few receiving docetaxel monotherapy, Merck have conducted additional comparisons to clinical trial data in wildtype NSCLC for docetaxel +/- nintedanib in the previously-treated setting. Very few patients are expected to receive chemotherapy at first-line according to clinical feedback, so these comparisons have not been updated using clinical trial data, which was agreed with NICE. As this is not the main comparison (most patients are expected to receive tepotinib at first line, and so first-line comparisons are the most relevant, as discussed in the ACD and in Comment **1** and **4** above), the comparisons are considered supplementary and have been provided in Appendix **2**. <u>Immunotherapy monotherapy</u> As highlighted in the above section, the real-world immunotherapy monotherapy outcomes, particularly for the relevant untreated METex14 skipping NSCLC population, are closely aligned to outcomes in previous studies in METex14 skipping NSCLC, as well as in expectations compared to clinical trials in wildtype NSCLC. Furthermore, the treatment mix was reflective of NHS practice. As part of the ACD response, Merck discussed this data source and outcomes with clinical experts, who all stated that using this METex14 skipping data was appropriate for immunotherapy monotherapy specifically. Therefore, Merck still consider this comparator data source and ITC to be relevant and appropriate for any comparison to immunotherapy monotherapy within the appraisal. Merck have now updated this comparison using the VISION A+C cohort and incorporating the French/GFPC data set within the real-world data set, described in detail in Appendix **2**. Nonetheless, as NICE have suggested the exploration of wildtype NSCLC comparisons, Merck has also conducted a comparison to pembrolizumab monotherapy specifically (PD-L1≥50%). Again, this is not the main comparison, as highlighted in the ACD. Most patients are expected to receive chemo-immunotherapy at first line, with only a small percentage of patients receiving immunotherapy monotherapy, based on PD-L1 expression above 50%. This was confirmed with clinical experts as well, who also stated that specifically in METex14 skipping NSCLC, clinicians would be very reluctant to use immunotherapy monotherapy. Furthermore, this comparison is not as relevant in the METex14 skipping population, as METex14 skipping specific data for immunotherapy monotherapy is available and aligned to clinical expectations. Nonetheless, the supplementary wildtype clinical comparison has been provided in the Appendix as well. Clinical expert opinion highlighted that very few patients receive immunotherapy at second-line, so these comparisons have not been updated using clinical trial data. These four comparators described above (pembrolizumab + pemetrexed + platinum; pembrolizumab monotherapy; docetaxel; docetaxel + nintedanib) were presented to NICE ahead of the ACD response, and confirmed as the relevant comparators for the ITC update. **Selection of comparators and clinical trials for comparisons of VISION to clinical trial data in wildtype NSCLC** To identify the relevant clinical trials for each of these comparisons, the company used the previous literature review conducted as part of the CS, and presented in Appendix G of the CS. Specifically this was the review of previous NICE appraisals in NSCLC (G.1.2). For each of the four comparators, the relevant NICE appraisal was identified, and the pivotal trial used within that appraisal was extracted (presented in Table 4 below). Each clinical trial identified was presented to three clinical experts, to be confirmed as the relevant clinical trial in wildtype NSCLC for use within the ITC. For pembrolizumab + pemetrexed + platinum, pembrolizumab monotherapy and docetaxel + nintedanib, the pivotal trial identified was aligned to the clinical expert opinion. However, for docetaxel monotherapy, 5 clinical trials were identified which could be used within the ITC, as docetaxel is often the comparator in RCTs for previously-treated NSCLC. The clinical experts were asked which trial should be selected for use within the ITC as the most relevant compared to tepotinib, and the rationale for this. The details of this, and the final selection, are summarised in Appendix **2**.

Table 4 presents the final comparators, clinical trials used within the ITC, and relevant associated subgroups.

Table 4. Comparator treatments, relevant clinical trials and subgroups, for use within the updated ITC in wildtype NSCLC

Comparator treatment	Relevant Technology Appraisal	Clinical trial used within updated ITC	Clinical trial reference used	Line of therapy	PD-L1 subgroups	Histology subgroups†
Base case, main comparison						
Pembrolizumab + pemetrexed + platinum	TA683[25]	KEYNOTE-189	Rodríguez-Abreu et al. 2021[16]	Untreated patients	All (>50%, <50%)	Non-squamous
Supplementary comparisons						
Pembrolizumab	TA531[26]	KEYNOTE-24	Reck et al. 2021[15]	Untreated patients	≥50%	Non-squamous or squamous
Docetaxel + nintedanib	TA347[27]	LUME-Lung 1	Reck et al. 2014[28]	Previously treated	All (>50%, <50%)	Adenocarcinoma
Docetaxel monotherapy	N/A*	TAX 320	Fossella et al. 2000[29]	Previously treated	All (>50%, <50%)	Non-squamous or squamous

*Docetaxel monotherapy was not identified with a relevant TA on the NICE website. Instead it was identified as a comparator treatment in a number of TAs in previously treated wildtype NSCLC (TA124, TA428, TA347, TA484, TA520, TA655).
†As per the ACD, non-squamous NSCLC is the key population for this appraisal. However not all clinical trials identified were in solely non-squamous NSCLC, although the clinical trial for the key comparator, pembrolizumab + pemetrexed + platinum, was in non-squamous patients only. For the other clinical trials, the MAIC was conducted using histology as a characteristic to match on, so the high prevalence of non-squamous patients in VISION was adjusted and accounted for within the MAIC where appropriate. Therefore, any small differences in histology have been accounted for across all comparisons.

Other comparisons

There were several comparisons that were initially presented in the CS that are not included in the revised ITC, for example first-line chemotherapy, and second-line immunotherapy. Due to time limitations and importantly, due to the fact that these comparisons do not reflect routine NHS practice, according to clinical expert feedback, they were not included in the new ITC and therefore not presented in this ACD response.

Methodology of updated indirect treatment comparison: Matching adjusted indirect comparison (MAIC)

Appendix **2** reports the full methodology and results of the MAICs conducted as part of the ACD response. A short summary of the methodology and results are given below, with a focus on the chemo-immunotherapy comparison, as the most relevant comparator to tepotinib, as detailed in the ACD.

In order to compare to the published studies, MAIC methodology was performed. MAIC was selected as the preferred methodology, as it works by weighting all patients in the individual patient data (VISION), such that the (selected) aggregate characteristics (from the clinical trials) match between groups. The assumption implicit being that should patients be identical in observed characteristics, the outcomes should be comparable, provided all important characteristics are matched on. The large differences in patient characteristics between VISION and the comparator clinical trials meant that this adjustment was required over a naïve comparison. This approach also is similar to the comparisons made previously using patient level data in the original submission (propensity score weighting). The treatment groups were balanced on all characteristics available from the list of important prognostic factors provided by clinicians for the original submission (for use in propensity scoring), which is reproduced below:

- Percentage of patients previously untreated

- ECOG
- Age (in published studies this is given variously as mean, median, % over 65)
- Sex
- Adenocarcinoma
- Smoking
- Metastatic vs advanced

MAICs were implemented matching on all characteristics available in each comparison.

For each comparison, patient characteristics were collected from each study (from Table 4 above), compared to the VISION (A+C) data and used to weight the VISION patients to match the reported patients of the comparator study.

Results of the MAIC

Chemo-immunotherapy

When comparing patient characteristics from VISION to the KEYNOTE-189 study, large differences in the populations were noted (see separate Appendix **2** for details), including for age (median 74 years for VISION versus 65 for KEYNOTE-189) and ECOG (ECOG 0, 28% versus 45%). Therefore as mentioned, MAIC was required to ensure like-for-like comparisons were performed between the different patient populations. As a result of the differences between populations, a large quantity of the sample size was lost when re-weighting VISION patients: from 148 untreated patients to an effective sample size (ESS) of 38.7. Despite this, the matching was successful, with matching on all reported variables achieved, creating a comparison which removes as much difference possible between the groups in prognostic characteristics.

The outcomes of this comparison are presented below in Table 5.

Table 5. MAIC outcomes comparing VISION A+C to KEYNOTE-189

	VISION A+C (weighted) (n=148; ESS = 38.7)	KEYNOTE-189 (pembrolizumab + pemetrexed + platinum (n=410)
Progression-free survival		
Median, months (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
p-value	[redacted]	
Overall survival		
Median, months (95% CI)	[redacted]	[redacted]
Hazard ratio (95% CI)	[redacted]	
p-value	[redacted]	

Key: CI, confidence interval; ESS, effective sample size; NA, not available

Compared to pembrolizumab + pemetrexed + platinum, tepotinib is shown to have a numerically greater median PFS, with an improvement of [redacted] months, nearly at the 5% significance level. On the Kaplan-Meier graph in Appendix **2** (Figure 13) tepotinib showed consistently greater PFS for the whole time duration. Tepotinib is also shown to have a numerically greater median OS ([redacted] months improvement), and on the Kaplan-Meier graph in Appendix **2** (Figure 13), tepotinib shows greater OS for the first 24 months, with similar OS after that time point.

Limitations

The main limitation of this comparison is that the comparison is between wildtype NSCLC and

	METex14 skipping NSCLC. Therefore, the matching conducted does not account for the presence of the METex14 skipping mutation. METex14 skipping was not collected or reported in KEYNOTE-189, and is only present in ~3% of NSCLC cases, and so the trial is expected to only contain a small number of METex14 skipping patients (if any at all). Therefore, the poorer performing patients in KEYNOTE-189 are expected to be closer to the METex14 population. For example, in KEYNOTE-189 patients over 65 years had an OS hazard ratio (comparing pembrolizumab + pemetrexed+ platinum versus pemetrexed + platinum) of 0.72 compared to 0.49 in the below 65 years group. As discussed previously, METex14 skipping is a known independent prognostic factor that predicts poorer survival in NSCLC,[30] particularly for immunotherapy-treated patients,[12] and so when even adjusting for age and other characteristics, the results of this comparison are likely to underestimate the OS and PFS benefit for tepotinib, which could be expected to be even greater. The other main limitation of this MAIC is that although the key prognostic factors were successfully matched (outside of METex14 skipping status), the differences between populations should be noted, and this results in a largely reduced sample size. There are some other differences which also cannot be adjusted such as PD-L1 status (which was not captured in the VISION trial). **Discussion** ***Base case comparison*** As noted in the ACD, chemo-immunotherapy in the untreated setting was considered the most relevant comparison for tepotinib in this appraisal. Given the limited data in the METex14 skipping real-world cohort for chemo-immunotherapy, an alternative method using wildtype NSCLC data was used to inform this comparison, with VISION data re-weighted to match KEYNOTE-189 for key prognostic factors including age, ECOG and sex. The results show that tepotinib has at least a comparable OS and a consistently greater PFS when patient characteristics are matched. This is in line with feedback from three clinical experts interviewed who all expected tepotinib to have greater PFS and OS compared to chemo-immunotherapy in a matched population, based on the tepotinib clinical data and targeted mechanism of action. Therefore, this provides a more robust comparison than the previous approach for chemo-immunotherapy presented in the original CS, with increased certainty in the comparator outcomes using the best available source for chemo-immunotherapy (clinical trial data), whilst also ensuring as close a match as possible in prognostic patient characterises between the different patient cohorts. Despite the limitations noted, the results demonstrate that tepotinib provides an important alternative to chemo-immunotherapy, based on better PFS and at least similar OS, whilst also targeted to the patient's specific mutation. Furthermore, tepotinib has a number of important patient-friendly benefits, including oral administration, allowing tepotinib to be taken at home, whereas chemo-immunotherapy requires patients to come into hospital for frequent, burdensome infusions. Furthermore, tepotinib has a much improved side-effect profile compared to chemo-immunotherapy, highlighted by clinical experts and in the ACD. Therefore, as well as the demonstrated PFS and OS compared to chemo-immunotherapy, tepotinib offers an important patient-friendly alterative in this elderly population. ***Supplementary comparisons*** The supplementary comparisons conducted by Merck are described in Appendix **2**. Although not the most relevant comparators to tepotinib, as per the ACD, they are included for completeness to further demonstrate tepotinib clinical effectiveness and address uncertainties discussed at the ACM. A number of comparisons to immunotherapy monotherapy are presented in Appendix **2**. However the ACD highlighted that this is not the main comparator for tepotinib, and this has been confirmed by three clinical experts interviewed by the company. They highlighted that most patients received chemo-immunotherapy anyway in wildtype NSCLC, and within the METex14 skipping population specifically, the poor response of patients to immunotherapy monotherapy means that clinicians would prefer to treat with chemo-immunotherapy in the absence of a targeted therapy. Nonetheless, in summary, tepotinib shows numerically greater PFS and similar OS compared to pembrolizumab monotherapy, using wildtype NSCLC clinical trial data (PD-L1≥50%). However the real-world cohort analysis in the METex14 skipping population has also been updated, which presents OS estimates that are aligned with the METex14 skipping population, and therefore, a much more appropriate comparison for

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	immunotherapy monotherapy, where tepotinib shows statistically greater median PFS and similar OS. Finally, comparisons to docetaxel +/- nintedanib in the previously treated setting are also presented in Appendix **2**. Tepotinib shows substantially greater OS and PFS to both, highlighting the large and important benefit tepotinib can offer patients in the previously-treated setting, where currently only poorly tolerated chemotherapy options are available, with limited clinical benefit and a high unmet need.
7 Economic model update: survival extrapolation	**ACD Section 3.9, page 12–23: *The comparator overall survival extrapolations are implausible, particularly for chemotherapy and chemo-immunotherapy*** As discussed in response to Comment **6**, new indirect treatment comparisons have been conducted to compare tepotinib to specific comparators in wildtype NSCLC to alleviate the uncertainty associated with the real-world data. Parametric survival models (PSMs) have been fit to the pseudo-patient level data derived from digitising the latest published OS and PFS Kaplan-Meier data for each comparison (see Table 4). For tepotinib, parametric survival curves were fit to the Kaplan-Meier data from VISION (Cohort A + C) after re-weighting to each of the published studies, and all options validated extensively with three clinical experts. Given that the untreated population in comparison to pembrolizumab + pemetrexed + platinum is considered the most relevant comparison, the curve selections presented here are focused on this comparison. Details of the curve selections for the other comparisons are presented within Appendix **1**. **Pembrolizumab + pemetrexed + platinum** To inform the efficacy of pembrolizumab + pemetrexed + platinum, three-year trial data was digitised from the latest KEYNOTE-189 publication.[16] Pseudo patient-level data was then created using the Guyot algorithm. PSMs were fitted to OS and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate over a life-time horizon. Visual fit, along with AIC/BIC score and clinical opinion of long-term estimates were then used to inform the most appropriate curve to take forward for the base case. ***Overall survival*** The statistical goodness of fit scores are presented in Table 6. Based on AIC and BIC scores, the Weibull distribution is the best fitting, however all models except log-normal provide reasonably similar fits (within five points) and so were visually compared in Figure 3. **Table 6: Statistical goodness-of-fit scores – KEYNOTE 189 – OS** Parameterisation / AIC / BIC / Rank (AIC / BIC) Exponential: 2260.89 / 2264.91 / 5 / 2 Weibull: 2256.10 / 2264.13 / 1 / 1 Gompertz: 2258.74 / 2266.77 / 3 / 3 Log-logistic: 2259.04 / 2267.07 / 4 / 4 Log-normal: 2271.88 / 2279.91 / 6 / 6 Generalised gamma: 2257.84 / 2269.89 / 2 / 5 Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival All curves appeared to fit the data well apart from the last few events of the Kaplan Meier data from year 3, which is likely driven by censoring at data cut off. Clinical expects consulted as part of the response to the ACD expected that survival of patients with wildtype NSCLC treated with chemo-immunotherapy would be around 15-20% at five-years and around 5-10% at 10 years. Both log-logistic and log-normal sat within this plausible range, although estimated 10-year OS at the higher end of this clinical estimate range (8.2% and 9.2%, respectively). Clinical experts agreed that these curves were the most plausible for wildtype NSCLC. As such, based on goodness of fit, visual fit and long-term plausibility, log-logistic was selected to inform the base case OS, as this provided a better statistical and visual fit over log-normal. **Figure 3: Parametric curve fits – KEYNOTE-189 – OS**

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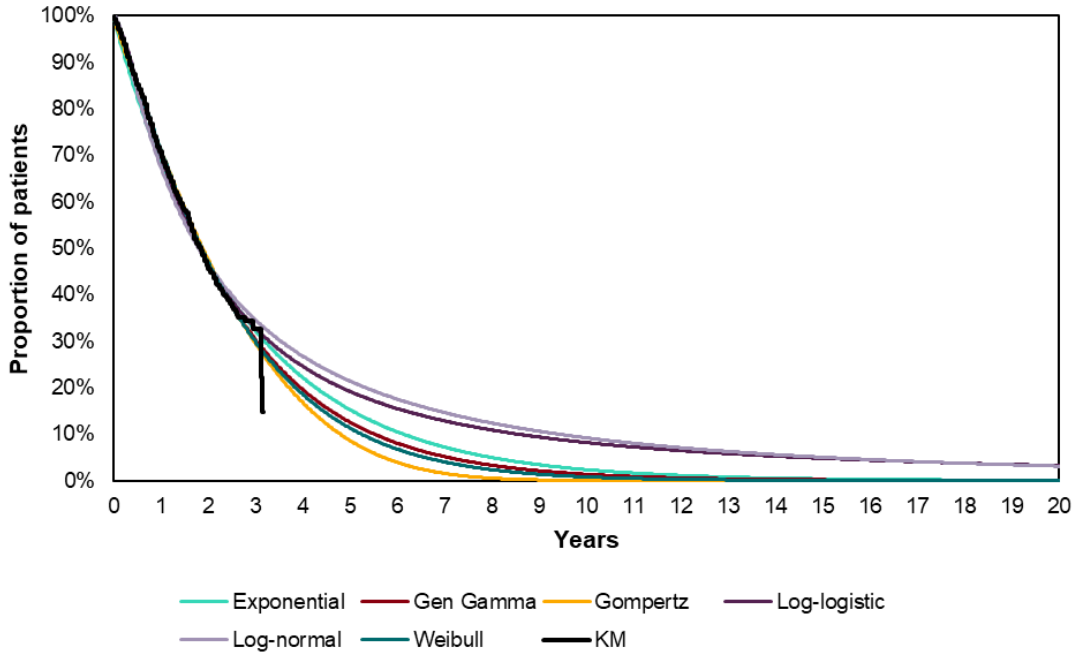

Key: KM, Kaplan-Meier; OS, overall survival

Progression-free survival

The statistical goodness of fit scores are presented in Table 7. Based on AIC and BIC scores, the log-normal distribution is the best fitting, closely followed by generalised gamma and log-normal which had reasonably similar fits (within five points). Therefore, the curves were visually compared in Figure 4.

Table 7: Statistical goodness-of-fit scores – KEYNOTE 189 – PFS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	2488.27	2492.28	5	4
Weibull	2487.46	2495.49	4	5
Gompertz	2489.51	2497.55	6	6
Log-logistic	2462.87	2470.90	3	2
Log-normal	2461.03	2469.06	1	1
Generalised gamma	2462.75	2474.80	2	3

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

All curves appeared to fit the data well throughout the observed period. Clinical expects consulted as part of the response to ACD expected that the PFS of patients with wildtype NSCLC treated with chemo-immunotherapy would be around 7.5-10% at five-years and around 2.5% at 10 years. Both log-logistic and log-normal were the closest to this plausible range, and clinical exerts thought that both of these curves were plausible. Given that log-logistic provided the higher of the two estimates and, based on goodness of fit, visual fit and long-term plausibility, log-logistic was selected to inform the base case PFS.

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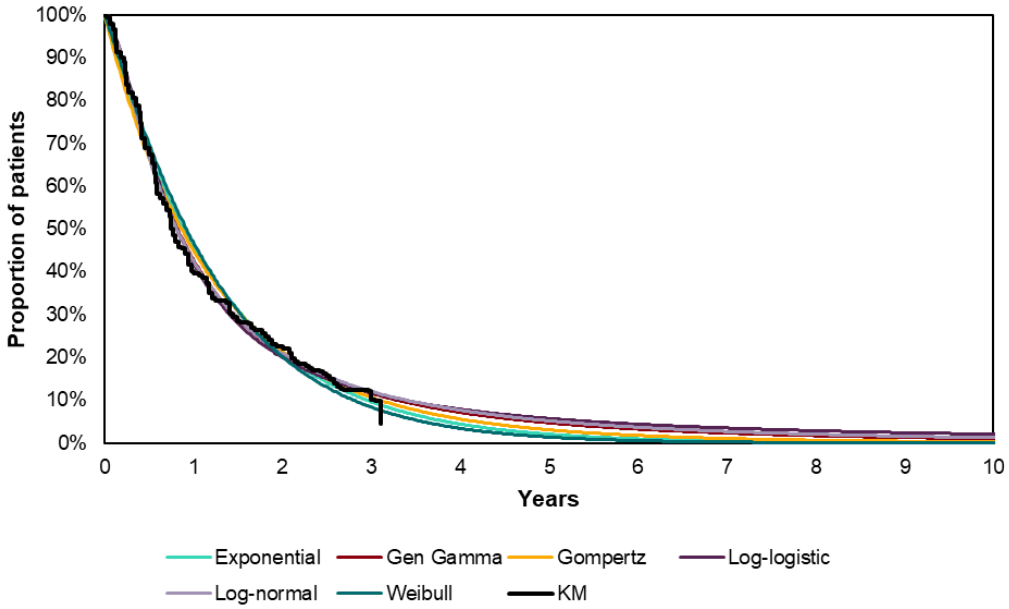
Figure 4: Parametric curve fits – KEYNOTE-189 – PFS



Key: KM, Kaplan-Meier; PFS, progression-free survival

Tepotinib

To inform the efficacy of tepotinib in comparison to pembrolizumab + pemetrexed + platinum, untreated VISION data (Cohort A+C) was matched to the KEYNOTE-189 clinical trial population.[16] PSMs were fitted to weighted OS and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate over a life-time horizon. Visual fit, along with AIC/BIC score and plausibility of long-term estimates were then used to inform the most appropriate curve to take forward for the base case.

Overall survival

The statistical goodness of fit scores are presented in Table 8. Based on AIC and BIC scores, the Weibull and exponential distributions are the best fitting, respectively, however all models provide reasonably similar fits (within five points) and so were visually compared in Figure 5.

Table 8: Statistical goodness-of-fit scores – VISION (weighted to KEYNOTE-189) – OS

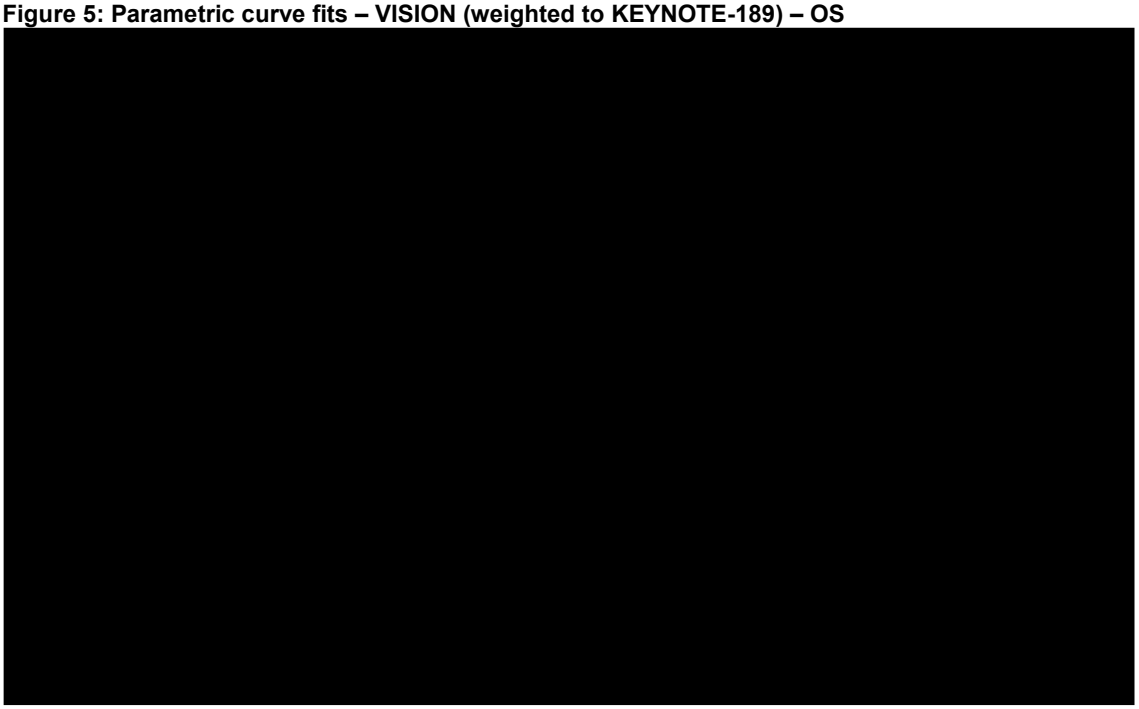
Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	210.74	213.74	3	1
Weibull	210.68	216.67	1	2
Gompertz	211.57	217.56	4	4
Log-logistic	210.69	216.68	2	3
Log-normal	212.45	218.45	5	5
Generalized gamma	212.64	221.63	6	6

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

All curves appeared to fit the data reasonably well until year 2 where the curves struggle to capture the large step in the KM which is likely driven by weighting of the VISION data and low ESS.

The three clinicians interviewed expected that survival of tepotinib would be least similar to that of patients treated with chemo-immunotherapy in a matched population, and likely greater for tepotinib, especially in the short term. As such, based on goodness of fit, visual fit and long-term plausibility, log-logistic was selected to inform the base case OS as this closely aligned with the pembrolizumab + pemetrexed + platinum estimates in the long term.

Figure 5: Parametric curve fits – VISION (weighted to KEYNOTE-189) – OS



Key: KM, Kaplan-Meier; OS, overall survival

Progression-free survival

The statistical goodness of fit scores are presented in Table 9. Based on AIC and BIC scores, the log-logistic and exponential distribution are the best fitting, respectively, however all models provide reasonably similar fits (within five points) and so were visually compared in Figure 6.

Table 9: Statistical goodness-of-fit scores – VISION (weighted to KEYNOTE 189) – PFS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	256.86	259.85	4	1
Weibull	257.54	263.54	5	4
Gompertz	258.85	264.85	6	5
Log-logistic	254.41	260.40	1	2
Log-normal	254.78	260.78	2	3
Generalized gamma	256.74	265.73	3	6

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

All curves appeared to fit the data well until around 1 year where the curves struggle to capture the large steps in the Kaplan Meier data, likely caused by the weighting of the tepotinib data and low ESS. Given that log-logistic had the best AIC and visually fits the data best towards the end of the KM, log-logistic was selected to inform the base case PFS. This also provides reasonable estimates when comparing against pembrolizumab + pemetrexed + platinum PFS, where clinicians expected tepotinib to have a greater PFS, as per the MAIC results.

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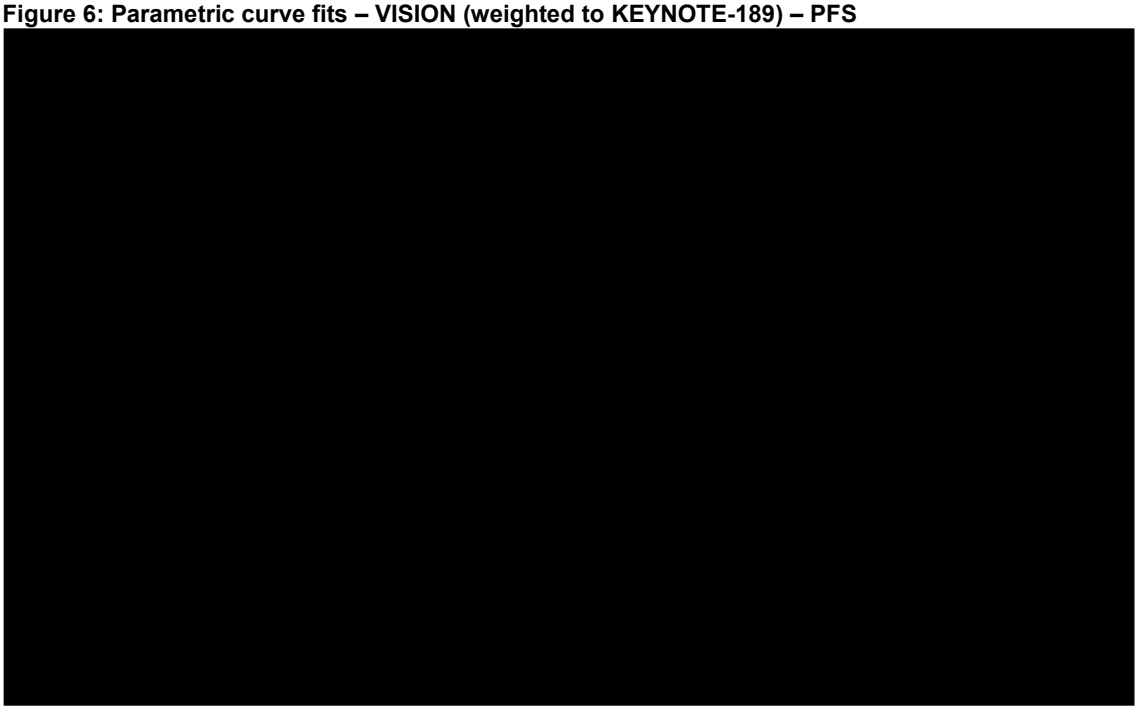
Figure 6: Parametric curve fits – VISION (weighted to KEYNOTE-189) – PFS



Key: KM, Kaplan-Meier; PFS, progression-free survival

Final base case

Figure 7 presents the final curves selected to inform the base case of tepotinib versus pembrolizumab + pemetrexed + platinum.

It is important to note that these curves reflect a wildtype NSCLC population. Patients with METex14 skipping mutations are expected to have poorer outcomes with immunotherapy, including chemo-immunotherapy. Furthermore, clinical experts highlighted that there is no evidence to suggest patients with METex14 skipping mutations treated with immunotherapy would respond any better when treated with chemo-immunotherapy, despite the difference in PD-L1 expression. As such, clinical experts interviewed expected METex14 patients to perform worse with chemo-immunotherapy compared to wildtype NSCLC, therefore the estimated differences between tepotinib and pembrolizumab + pemetrexed + platinum are conservative using the wildtype data, even after adjusting for patient characteristics.

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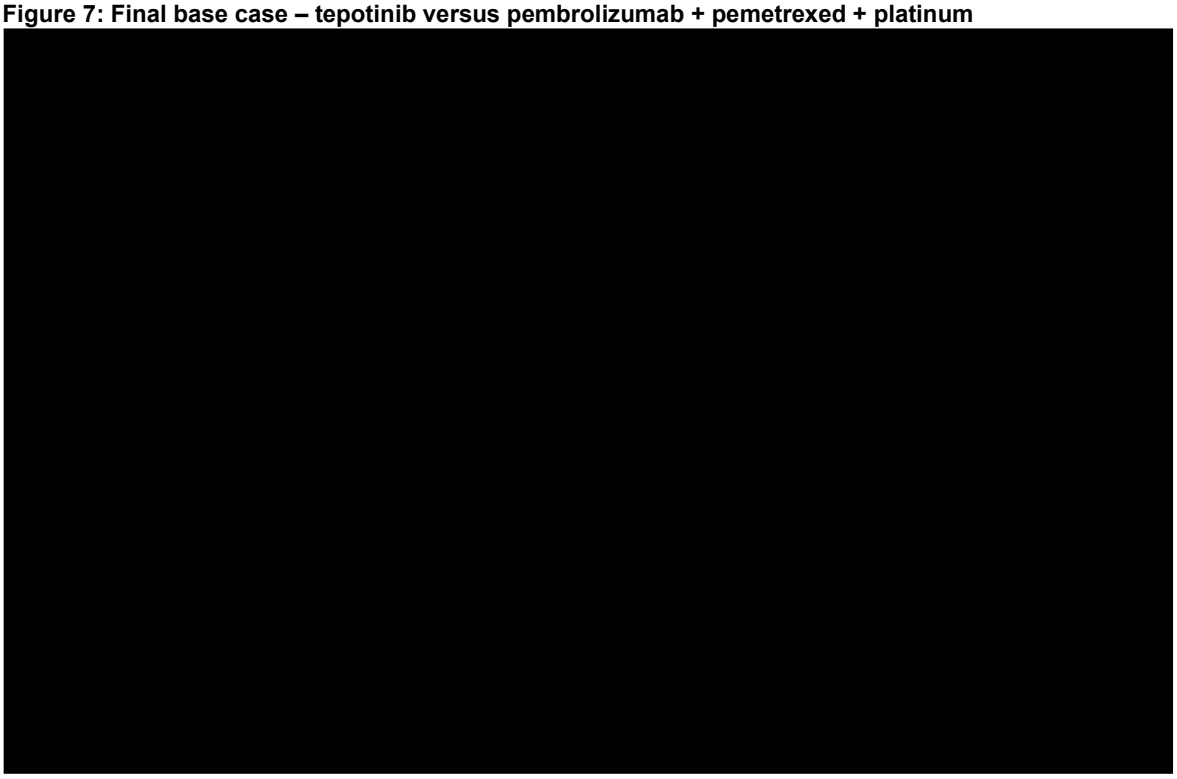
	Figure 7: Final base case – tepotinib versus pembrolizumab + pemetrexed + platinum  Key: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival
8 Economic model update: subsequent treatment	**ACD Section 3.10, page 13–14:** ***Separate subsequent treatment distributions based on prior treatment status, and for people having chemo-immunotherapy, are needed*** **Summary** • **The VISION trial and real-world cohort data were reflective of the subsequent treatment distributions that patients would receive in NHS practice for the most part, with the main exception being use of subsequent crizotinib or other MET inhibitors.** • **The company have elicited feedback from three clinical experts who advised on the expectations of subsequent treatments in NHS practice after tepotinib (untreated or previously treated groups) as well as the key comparators in the updated economic model.** • **The economic model has been updated to reflect NHS practice for subsequent treatment distributions, with a number of scenarios run to explore different possibilities in the subsequent treatment distributions.** As described in Comment **3,** VISION was mostly reflective of the subsequent treatments that patients would expect to receive in NHS practice after treatment with tepotinib, primarily immunotherapy or chemotherapy (platinum-based chemotherapy, or docetaxel +/- nintedanib) depending on line of therapy, prior treatment and PD-L1 expression. This was confirmed by clinical experts interviewed as part of the ACD response. The main exception was the minority of patients who received a subsequent MET inhibitor or another investigational treatment which are not used in the UK to treat METex14 skipping patients. This clinical feedback was similar for the real-world cohorts, where the majority of patients received chemotherapy or immunotherapy in the chemotherapy cohort, or chemotherapy alone in the immunotherapy cohort (Table 58 of CS Document B, Tables 36 and 54 of CS Appendix). Again, the main exception was the minority of patients who received a subsequent MET inhibitor. Nonetheless, the company have updated the subsequent treatment distributions in the base case

analysis for all comparators and tepotinib, in line with clinical feedback on standard NHS practice, based on interviews with three clinical experts. The details of the clinical expert feedback is presented in the ACD response Appendix **1**.

In the updated analysis, all patients are assumed to go onto subsequent treatments for simplicity (except for docetaxel +/- nintedanib). Where relevant, the subsequent treatment distributions accounted for prior treatment and PD-L1 expression. However, clinicians consulted as part of the ACD response said that not all patients would go onto subsequent therapy, and that it is more likely to be between 20% and 70% depending on subsequent therapy. Two of three experts said that under half of patients would go into subsequent therapy at all. Therefore, scenarios are considered assuming that only 50% patients go onto subsequent treatment in all treatment arms.

Otherwise, subsequent treatments are calculated in the same way as described in B.3.5.4.1 of the CS and applied as a one-off cost.

The subsequent treatment distributions and assumptions used in the updated economic model are detailed in Table 10 below.

Table 10. Subsequent treatment distributions used in the updated economic model, to reflect NHS practice following treatment with tepotinib and each key comparator

Treatment	Subsequent treatment distributions	Assumptions
Untreated patients		
Pembrolizumab + pemetrexed + platinum (untreated, PD-L1 <50%, ≥50%)	100%: Docetaxel +/- nintedanib (90% with nintedanib)	• All patients go on to docetaxel +/- nintedanib, with 90% for docetaxel + nintedanib and 10% with just docetaxel. However a scenario is included in the model where the split is 50/50 with/without nintedanib. • The subsequent treatments do not vary by PD-L1 according to the clinical experts.
Pembrolizumab monotherapy (untreated, PD-L1≥50%)	Second-line treatment: 100%: Platinum-based chemotherapy, specifically carboplatin + pemetrexed, Last-line treatment: 100%: Docetaxel +/- nintedanib (90% with nintedanib)	• All patients are assumed to go onto platinum-based chemotherapy, and then all go onto docetaxel +/- nintedanib • It is assumed that all patients received carboplatin + pemetrexed specifically, and a 90/10 split between with/without nintedanib. Scenarios have also been included with a different split with/without nintedanib (50/50). • The subsequent treatments do not vary by PD-L1 as this is only in the PD-L1≥50% group anyway.
Tepotinib (untreated, PD-L1 <50%, ≥50%)	Second-line treatment: 75%: Immunotherapy monotherapy (all pembrolizumab) 25%: Platinum-based chemotherapy (all carboplatin + pemetrexed) Last-line treatment: 100%: docetaxel +/- nintedanib (90% with nintedanib)	• Patients will either go on to immunotherapy monotherapy or platinum-based chemotherapy after tepotinib at first line, according to clinical expert feedback. • Based on clinical feedback, some clinicians will not prescribe immunotherapy monotherapy in the METex14 skipping population at all, due to the poorer associated outcomes. Therefore, the clinical feedback was that the split between subsequent immunotherapy and chemotherapy after tepotinib would range between 50% and 90% in favour of immunotherapy. The base case assumes 75%, however different splits are explored in scenarios. • All immunotherapy is assumed to be pembrolizumab, however scenarios are run where there is also a split between pembrolizumab, nivolumab and atezolizumab after tepotinib at first line.

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			• All patients eventually go onto docetaxel +/- nintedanib as a last-line treatment.
	Previously treated		
	Docetaxel monotherapy (previously treated, PD-L1 <50%, ≥50%)	No subsequent treatment	• Clinical expert feedback states this is the last line of treatment available to patients, so they just move onto best supportive care afterwards.
	Docetaxel + nintedanib (previously treated, PD-L1 <50%, ≥50%)	No subsequent treatment	• Clinical expert feedback states this is the last line of treatment available to patients, so they just move onto best supportive care afterwards.
	Tepotinib (previously treated, PD-L1 <50%, ≥50%)	<u>For those with 1L chemo-IO (80% of total):</u> Docetaxel +/- nintedanib (90% with nintedanib) as last line after tepotinib <u>For those with 1L IO (20% of total):</u> Platinum-based chemotherapy, specifically carboplatin + pemetrexed, then docetaxel +/- nintedanib (90% of these patients with nintedanib) as last line after tepotinib	• In line with clinical expert feedback, patients who have tepotinib at second-line will have had chemo-immunotherapy or immunotherapy monotherapy at first line, based on PD-L1 expression. • Patients who had chemo-immunotherapy at first line will go onto docetaxel +/- nintedanib after tepotinib. • Patients who had immunotherapy monotherapy will go onto platinum-based chemotherapy after tepotinib. They will then go onto docetaxel +/- nintedanib afterwards. • An estimated 30% of NSCLC patients are PD-L1≥50%,[31] but clinical feedback is that roughly a third of these patients will go onto chemo-immunotherapy anyway. So 80% are assumed to have chemo-immunotherapy and 20% immunotherapy monotherapy at first line.

A number of scenarios were developed to explore the ranges of subsequent treatment distributions given by the three recently interviewed clinical experts. Scenarios included in the updated economic model are:

- The split between docetaxel + / - nintedanib is 50% for docetaxel + nintedanib and 50% with just docetaxel rather than 90% versus 10%. The feedback from clinical experts is that the use of docetaxel can vary by NHS Trust and region.
- After tepotinib as a first-line treatment, 50% or 90% of patients go onto immunotherapy monotherapy, not 75%, in line with range given by clinical experts interviewed.
- After tepotinib as a first-line treatment, the immunotherapy split is a third pembrolizumab, nivolumab and atezolizumab, rather than all pembrolizumab.
- After tepotinib second-line treatment, 50% of patients go on to platinum-based chemotherapy, assuming a higher proportion of patients had pembrolizumab treatment up front, as clinical experts said this could also vary by NHS Trust and clinician preference.
- Only 50% of patients go onto subsequent treatment, in line with feedback from clinical experts that not all patients receive subsequent treatments in NHS practice.

9 Economic model update: ToT extrapolation	**<u>ACD Section 3.11, page 14: *There is uncertainty about the most appropriate time-on-treatment model for tepotinib, but the company's base case is likely appropriate*</u>** **Summary** • **Based on clinical feedback, the two most clinically plausible time-on-treatment (ToT) curves for tepotinib were the exponential model and generalised gamma** • **In the interest of being conservative for tepotinib, the company selected the ToT curve with higher estimates for tepotinib (generalised gamma). Scenario analyses using the other plausible curve, exponential, results in a decrease to the tepotinib ICER.**

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	Based on the UK advisory board, previously reported in the CS (Section B.3.3.3) and Technical Engagement response (Key Issue 12), clinical opinion indicated the majority of patients would be off tepotinib treatment at 5 years, with only small numbers of patients remaining on treatment at this time. This was confirmed by the three recent clinical expert interviews. The log-logistic curve provides one of the best fitting parametric statistical fit according to AIC and BIC (AIC rank 1, BIC rank 2) but predicts 4.3% of patients on tepotinib treatment at 5 years, which was considered too high by clinical experts. The exponential model provides the next best parametric statistical fit (AIC rank 3, BIC rank 1) and predicts 0.6% of patients on treatment at 5 years. The generalised gamma predicts 1.4% of patients on treatment at 5 years. The clinical experts thought that these lower estimates of long-term treatment were the most plausible (generalised gamma or exponential). In the interests of being conservative for tepotinib, of the two options, the company selected the curve which estimated a higher proportion of patients still on treatment at later time points, i.e., generalised gamma. However the company provided a scenario analysis which uses the exponential model for ToT in CS scenario analysis section (Table 64 and 65, Section B.3.8.3), which results in a decrease to the ICER.
10 End of life criteria: life expectancy	**ACD Section 3.12, page 14–15: *Life expectancy for people with METex14 skipping NSCLC is likely to be less than 2 years in the overall population*** **Summary** • **Merck agree that agree that the life expectancy of patients with advanced NSCLC harbouring METex14 skipping alterations is expected to be below 2 years, regardless of treatment.** • **However Merck also previously provided evidence that tepotinib meets end-of-life criteria in the previously-treated setting specifically. This has now also been presented for the updated wildtype clinical trial comparison as well.** • **Regardless of data source used, tepotinib meets end-of-life criteria in the previously-treated setting.** The ACD stated that "*Because it would prefer to consider the cost-effectiveness results for previously treated and untreated disease separately (see section 3.2), the committee concluded that although life expectancy for people with METex14 skipping NSCLC is likely to be less than 2 years in the company's base case population, this would not be used to inform its decision-making on the end-of-life criteria*. Merck agree that the life expectancy of patients with advanced NSCLC harbouring METex14 skipping alterations is expected to be below 2 years, regardless of treatment. Extensive evidence of this was provided in the CS (Section B.2.13.1) and the Technical Engagement response, and was confirmed by clinical experts interviewed. However, Merck did also provide analysis of end-of-life criteria by untreated and previously treated disease separately, as detailed in the Table 9 of the Technical Engagement response. This analysis demonstrated that tepotinib qualifies for end-of-life criteria in the previously-treated setting, regardless of treatment. The updated ITC and model results, using clinical trial wildtype data for docetaxel +/- nintedanib in the previously treated setting, as well as previously presented real-world cohort comparisons, are presented in Table 11 to Table 13 below. The ITC was not updated using previously treated immunotherapy data, as this was determined by clinical experts and in the ACD to not be a relevant treatment in the second-line setting, and also due to limited time for this response. However, the observational data outcomes for previously-treated immunotherapy is presented in the table below for completeness. This shows that regardless of data source used, tepotinib meets end-of-life criteria in the previously-treated setting. This is especially important for the clinical trial comparisons, which are now deemed to be more reflective of NHS practice. **Table 11. Mean and median survival for VISION versus docetaxel in the previously-treated group (PD-L1<50%, ≥50%)** **Evidence, months** | | **Tepotinib (weighted)** | **Docetaxel** MAIC results (Clinical trial /VISION) | Median | [redacted] | 6.0

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	CE model | Mean | [redacted] | 12.0 **Table 12. Mean and median survival for VISION versus docetaxel + nintedanib in the previously-treated group (PD-L1<50%, ≥50%)** **Evidence, months** | **Tepotinib (weighted)** | **Docetaxel + nintedanib** MAIC results (Clinical trial /VISION) | Median | [redacted] | 12.9 CE model | Mean | [redacted] | 17.6 **Table 13. Mean and median survival from real-world cohort comparisons in the previously-treated group (PD-L1<50%, ≥50%)** **Evidence, months** | **Tepotinib** | **Immunotherapy†** | **Chemotherapy** Observed data (ITC/VISION) | Median | [redacted] | [redacted] | [redacted] CE model | Mean | [redacted] | [redacted] | [redacted] *As highlighted in Key Issue 10 and Section B.3.2 of the company submission, the modelled mean OS and the median OS from the real-world cohorts is considered to be overstated for chemotherapy, likely due to the high number of subsequent treatments, and inclusion of subsequent treatments not seen in UK clinical practice (e.g. crizotinib for wildtype NSCLC or METex14 skipping NSCLC patients). Therefore, the modelled mean OS is considered to be the absolute maximum expected, and likely will be lower in practice. †Immunotherapy was determined by clinical experts to not be a relevant treatment in the second-line setting, however has been included here for completeness, as this was presented in the Technical Engagement response.
11 End of life criteria: survival gain	**ACD Section 3.13, page 15–16: *It is uncertain whether tepotinib extends life by more than 3 months, so it does not meet the end-of-life criteria*** **Summary** • **Merck have presented evidence that tepotinib provides a 3-month survival gain compared to all comparators in the real-world cohort, and the key comparators of docetaxel +/- nintedanib in the wildtype clinical trial comparisons for the previously treated population. This was confirmed with clinical experts, who all expected tepotinib to have at least a 3 month survival gain compared to docetaxel +/- nintedanib.** • **Regardless of data source used, tepotinib meets end-of-life criteria in the previously treated setting.** In Section 3.13 of the ACD, it stated: "*The committee agreed that because of the uncertainty in the data and the lack of a statistically significant overall survival benefit for tepotinib from the indirect treatment comparisons, the estimates of the extension to life for tepotinib were not sufficiently robust*" However the survival gain from the modelled mean (using curves for both chemotherapy and immunotherapy comparators which were deemed in the ACD to be optimistic) were all greater than 3 months. Statistical significance is not highlighted in the NICE Guide to the Methods of Technology Appraisal 2013 (wording below) as being a requirement for end-of-life criteria. Nonetheless, in the updated comparison to the relevant previously treated comparators (docetaxel +/- nintedanib), tepotinib has also shown a median OS benefit of substantially greater than 3 months ([redacted] and [redacted] months, respectively), and the modelled means show a benefit for tepotinib substantially greater than 3 months as well ([redacted] months and [redacted] months, respectively). **"*Section 6.2.10:*** *In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met:* • *the treatment is indicated for patients with a short life expectancy, normally less than 24 months and* • *There is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS*

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	treatment. As such, Merck has now provided comparisons in the previously-treated population using all possible data sources, i.e. in observational data in the METex14 skipping population, as well as clinical trial data in wildtype NSCLC. Taken together with evidence presented in Comment **10**, we demonstrate here that the 3-month OS gain is achieved in all comparisons in the previously treated-setting, using the modelled means. Therefore, for all of these comparisons, tepotinib is shown to meet end-of-life criteria, and this collectively represents the most robust and plausible analysis possible.
12 Economic model results	**ACD Section 3.14, page 16: A plausible ICER could not be determined because of problems with the company's modelling approach and uncertainty in the model parameters, so tepotinib is not recommended for routine use** The economic model has been updated to address the committee's concerns noted in Section 3.14 of the ACD, around the indirect comparison, survival extrapolations and subsequent treatment distributions. In summary: • New indirect treatment comparisons have been conducted comparing VISION to published wildtype NSCLC clinical trial data for the key comparators (see response to Comment **6**), including the main comparator chemo-immunotherapy. Where the real-world cohort data in the METex14 skipping population is still most appropriate (immunotherapy monotherapy comparison using RWD), this ITC has also been updated to include VISION Cohort A+C and an additional METex14 skipping dataset, to increase certainty • The survival extrapolations have also been updated to reflect the new and updated ITCs, which has been validated with three clinical exerts and deemed to be clinically plausible (please see Comment **7** and Appendix **1**) • Subsequent treatments have been updated to reflect NHS practice and expectations after tepotinib, based on clinical expert opinion (please see Comment **8**) Other updates to the economic model are covered in Appendix **1**, and include: • Updated patient characteristics to reflect the source clinical trial • Updated utility and adverse event data to reflect Cohort A+C for tepotinib • Removal of testing costs for squamous patients to reflect the relevant non-squamous population highlighted in the ACD response • A larger PAS for tepotinib has been submitted to PASLU (now [redacted]% off the list price). The model and all results have been updated to reflect this new PAS The updates and comparisons have been incorporated into the economic model to assess the cost-effectiveness of tepotinib to each comparator within both the untreated and previously treated populations. **Base case results for chemo-immunotherapy** As per feedback from the ACD, the most relevant comparator is chemo-immunotherapy (i.e., pembrolizumab + pemetrexed + platinum). Therefore, full cost-effectiveness results are presented for this comparison below. Supplementary deterministic results for the other comparisons are also presented in Appendix **1**. Table 14 presents the base case results for tepotinib compared to pembrolizumab + pemetrexed + platinum. The results show that tepotinib is projected to be less costly and more effective than pembrolizumab + pemetrexed + platinum (dominant) using the wildtype clinical trial data. Given the expectations of a worse response to chemo-immunotherapy in METex14 skipping NSCLC, tepotinib could be expected to be even more cost-effective if data were available for chemo-immunotherapy in this population.

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Table 14: Base case results – tepotinib versus pembrolizumab + pemetrexed + platinum

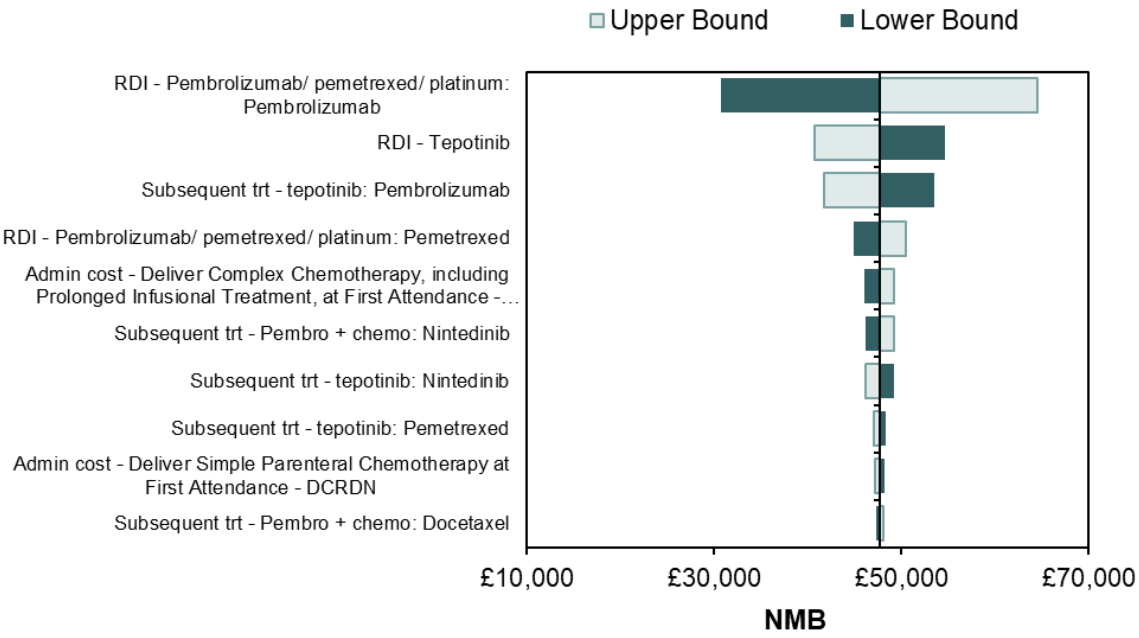
Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Tepotinib	[redacted]	4.26	[redacted]				
Pembrolizumab + pemetrexed + platinum	[redacted]	3.65	[redacted]	[redacted]	0.62	[redacted]	Dominant

Key: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years

One-way sensitivity analysis

Figure 8 present the tornado diagram showing the parameters with the greatest impact on the net-monetary benefit (NMB) after varying each parameter individually within their 95% confidence intervals. The inputs which had the most impact are the relative dose intensity (RDI) and proportion receiving subsequent treatments. However, all results demonstrated that tepotinib is cost-effective within the £30,000 willingness-to-pay (WTP) threshold.

Figure 8: Tornado plot – tepotinib versus pembrolizumab + pemetrexed + platinum (WTP = £30,000)



Key: DCRDN, day case regular day and night; NMB, net-monetary benefit; RDI, relative dose intensity; WTP, willingness-to-pay

Probabilistic sensitivity analysis

The mean results from the probabilistic sensitivity analysis (PSA) are presented in Table 15 with visual results presented in Figure 9. The probabilistic results are consistent with the deterministic results with all iterations showing tepotinib is cost-effective at the £30,000 threshold.

Table 15: PSA results – tepotinib versus pembrolizumab + pemetrexed + platinum

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Tepotinib	[redacted]	4.33	[redacted]				
Pembrolizumab + pemetrexed + platinum	[redacted]	3.64	[redacted]	[redacted]	0.69	[redacted]	Dominant

Key: ICER, incremental cost-effectiveness ratio; LYs, life-years; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted

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life-years

Figure 9: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus pembrolizumab + pemetrexed + platinum

Key: PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years

Figure 10 present the cost-effectiveness acceptability curve at different WTP thresholds. At the £30,000 threshold, the probability of tepotinib being cost-effective is 100%.

Figure 10: Cost-effectiveness acceptability curve – tepotinib versus pembrolizumab + pemetrexed + platinum

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Scenario analysis

To address the key uncertainties regarding long-term survival estimates and subsequent treatments, a number of scenarios were included, comprising:

- Each parametric curve selected for tepotinib and pembrolizumab + pemetrexed + platinum is varied in turn for OS and PFS
- A scenario assuming tepotinib has equal OS to pembrolizumab plus chemotherapy for the whole time period
- A number of scenarios for subsequent treatments described in Comment **8**.

Table 16: Scenario results – tepotinib versus pembrolizumab + pemetrexed + platinum

Parameter	Base case	Scenario	Incremental		ICERs
			Costs	QALYs	
OS - tepotinib	Log-logistic	Exponential	[redacted]	[redacted]	**Dominant**
		Gen Gamma			£255,979 (SW)
		Gompertz			£122,191 (SW)
		Log-logistic			**Dominant***
		Log-normal			**Dominant**
		Weibull			£183,747 (SW)
		Assume same as pembro + chemo			Dominant
PFS - tepotinib	Log-logistic	Exponential			Dominant
		Gen Gamma			**Dominant**
		Gompertz			Dominant
		Log-logistic			**Dominant***
		Log-normal			**Dominant**
		Weibull			Dominant
OS – pembro + chemo	Log-logistic	Exponential			Dominant
		Gen Gamma			Dominant
		Gompertz			Dominant
		Log-logistic			**Dominant***
		Log-normal			**Dominant**
		Weibull			Dominant
PFS – pembro + chemo	Log-logistic	Exponential			Dominant
		Gen Gamma			Dominant
		Gompertz			Dominant
		Log-logistic			**Dominant***
		Log-normal			**Dominant**
		Weibull			Dominant
Subsequent treatments – after tepotinib (untreated)	75% pembrolizumab; 25% platinum-based chemotherapy	50% pembrolizumab vs platinum chemotherapy	[redacted]	[redacted]	Dominant
		90% pembrolizumab vs platinum chemotherapy			Dominant
		75% immunotherapy split between pembrolizumab/ atezolizumab/nivolumab			Dominant
Subsequent treatments	90% docetaxel + nintedanib; 10% docetaxel monotherapy	50% docetaxel + nintedanib; 50% docetaxel monotherapy			Dominant
Proportion receiving subsequent treatment	100%	Assuming 50% receive subsequent treatment after progressing			Dominant

Key: ICERs, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life-years; SW, South-West quadrant, showing tepotinib is cost-effective by being cheaper with lower QALYs.
Bold: Clinically plausible curves based on the clinical expert estimates of OS and PFS
*Selected curve used in the base case model

Tepotinib remains cost-effective across all scenarios analysed.

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	When looking at chemo-immunotherapy OS, the ICER remains dominant when the other clinically plausible curve (log-normal) is selected. This remains true when the other clinically plausible PFS curve (log-normal) is selected. Similarly for the tepotinib OS curve, the three plausible curves based on clinical expert expectations of at least similar OS to chemo-immunotherapy (in line with MAIC results too) were log-logistic, exponential and log-normal. For the two curves not chosen (log-normal and exponential), tepotinib remains dominant. Similarly for the three plausible tepotinib PFS curves based on clinical expert feedback and MAIC results (log-logistic, log-normal, generalised gamma), tepotinib remains dominant. Even with the very conservative assumption that the OS for tepotinib and pembrolizumab + pemetrexed + platinum are equal throughout the time period, tepotinib remains dominant and therefore cost-effective. **Supplementary results** Supplementary economic results for the other comparators are presented in Appendix **1**. For all remaining comparisons, tepotinib remains cost-effective at the relevant £30,000 and £50,000 thresholds. **Conclusions** Tepotinib is clinically and cost-effective compared to the main comparator pembrolizumab + pemetrexed + platinum in the untreated setting, as well as in the supplementary comparisons that Merck have conducted to other treatments (Appendix **2**). Given that patients with METex14 skipping mutations have a poorer prognosis than in wildtype NSCLC, especially when on immunotherapy, the clinical and economic benefits are likely to be even greater for tepotinib compared to what is estimated from the MAICs based on a wildtype NSCLC population. These results support the conclusions presented in the initial submission and real-world METex14 skipping cohort comparisons, where tepotinib was shown to be cost effective to chemo-immunotherapy. Although data sources are limited, Merck have provided comparisons for both METex14 skipping data and clinical trial data in wildtype NSCLC, covering every possible data source available for this appraisal. For each one, we demonstrate the clinical and economic benefits associated with tepotinib. A number of scenarios have been analysed to address the uncertainty in the population and associated long term survival. In nearly all of these scenarios, and in all the clinically plausible scenarios based on expert feedback, tepotinib remains cost-effective, projecting lower costs than chemo-immunotherapy and greater QALYs. Furthermore, tepotinib was demonstrated to be budget saving for the NHS, by replacing more expensive chemo-immunotherapy, which was confirmed by NICE Budget Impact Analysis. Given the very limited timeframe we had to update the model with the new data and analyses, the focus of the results is on the untreated population from VISION versus pembrolizumab + pemetrexed + platinum, as this was confirmed as the most relevant comparison by the committee and clinical experts. However results for the other comparisons are presented for completeness in Appendix **2**, and demonstrates that tepotinib remains clinically and cost-effective against all comparators, again consistent with the previous analysis conducted in the METex14 skipping population comparing to the real-world cohort data.

Insert extra rows as needed

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Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [ID3761]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [ID3761]

Appraisal Consultation Document (ACD) response: Appendix 1

February 2022

File name	Version	Contains confidential information	Date
Tepotinib in NSCLC with MET gene alterations response Appendix 23Feb22	1	Yes – ACIC redacted	23 February 2022

Contents

Appendix 1a: Publications on tepotinib and METex14 skipping NSCLC in the UK

Cui. W et al. Tepotinib in patients with MET exon 14 skipping NSCLC: Results from the VISION study and local UK experience. Presented at the 20th British Thoracic Oncology Group (BTOG) Annual Conference | January 27 28, 2022[1]

In this presentation, updated outcomes from the VISION study were presented (Cohort A+C, February 2021 data cut) as well as local UK experience of using tepotinib, based on the Early Access to Medicines Scheme (EAMS) and compassionate use requests.

There were no UK study sites in VISION; however, some patients with METex14 skipping NSCLC received tepotinib through EAMS or compassionate use requests. This publication reported patient characteristics and responses for 15 UK patients with Stage IV METex14 skipping NSCLC. For these 15 patients:

- The age range was 43–89 years, although the majority of patients (11/15) were above 70 years, with 4 patients above 80 years
- PD-L1 expression was ≥1% in 12 patients, and ≥50% in eight patients
- 14/15 patients had adenocarcinoma histology, with 1 squamous histology patient
- Ten were treatment naïve and five were treatment experienced

Of ten patients who received tepotinib first line, seven had tumour responses, and three were still receiving treatment with ongoing partial responses at the time of publication.

A summary of the patient characteristics and responses are provided in Figure 1 and Figure 2. These data support the generalisability of VISION to the UK METex14 skipping population as the characteristics of the EAMS population aligns with those observed in UK practice and in VISION. These data also show the local UK patient experiences through EAMS, supporting the efficacy and tolerability of tepotinib in patients with METex14 skipping NSCLC.

Figure 1. UK patient cases*: Treatment naïve patients

Age, years	Smoking history	Metastatic sites	Histologic subtype	PD-L1 expression, %	*MET*ex14 skipping detection method	Time on treatment, months†	Adverse events
86	Never-smoker	Bone, lung	ADC	<1	LBx		Generalised oedema (Grade 1), DVT (Grade 2)
73	Ex-smoker	Lymph nodes, lung	ADC	100	TBx	→	Fatigue (Grade 1), oedema (Grade 1)
43	Ex-smoker	Lymph nodes, brain	ADC	100	TBx	→	Fatigue (Grade 1), myalgia (Grade 1), oedema (Grade 2)
77	Ex-smoker	Lymph nodes, lung, liver, bone, brain	ADC	95	LBx, TBx		Fatigue (Grade1), oedema (Grade 2)
75	Ex-smoker	Pleura	ADC	100	TBx	→	Keratoconjunctivitis sicca (Grade 1), peripheral oedema (Grade 1)
81	Ex-smoker	Adrenal glands, peritoneum, subcutaneous, muscle, bone	ADC	>60	LBx		Pneumonitis (Grade 3)
74	Ex-smoker	Adrenal glands, brain	SCC	1–2	LBx		Fatigue (Grade 1), alopecia (Grade 1), pleural effusion (Grade 2), low TFT (Grade 2), low cortisol (due to steroid use, Grade 2)
71	Ex-smoker	Pancreas, bone	ADC	>60	LBx, TBx		Nausea (Grade 1), vomiting (Grade 1), peripheral oedema (Grade 1)
87	Never-smoker	Pleura	ADC	>60	TBx		None
89	Never-smoker	Bone	ADC	<1	TBx	¶	None

Best response§: PR, SD, PD, N/A, → Ongoing

*UK patients received tepotinib outside of the VISION study, through EAMS and compassionate use requests. †Treatment ongoing as of January 2022 for two patients, and for one patient as of December 2021. One patient died due to non-neutropenic sepsis secondary to bronchopneumonia (unrelated to tepotinib) shortly after treatment initiation and, as such, response assessment was not available for this patient. §Best response as reported by the physician; criteria used for response assessment may have varied.
ADC, adenocarcinoma; DVT, deep vein thrombosis; EAMS, Early Access to Medicines Scheme; LBx, liquid biopsy; MET, mesenchymal-epithelial transition factor; METex14, MET exon 14; N/A, not assessed; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease; TBx, tissue biopsy; TFT, thyroid function test.

Figure 2. UK patient cases*: Previously treated patients

Age, years	Smoking history	Metastatic sites	Histologic subtype	PD-L1 expression, %	*MET*ex14 skipping detection method	Time on treatment, months	Adverse events
84	Never-smoker	Pleura	ADC	2	TBx	→	Pneumonitis (Grade 2), peripheral oedema (Grade 2), neutropenia (no fevers, Grade 2), pleural effusion (Grade 1)
66	Never-smoker	Pleura, lymph nodes, adrenal glands	ASC	1–49	LBx, TBx	→	Constipation (Grade 2)
58	Never-smoker	Lung	ADC	Negative	TBx	→	Lethargy (Grade 1), leg oedema (Grade 2)
66	Never-smoker	Lung, liver, bone, adrenal glands	ADC	75	TBx	§	None
71	Ex-smoker	Lung	ADC	1–49	TBx		None

Best response‡: PR, SD, PD, N/A, → Ongoing

*UK patients received tepotinib outside of the VISION study, through EAMS and compassionate use requests. ‡Best response as reported by the physician; criteria used for response assessment may have varied. §Response could not be assessed in one patient due to rapid deterioration shortly after treatment initiation; this patient died due to disease-related causes.
ADC, adenocarcinoma; ASC, adenosquamous carcinoma; EAMS, Early Access to Medicines Scheme; LBx, liquid biopsy; MET, mesenchymal-epithelial transition factor; METex14, MET exon 14; N/A, not assessed; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; TBx, tissue biopsy.

Baijal S. Evolving genetic testing and treatment pathways in non-small cell lung carcinoma: a Healthcare Professional survey of current practices in the UK. Presented at the 20th British Thoracic Oncology Group (BTOG) Annual Conference | January 27 28, 2022[2]

This survey aimed to understand the current UK NSCLC patient pathway in relation to oncogenic mutation testing practices, diagnosis, treatment guidelines, treatment preferences as well as anticipated future trends considering the evolving treatment landscape.

Between March 2021 and June 2021, a survey with 57 healthcare professionals (HCPs) involved in the secondary care management of patients with NSCLC across the UK was conducted. HCPs were invited to represent a geographically dispersed sample across UK NHS Trusts. The survey was conducted using a structured questionnaire. A steering committee consisting of three external clinical leads (medical oncologist, respiratory physician and a senior clinical nurse specialist) supported in the development of the structured questionnaire.

Full results are reported in the reference provided. However of note:

- Genomic and histopathology tests which respondents perceived to be of clinical value but are not currently routinely available or NICE reimbursed included MET exon14 skipping mutation which received the most responses (30%; n=16), followed by MET Amplification (28%; n=15) and HER 2 (25%, n=13).
- For patients with high PD-L1 expression and a driver mutation, 100% of respondents (n=57) preferred to use a targeted therapy over an immuno-oncology treatment as first line therapy.
- The most common reasons for using an immuno-oncology treatment over targeted therapy was that there was no targeted therapy available (69%, n= 37), lack of access to a targeted therapy (54%, n=29) or excessive molecular testing turnaround times (39%, n=21).

Appendix 1b: Clinical expert opinion elicited as part of the ACD response, minutes

As part of the ACD response, Merck interviewed three clinical experts who are highly experienced in treating NSCLC in England. The experts were leading medical and clinical lung cancer oncologists from a range of centres across England and therefore, were able to provide a variety of expert perspectives representative of clinical practice in England. The three clinical experts consulted as part of the ACD response are separate to the clinical experts who took part in the advisory board as part of the original submission (Section B.3.8.5). As such, we have sourced clinical expert opinion from seven different lung cancer oncologists to inform our assumptions as part of this appraisal.

A number of questions were asked related to the tepotinib ACD and updated analysis provided by Merck. The different topics discussed, and a summary of the clinical expert feedback, is provided below.

Population

Questions

- All experts were asked about the relevant population for tepotinib proposed by NICE (untreated, non-squamous NSCLC) and if this was appropriate.

Responses

- All of the experts agreed they would treat METex14 skipping patients with tepotinib as a first-line treatment where possible, but stated that access in previously-treated patients still is important and desired due to possible delays in receiving genomic test results, or for those who received previous lines of current SOC treatment prior to detection of METex14 skipping mutation.
- They all agreed that non-squamous histology is the most relevant population for tepotinib, as testing is not routinely available in squamous patients. Some centres may conduct testing in squamous patients, and so it could be relevant for a very small proportion of patients, but not for most. They said they would treat squamous patients with tepotinib if a positive test was confirmed, but this would not be detected in most patients.

Comparators and clinical trials in wildtype NSCLC

Questions

- The clinical experts were presented with the updated clinical trial comparisons proposed by Merck and agreed to by NICE:
    - Chemo-immunotherapy
        - Treatment: Pembrolizumab + pemetrexed + platinum
        - Subgroups: Untreated patients, all PD-L1 subgroups
        - Clinical trial: KEYNOTE-189
    - Immunotherapy monotherapy
        - Treatment: Pembrolizumab monotherapy
        - Subgroups: Untreated, PD-L1≥50%
        - Clinical trial: KEYNOTE-24
    - Chemotherapy:
        - Treatment: Docetaxel

        - Subgroups: Previously treated, all PD-L1 subgroups:
        - Clinical trials: TAX320, KEYNOTE-010, CheckMate-017, CheckMate-057, REVEL NSCLC
    - Chemotherapy:
        - Treatment: Docetaxel + nintedanib
        - Subgroups: Previously treated, all PD-L1 subgroups:
        - Clinical trials: LUME Lung 1
- The clinical experts were all asked if these were the key comparators to be considered in the updated analysis, and if they represent the treatments that most patients receive in NHS practice.
- They were also asked if these were the appropriate clinical trials to use for the updated comparisons. For docetaxel, where there were multiple possible clinical trials that could be included, they were asked if any would be more or less appropriate.

Responses

- All the experts agreed that the key comparator for untreated non-squamous NSCLC is chemo-immunotherapy, and specifically pembrolizumab + pemetrexed + platinum.
- They also noted that pembrolizumab monotherapy is also a comparator in this group, but only for PD-L1≥50%, and that relatively few patients receive this treatment compared to the chemotherapy combination.
    - They expected fewer than the 30% of patients who are PD-L1≥50% to receive monotherapy over the combination treatment in wildtype NSCLC.
    - One expert estimated around one third of patients with PD-L1>50% would receive chemo-immunotherapy anyway, if a rapid response is required, e.g. with aggressive disease.
    - Another expert estimated that nearly all METex14 skipping would be given chemo-immunotherapy over immunotherapy monotherapy, even with high PD-L1 expression, due to the poor responses seen with immunotherapy monotherapy.
- In the previously treated setting, all experts agreed that nearly all patients are given docetaxel + nintedanib (rather than docetaxel alone). The proportion of patients given docetaxel with nintedanib versus without nintedanib ranged from 80% to 100%.
    - Some patients receive platinum-based chemotherapy in this setting after immunotherapy monotherapy, but most receive chemo-immunotherapy and so go straight on to docetaxel +/- nintedanib.
- They also agreed that the clinical trials listed are the key ones to consider for each treatment.
    - LUME Lung 1 is appropriate for docetaxel + nintedanib.
    - Most experts said that any of the listed trials for docetaxel monotherapy would be appropriate, although one said it would be best not to include KEYNOTE-010, as this is in patients with PD-L1≥1%, which is not aligned with the NICE-recommended population for docetaxel.
    - Another suggested that we could use trials which were conducted before immunotherapy treatments were available (TAX320, REVEL NSCLC), and to avoid crossover to immunotherapy. Immunotherapy is not given after docetaxel in NHS practice, so it was considered preferable to avoid crossover. They said typically in current practice, immunotherapy is given before docetaxel, which would not be captured in any trials.
    - Another expert suggested to look at the patient characteristics and see what matched closest to VISION.

- Finally, another expert suggested looking for a crizotinib ALK clinical trial (e.g. PROFILE 1007), where docetaxel has been a comparator, as this could be a more similar population to METex14 skipping. This would not be in wildtype NSCLC however.

Comparison of outcomes in wildtype NSCLC and METex14 skipping NSCLC

Questions

- All experts were asked if they expected METex14 skipping patients to respond differently to immunotherapy (monotherapy and combination) compared to wildtype NSCLC. They were also asked if the immunotherapy real-world data (RWD) outcomes were aligned to expectations in this population.

Responses

- All experts expected METex14 skipping patients to have a poorer prognosis than wildtype NSCLC patients, particularly when treated with immunotherapy. The experts stated that this is consistent with what they observe in their clinical practice for other oncogenic driver mutations as well (EGFR, ALK).
    - Two of the experts expected the survival rates in the METex14 skipping population to be less than 50% that of wildtype NSCLC, if not even lower. The third expert thought the difference would be less pronounced, but still lower for METex14 skipping. He also stated there were limited data to draw robust conclusions at this stage however.
    - For example, one of the experts thought that in METex14 skipping patients, only 5% of patients would be alive at 5 years after treatment with immunotherapy monotherapy, with only 1-2% alive at 10 years. This was substantially lower than estimates for wildtype NSCLC (see below). This expert also suggested that only 2.5% METex14 patients would be progression free at 5 years, and 0.5-1% at 10 years, with immunotherapy monotherapy.
- Furthermore, one expert said there is no evidence to suggest patients that METex14 skipping patients treated with immunotherapy monotherapy would respond any better than when treated with chemo-immunotherapy, despite the difference in PD-L1 expression.

Survival expectations and curve selection

Questions

- All experts were asked about their long-term OS and PFS expectations for wildtype NSCLC and METex14 skipping NSCLC with the comparator treatments.
- The final two experts were also presented with the survival extrapolations generated using the ITC results, and asked to pick the most appropriate curves for comparators and tepotinib.

Responses

OS

Chemo-immunotherapy

- All experts agreed that the higher estimates of 5 and 10 year survival for chemo-immunotherapy in wildtype NSCLC would be appropriate (range from 15-20% alive at 5 years, 5-10% at 10 years) and that the higher parametric curves would be more

appropriate (log logistic, log normal). In METex14 skipping NSCLC, experts stated that OS would be substantially lower.
- All experts expected tepotinib to have higher OS and PFS compared to chemo-immunotherapy in a matched population, given the current tepotinib clinical data and targeted mechanism of action, which agreed with the MAIC results seen.

Immunotherapy

- Similar to chemo-immunotherapy, the higher estimates of survival were deemed to be appropriate in wildtype NSCLC for immunotherapy (log logistic and log normal). They all suggested to use the 5-year survival from KEYNOTE-024 to guide this (30% alive at 5 years). 15% were projected by the experts to be alive at 10 years.
- All experts expected tepotinib to have at least similar if not higher OS compared to immunotherapy in the same population, given the current tepotinib clinical data and targeted mechanism of action, again agreeing with the MAIC results presented.

Docetaxel +/- nintedanib

- All experts expected similar long term survival estimates between docetaxel and nintedanib + docetaxel.
- Patients have a very poor prognosis in the previously treated setting when they progress on first-line treatment and move on to docetaxel+/- nintedanib. Two experts predicted very low survival rates (1-3%) at 5 years, with next to no patients alive at 10 years. They deemed any curves which aligned with these estimates to be appropriate.
    - One expert estimated slightly higher 5 year survival rates (~10%) given the expectation that these patients would have had previous immunotherapy. However he said typically these second-line patients still have a poor prognosis on these specific treatments.
- They all expected tepotinib to have substantially higher OS compared to docetaxel +/- nintedanib, given the current tepotinib clinical data and targeted mechanism of action.

Table 1. OS estimates based on three interviews with clinical experts

	5 year (wildtype)	**10 year (wildtype)**
Pembro+chemo	15-20%	5-10%
Pembro mono	30%	15%
Docetaxel	1-3% (two experts) ~10% (one expert)	0% (two experts), 2% (one expert)
Doc + nintedanib	1-3% (two experts) ~10% (one expert)	0% (two experts), 2% (one expert)

PFS

- All experts estimated lower rates of PFS compared to OS. One suggested roughly just under half the rates of PFS compared to OS at the same timepoints (in line with 5-year KEYNOTE-24 data).
- They all expected much lower PFS rates in METex14 skipping compared to wildtype NSCLC.
- They also expected tepotinib to have greater PFS compared to all comparators in a matched population, based on the clinical data and mechanism of action. This is consistent with all MAIC results seen. It was noted that tepotinib has higher PFS in a naive comparison to pembrolizumab + pemetrexed + platinum, and pembrolizumab

monotherapy, despite the large differences in population and worse prognostic characteristics for VISION.

Chemo-immunotherapy

- All experts expected the more optimistic curves to best represent PFS in wildtype NSCLC (Weibull, log logistic, log-normal).

Immunotherapy

- The experts expected the more optimistic curves to be the most representative of PFS in wildtype NSCLC, with the exception of Gompertz which is not clinically plausible.

Docetaxel +/- nintedanib

- The experts fed back that nearly all patients are expected to have progressed at 5 years, so any curves which reflect this are appropriate.

Table 2. PFS estimates based on three interviews with clinical experts

	5 year (wildtype)	**10 year (wildtype)**
Pembro+chemo	7.5-10%	2.5%
Pembro mono	12.8%	5-10%
Docetaxel	1-1.5% (two experts) ~3% (one expert)	0%
Doc + nintedanib	1-1.5% (two experts) ~3% (one expert)	0%

Subsequent treatment expectations in NHS practice

Questions

- All experts were asked about their expectations for subsequent treatments for each of the comparator treatments and for tepotinib at each line of therapy.
- The results given were consistent across all experts, with the main variations:
    - The proportion of patients who receive docetaxel monotherapy versus docetaxel + nintedanib.
    - The proportion of patients who would go onto immunotherapy versus chemotherapy after tepotinib as a first-line treatment.

Responses

- It was firstly noted that not all patients go onto subsequent treatments at all. This was estimated to be between 20% and 70% of patients by the different clinical experts, and two experts expected less than half of patients to go onto subsequent treatments at all.

- **Pembrolizumab + pemetrexed + platinum:**
    - All patients who receive subsequent treatment would go on to docetaxel +/- nintedanib
        - Most patients have docetaxel with nintedanib. The split between docetaxel with nintedanib versus without nintedanib ranged from 80% with nintedanib to 100% with nintedanib.

- **Pembrolizumab monotherapy:**

    - Nearly all patients go onto platinum (carboplatin specifically) + pemetrexed, and then docetaxel +/- nintedanib.
        - This feedback was consistent across experts.

- **Docetaxel +/- nintedanib**
    - No subsequent treatments, just best supportive care (BSC). Some could go onto a clinical trial, or another single agent chemotherapy, but according to NICE guidelines and standard practice, docetaxel +- nintedanib is the last line of treatment.
        - This feedback was also consistent across experts.

- **Tepotinib (treatment naïve):**
    - All clinical experts agreed that patients will receive either immunotherapy monotherapy or platinum-based chemotherapy as a second-line treatment after tepotinib. Patients could then receive docetaxel +/- nintedanib as a third line treatment.
    - The split between those receiving immunotherapy and those receiving platinum-based chemotherapy ranged between 50/50 to 90/10 in favour of immunotherapy. PD-L1 could impact decision making here, as one clinician said that in PD-L1 positive patients they would be more likely to use subsequent immunotherapy after tepotinib.
    - Most patients would receive carboplatin + pemetrexed as chemotherapy, although some could receive carboplatin + gemcitabine, or carboplatin + vinorelbine, if they had associated issues or contraindications.
    - Most who go onto immunotherapy would receive pembrolizumab as immunotherapy, rather than atezolizumab or nivolumab.

- **Tepotinib (previously treated)**:
    - If a patient receives chemo-immunotherapy up front before tepotinib, then docetaxel +/- nintedanib will be given as a third-line treatment, or in some specific cases, another single agent chemotherapy such as paclitaxel (off label use). Most patients receive chemo-immunotherapy up front, so after tepotinib, most patients will receive subsequent docetaxel +/- nintedanib.
    - If immunotherapy monotherapy is given up front (in patients with PD-L1 expression ≥50%), then after tepotinib, platinum-based chemotherapy will be given. This will mostly be carboplatin + pemetrexed, but some could get other options (such as gemcitabine/vinorelbine) in combination with carboplatin.
        - Two experts stated that in real life, patients would be very reluctant to go from a targeted treatment with minimal side effects to burdensome chemotherapy with a poor side effect profile, after second-line treatment.
    - If a patient has not had any immunotherapy first-line, they could receive immunotherapy third-line after tepotinib, but this is unlikely and will be very rare (although possible within NHS practice).

Generalisability of VISION to the UK population and NHS practice

- All the clinical experts thought that the VISION trial was reflective of the METex14 skipping population, including for UK patients.

- The experts were not concerned with the lack of UK patients in VISION, as over half were European. One expert stated that global clinical trials are the norm, and that this is consistent with many NICE appraisals before, even in NSCLC.

Other feedback

- Very few patients would still be on treatment with tepotinib at 5 years if any, according to all the experts.

Appendix 1c: Updated data used in the updated economic model

VISION cohort A+C

In the original submission to NICE in July 2021, data from Cohort A of the phase II VISION study (data cut 1 February 2021) informed the efficacy and safety for tepotinib. Further to this, the VISION study also enrolled patients into a confirmatory cohort, Cohort C, where patients were administered the same treatment schedule as in Cohort A. In the ACD, the committee stated a preference for using the combined data from Cohorts A and C (Cohort A+C) to inform the tepotinib data in the economic model. Therefore, Merck has updated the analyses in the ITC (see ACD response Appendix **2**) and the economic model to incorporate the additional patients from Cohort C.

Patient characteristics

The confirmatory VISION Cohort C provides data for an additional 139 patients. Table 3 presents the patient characteristics for Cohort A and Cohort A+C combined. Similar characteristics are observed between cohorts (within a few percentage points).

Table 3: VISION patient characteristics, Cohort A versus Cohort A+C

Characteristics	Cohort A	Cohort A+C
n	[redacted]	[redacted]
Age (mean, (SD))	[redacted]	[redacted]
Proportion age over 75	[redacted]	[redacted]
Prior treatment		
Untreated (%)	[redacted]	[redacted]
Treatment Experienced (%)	[redacted]	[redacted]
Sex		
Female (%)	[redacted]	[redacted]
Male (%)	[redacted]	[redacted]
Race		
Asian	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Other	[redacted]	[redacted]
White	[redacted]	[redacted]
Unknown	[redacted]	[redacted]
History of smoking (%)		
No (%)	[redacted]	[redacted]
Yes (%)	[redacted]	[redacted]
ECOG		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
Stage (%)		
IIIB/C	[redacted]	[redacted]

Characteristics	Cohort A	Cohort A+C
IIIB	[redacted]	[redacted]
IV	[redacted]	[redacted]
IVB	[redacted]	[redacted]
NA	[redacted]	[redacted]
Metastatic disease (%)		
No (%)	[redacted]	[redacted]
Yes (%)	[redacted]	[redacted]
Histology		
Adenocarcinoma	[redacted]	[redacted]
Squamous	[redacted]	[redacted]
Others	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Key: SD, standard deviation.

The observed outcomes are also similar between cohorts (see ACD response Appendix **2**).

Utilities

The utility values incorporated in the updated model are calculated from VISION Cohort A+C. The same methodology as per the original submission (detailed in company submission Section B.3.4.1.) were used to calculate the updated values, presented alongside the original values in Table 4 below.

Table 4: Model utility values

Health state	Mean utility (Cohort A)	Mean utility (Cohort A+C)
Pre-progression	0.7180	0.7086
Post-progression	0.6363	0.6464

Adverse events

The grade ≥3 adverse event (AE) incidence rates are calculated from VISION Cohort A+C in the updated analysis. Table 5 presents the AE incidence for Cohort A (original submission) and Cohort A+C (updated analysis).

Table 5: Grade ≥3 adverse event incidence – Cohort A, Cohort A+C

Adverse event	Cohort A	Cohort A+C
Alanine aminotransferase) increase	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]
Amylase increase	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Bilirubin increased	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Cough	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Hypoalbuminemia	[redacted]	[redacted]
Hypomagnesemia	[redacted]	[redacted]
Infection	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]
Lipase increase	[redacted]	[redacted]
Lymphocyte count decrease	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Neuromotor	[redacted]	[redacted]
Neurosensory	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Neutrophil count decrease	[redacted]	[redacted]
Oedema peripheral/other	[redacted]	[redacted]
Pain	[redacted]	[redacted]
Platelet count decrease	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]
Pneumonitis / pneumonia	[redacted]	[redacted]
Pulmonary/ respiratory tract infection	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
White blood cell count decrease	[redacted]	[redacted]

Subsequent treatments

The subsequent therapy distributions applied in the model (when the option to use VISION data is selected) were calculated from the subsequent treatments received by patients in VISION Cohort A+C. The distributions used in the original and updated models are presented in Table 6. Please note, the use of VISION data to inform subsequent treatment

mix after tepotinib is no longer the base case. The base case assumptions around subsequent treatment for tepotinib have been revised to align with NHS practice. Please see Comment 8 in the ACD response and Section B.3.5.4.1 of the original company submission for further detail.

Table 6: Subsequent treatment distributions for tepotinib patients applied in the model – Cohort A, Cohort A+C

Treatment category	Treatment	Cohort A	Cohort A+C
Patient who had at least one subsequent treatment		[redacted]	[redacted]
Immunotherapy	Pembrolizumab	[redacted]	[redacted]
	Atezolizumab	[redacted]	[redacted]
	Nivolumab	[redacted]	[redacted]
Chemotherapy	Pemetrexed	[redacted]	[redacted]
	Vinorelbine	[redacted]	[redacted]
	Paclitaxel	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]
	Gemcitabine	[redacted]	[redacted]
Platinum	Cisplatin	[redacted]	[redacted]
	Carboplatin	[redacted]	[redacted]
Targeted	Brigatinib	[redacted]	[redacted]
	Nintedanib	[redacted]	[redacted]
MET inhibitor	Crizotinib	[redacted]	[redacted]

Real-world cohort – Inclusion of GFPC data for the untreated population comparison to immunotherapy

In the ACD the committee noted that the survival projections from the ITC using the real-world cohort were not reflective of clinical practice, particularly for chemotherapy where the OS estimates were overly optimistic. As a result, the committee requested that indirect comparisons be performed between the tepotinib VISION data and published wildtype NSCLC studies. Whilst Merck have performed this analysis based on the committee's feedback, we have demonstrated in the ACD response that the real-world cohort in the METex14 population has several advantages over the comparison to wildtype NSCLC studies, particularly for the comparison to immunotherapy in the untreated population, where the outcomes from the real-world cohort are in line with clinical expectations and against previous studies.

Furthermore, additional real-world data has become available to Merck from the Group Francais de Pneumo-Cancérologie (GFPC), which was first mentioned in the Company Decision Problem Form as well as Technical Engagement response Key Issue 4, and also described in Appendix **2** of this ACD response. As such, this data has been incorporated into the propensity score weighting ITC for immunotherapy compared to tepotinib for the

untreated population, to increase patient numbers (from 20 to 32) and reduce uncertainty in the resulting estimates. Full details of the updated ITC analysis are available in ACD response Appendix **2**.

Due to the limited time available in which to update the analysis for the ACD response, it was not possible to fully incorporate the GFPC data into all real-world ITC analyses in the model. As such, only the comparison to immunotherapy in the untreated population was updated with this additional real-world data from the GFPC. The main reason for this is that the committee felt the immunotherapy survival estimates from the real-world cohort were more aligned with clinical practice versus the chemotherapy estimates, which were deemed to be implausible. Therefore, the addition of GFPC data to this comparison was expected to further enhance reliability, in a population where survival estimates are already reflective of expected UK clinical practice in METex14 skipping patients, according to clinical experts and extensive validation. Also, immunotherapy monotherapy was highlighted by clinical experts as most likely to be given in the untreated setting, and no patients receive this as a second-line treatment.

As such, due to limited timings, Merck focused on the presentation and interpretation of the wildtype NSCLC data analysis to inform the second-line chemotherapy comparison (reported in Appendix **2**).

Untreated immunotherapy treatment distribution

Table 7 presents the treatments received by the immunotherapy patients in the untreated population in the model. Unspecified immunotherapy has been redistributed to pembrolizumab and nivolumab.

Table 7: Immunotherapy treatment distribution for the untreated population

Treatment	**Immunotherapy Untreated**
Pembrolizumab	[redacted]
Atezolizumab	[redacted]
Nivolumab	[redacted]
Nivolumab/ipilimumab	[redacted]

The updated results to the ITC are presented in Appendix **2**.

Appendix 1d: Supplementary curve fits

Untreated population (vs immunotherapy monotherapy, PD-L1≥50%)

Immunotherapy (updated real-world cohort in the METx14 skipping population)

To inform the efficacy of immunotherapy, the real-world cohort data was updated to include the French, GFPC data set (see ACD response Appendix **2**). The same approach as per the original company submission was taken to produce parametric survival curves of the immunotherapy data matched to the untreated VISION population.

Parametric survival models (PSMs) were fitted to OS and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate outcomes over a lifetime horizon. As per the original submission splines and piece-wise models were also considered.

Overall survival

The statistical goodness-of-fit of all fitted PSMs to the immunotherapy OS data is provided in Table 8. From the parametric models, the exponential PSM provided the best statistical fit to the immunotherapy arm with the others providing similar fits to the data (within 5 points). Figure 3 presents the visual fit of all PSMs. Of the spline models, the 2-knot normal provided the best statistical fit with similar fits (within 5 points) seen with the other 2 and 3-knot models. These spline model fits to the immunotherapy curve provided an improved statistical and visual fit compared to the parametric models, shown in Figure 4.

Table 8: Statistical goodness-of-fit scores - Immunotherapy OS (weighted)

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Immunotherapy – parametric curves				
Exponential	676.44	677.91	1	1
Weibull	678.42	681.36	3	3
Gompertz	678.33	681.26	2	2
Log-logistic	681.18	684.11	5	4
Log-normal	681.51	684.45	6	6
Generalised-gamma	679.86	684.26	4	5
Immunotherapy – splines				
Odds 1 knot	682.02	686.42	9	9
Odds 2 knot	672.61	678.47	3	2
Odds 3 knot	673.26	680.59	4	5
Hazard 1 knot	680.33	684.73	7	7
Hazard 2 knot	674.47	680.33	5	4
Hazard 3 knot	674.60	681.93	6	6
Normal 1 knot	680.57	684.97	8	8
Normal 2 knot **(Selected)**	670.48	676.35	1	1
Normal 3 knot	671.40	678.72	2	3

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival.

Figure 3: Parametric curve fits – Immunotherapy OS (weighted) – untreated population

Key: KM, Kaplan-Meier; OS, overall survival

Figure 4: Spline curve fits – Immunotherapy OS (weighted) – untreated population

Key: KM, Kaplan-Meier; OS, overall survival

The parametric models produced poorer visual vits, unable to capture the KM data between one to two years. Spline models provided much better visual fits, and from these curves, the spline 2 knot normal provided the best visual and statistical fit to the data. Therefore, the 2 knot normal was selected as the base case. This is also aligned with the approach taken in

the original submission where the 2-knot normal model was selected for untreated, immunotherapy monotherapy, based on statistical and visual fit, in combination with the estimates of long-term survival by clinical experts in the METex14 skipping population that was obtained prior to the original submission.[3] Furthermore, in the additional interviews with clinical experts as part of this ACD response (described above) one expert estimated only roughly 5% of METex14 skipping patients would be alive at 5 years, with 1-2% alive at 10 years when treated with immunotherapy monotherapy. All estimated that the survival would be substantially lower in the METex14 skipping population compared to wildtype NSCLC population (30% at 5 years and 15% at 10 yeas). These lower estimates of survival aligns with the spline 2 knot normal selected.

Progression-free survival

Similarly to OS, as well as parametric curves, odds, hazard and normal spline models were fit to the immunotherapy data and piece-wise models for immunotherapy using the cut-off 2.8 months in line with the median time point. Given the poor fits of the full parametric curves for immunotherapy, only piece-wise and spline models are presented for consideration.

The statistical goodness-of-fit of all fitted PSMs to the immunotherapy PFS data is provided in Table 9. From the piece-wise parametric models, the log-normal PSM provided the best statistical fit to the immunotherapy arm with all the other models also providing a reasonable fit to the data. Of the splines, the three knot hazard curve provided the best statistical fit with the remaining providing a similar fit. Figure **5** presents the visual fit of all PSMs, and spline model fits in Figure 6.

Table 9: Statistical goodness-of-fit scores - Immunotherapy PFS (weighted) – untreated population

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Immunotherapy – piece-wise parametric curves				
Exponential	290.69	291.39	2	2
Weibull **(Selected)**	292.68	294.10	6	6
Gompertz	292.17	293.58	5	5
Log-logistic	291.08	292.49	4	3
Log-normal	289.29	290.71	1	1
Generalised-gamma	290.75	292.87	3	4
Immunotherapy – splines				
Odds 1 knot	749.55	753.95	4	3
Odds 2 knot	750.43	756.29	8	8
Odds 3 knot	745.75	753.08	2	2
Hazard 1 knot	749.76	754.16	6	5
Hazard 2 knot	749.98	755.84	7	7
Hazard 3 knot	744.71	752.04	1	1
Normal 1 knot	749.62	754.02	5	4
Normal 2 knot	749.15	755.01	3	6

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival.

Figure 5: Parametric piece-wise curve fits – Immunotherapy PFS (weighted) – untreated population

Key: KM, Kaplan-Meier; PFS, progression-free survival.

Figure 6: Spline curve fits – Immunotherapy PFS (weighted) – untreated population

Key: KM, Kaplan-Meier; PFS, progression-free survival.

The piece-wise parametric models and spline models produced reasonable visual fits to the data. Considering these, the piece-wise Weibull curve was selected as the base case as this is in line with what was selected in the original submission, and in line with the original estimates of PFS by clinical experts in the METex14 skipping population. This also aligns with the recent interviews with clinical experts, who expected long term PFS for immunotherapy monotherapy to be substantially lower in METex14 skipping NSCLC compared to wildtype NSCLC. One expert estimated that roughly 2.5% of patients would

remain PFS with immunotherapy monotherapy at 5 years, with 0.5-1% at 10 years. The curve selected aligns with these estimates.

Tepotinib

To inform the efficacy of tepotinib in comparison to immunotherapy, data from VISION (Cohort A+C - untreated) was used. The same approach as per the original submission was used to extrapolate OS and PFS for a patient's lifetime.

Overall survival

The statistical goodness-of-fit of all fitted PSMs is provided in Table 10. Based on the AIC and BIC scores, all models provided a reasonably similar fit to the data (within five points for AIC) and so were visually compared in order to select the base-case extrapolation (shown in Figure 7).

Table 10: Statistical goodness-of-fit scores - VISION (A+C) OS (untreated population)

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Exponential	516.44	519.44	2	1
Weibull	516.78	522.77	3	3
Gompertz	518.18	524.17	5	4
Log-logistic **(Selected)**	515.77	521.77	1	2
Log-normal	518.65	524.64	6	5
Generalised-gamma	518.06	527.05	4	6

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

Figure 7: Parametric curve fits – VISION (A+C) OS (untreated population)

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

All models provided a reasonable fit to the Kaplan-Meier data, with exponential providing the best statistical fit according to BIC and log-logistic according to AIC. Given log-logistic provided a better visual fit to the observed data, this was selected for the base case for the untreated population and is in line with what was selected in the original company submission. The clinical experts expected tepotinib to have greater long term OS in METex14 skipping patients compared to immunotherapy monotherapy, and curve selection aligned to that.

Finally, the original submission focused on ensuring that the selected model predicts improved survival for the untreated population compared to the overall population. Both the log-logistic and log-normal distributions provided more optimistic projections of survival than estimated for the overall group therefore, due to an improved visual fit and having the best AIC fit, the log-logistic model was selected.

Progression-free survival

The statistical goodness-of-fit of all fitted PSMs to the tepotinib PFS data is provided in Table 11. Based on the AIC and BIC scores, the log-logistic model provided the best statistical fit to the tepotinib PFS data, closely followed by log-normal and generalised gamma (within five points) and so were visually compared in order to select the base-case extrapolation (shown in Figure 8).

Table 11: Statistical goodness-of-fit scores - VISION (A+C) PFS (untreated population)

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Exponential	562.63	565.63	4	3
Weibull	564.13	570.12	6	6
Gompertz	563.51	569.51	5	5
Log-logistic	556.59	562.58	1	1
Log-normal **(Selected)**	558.11	564.11	2	2
Generalised-gamma	559.86	568.86	3	4

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression free survival

Figure 8: Parametric curve fits – VISION (A+C) PFS (untreated population)

Key: KM, Kaplan-Meier; PFS, progression-free survival

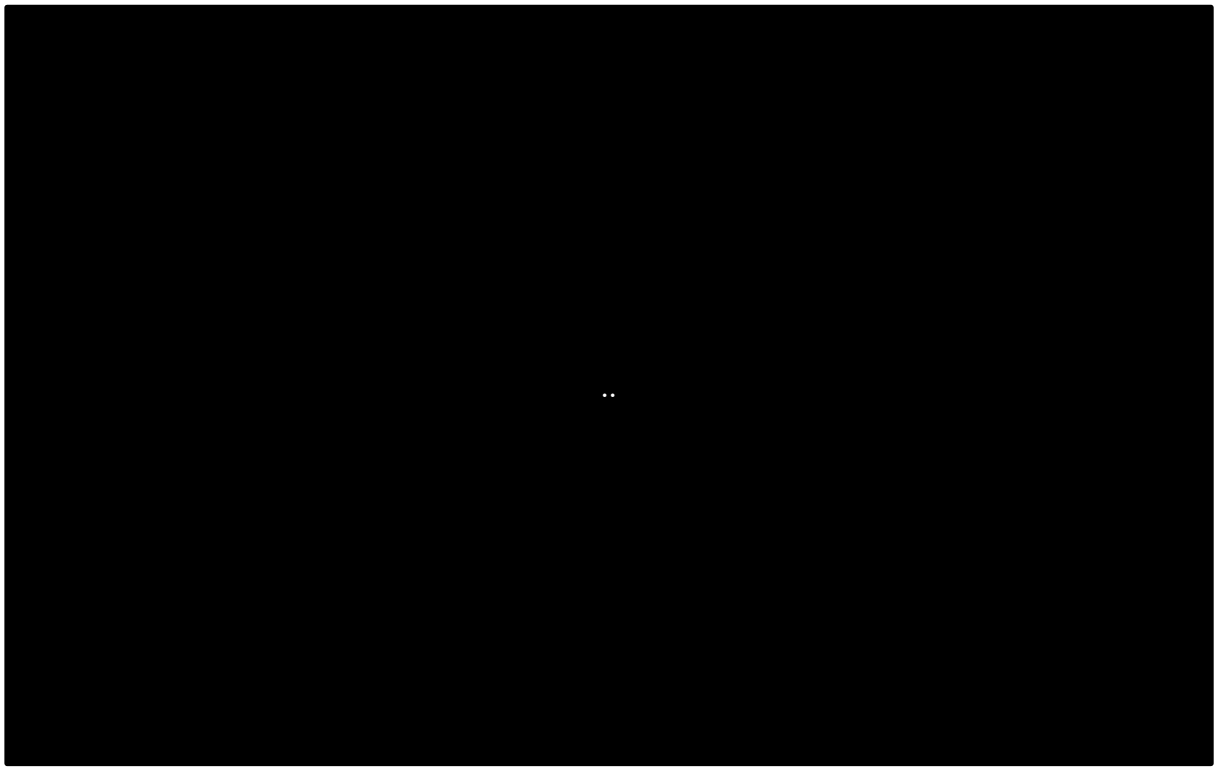
The parametric curves appear to fit the data reasonably well, with a slight over estimation between six and 18 months and possible under estimation towards the tail of the KM data. Based on visual fit, goodness of fit scores and in line with what was previously selected, the log-normal was selected for the base case.

Final curves

The final curves for the base case untreated population in comparison to immunotherapy are presented in Figure 9. The long term OS and PFS projections are in line with the clinical feedback received as part of the original submission (advisory board with four clinical experts), and updated feedback as part of the ACD response (interviews with three clinical experts) who all expected tepotinib to have greater long term OS and PFS than immunotherapy in this population, due to the targeted mechanism of tepotinib and the poorer outcomes observed with immunotherapy in this population.

Furthermore, the immunotherapy long-term outcomes are aligned with the outcomes from studies in METex14 skipping NSCLC (shown in Comment 6 of the ACD response, as well as Key Issue 10 in the Technical Engagement response document), as well as in expectations compared to clinical trials in wildtype NSCLC therefore, are considered to be plausible. As such, the same curves as per the original submission were deemed appropriate.

Figure 9: Final base case curves – untreated population – tepotinib versus immunotherapy (RWD)



Key: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.

Untreated population (vs pembrolizumab in wildtype NSCLC, PD-L1≥50%)

Pembrolizumab

To inform the efficacy of pembrolizumab and perform survival extrapolations, clinical trial data was digitised from the latest KEYNOTE-024 publication, described in Appendix **2**.[4] Pseudo patient-level data was then created using the Guyot algorithm. PSMs were fitted to OS and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate over a life-time horizon. Visual fit, along with AIC/BIC score and clinical opinion of long-term estimates were then used to inform the most appropriate curve to take forward for the base case.

Overall survival

The statistical goodness of fit scores are presented in Table 12. Based on AIC and BIC scores, the log-normal distribution is the best fitting, however all models provide reasonably similar fits (within five points) and so were visually compared in Figure 10.

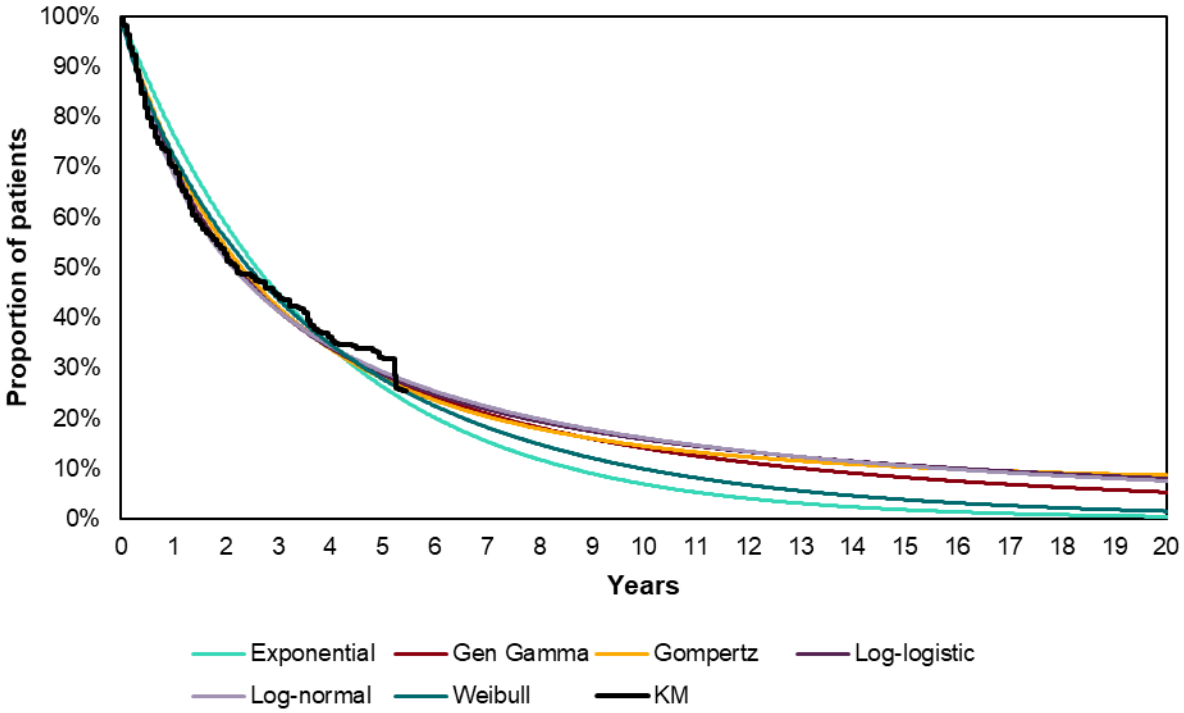
Table 12: Statistical goodness-of-fit scores – KEYNOTE 024 – OS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	1068.94	1071.98	6	3
Weibull	1066.94	1073.01	5	5
Gompertz	1066.54	1072.61	4	4
Log-logistic	1065.70	1071.78	3	2
Log-normal **(Selected)**	1064.47	1070.54	1	1
Generalised gamma	1065.67	1074.78	2	6

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

All curves appeared to fit the data well. Clinicians interviewed as part of the ACD response expected that survival of patients with wildtype NSCLC treated with immunotherapy would be around 30% at five-years (in line with KEYNOTE-024 outcomes) and around 15% at 10 years. All curves except exponential and Weibull sat within this plausible range. They also thought that the curves with higher estimates of long term survival were the most appropriate (log-normal, log-logistic). As such, based on goodness of fit, visual fit and long-term plausibility, log-normal was selected to inform the base case OS.

Figure 10: Parametric curve fits – KEYNOTE-024 – OS



Key: KM, Kaplan-Meier; OS, overall survival

Progression-free survival

The statistical goodness of fit scores are presented in Table 13. Based on AIC and BIC scores, the generalised gamma distribution is the best fitting, closely followed by log-normal and log-logistic which had reasonably similar fits (within five points). Therefore the curves were visually compared in Figure 11.

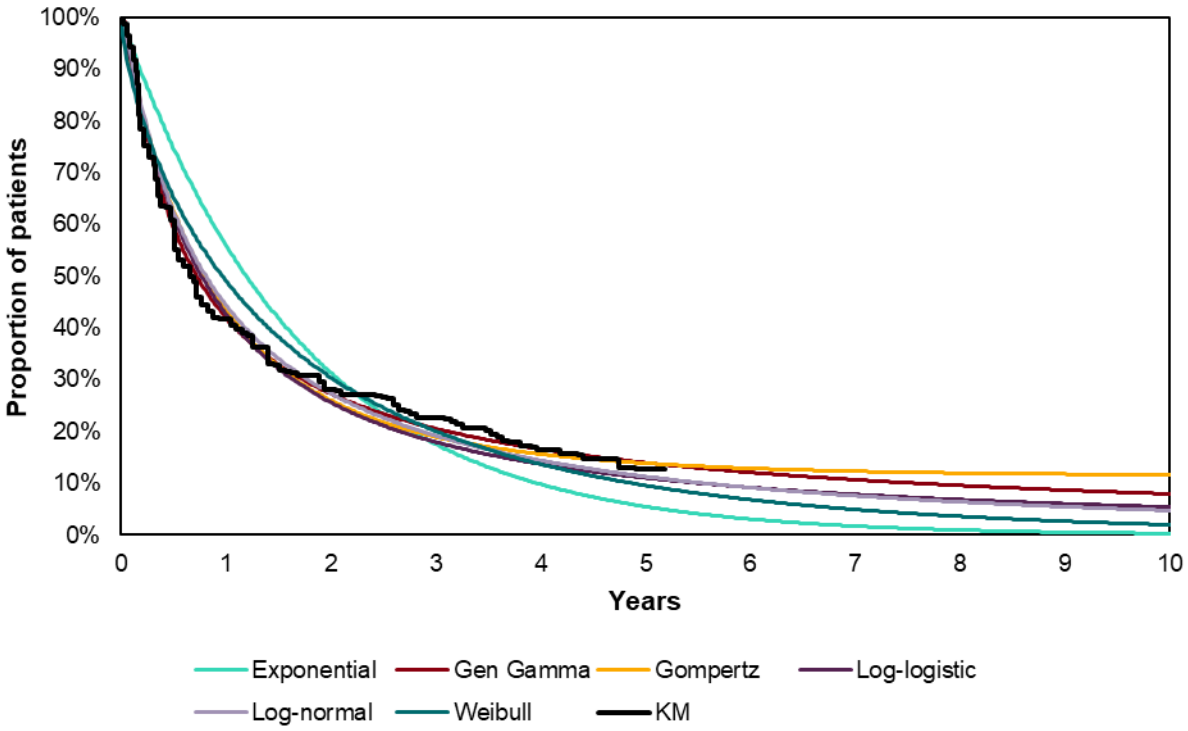
Table 13: Statistical goodness-of-fit scores – KEYNOTE 024 – PFS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	1017.59	1020.62	6	6
Weibull	999.40	1005.47	5	5
Gompertz	984.53	990.60	4	4
Log-logistic	979.83	985.91	3	3
Log-normal	975.47	981.54	2	2
Generalised gamma	972.19	981.30	1	1

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

All curves appeared to fit the data well apart from exponential and Weibull. Clinicians interviewed as part of this ACD response expected that the percentage of wildtype NSCLC patients who remain PFS with wildtype NSCLC treated with immunotherapy would be around 12-13% at five-years (based on KEYNOTE-24 outcomes) and around 5-10% at 10 years. Generalised gamma was the closest to this plausible range (14.0% and 8.0% respectively). As such, based on goodness of fit, visual fit and long-term plausibility, generalised gamma was selected to inform the base case PFS.

Figure 11: Parametric curve fits – KEYNOTE-024 – PFS



Key: KM, Kaplan-Meier; PFS, progression-free survival

Tepotinib

To inform the efficacy of tepotinib in comparison to pembrolizumab, untreated VISION data (A+C cohort) was matched to the KEYNOTE-024 trial, as described in Appendix 2. PSMs were fitted to weighted OS and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate over a life-time horizon. Visual fit, along with AIC/BIC score and plausibility of long-term estimates were then used to inform the most appropriate curve to take forward for the base case.

Overall survival

The statistical goodness of fit scores are presented in Table 14. Based on AIC and BIC scores, the exponential distribution is the best fitting, respectively, however all models provide reasonably similar fits (within five points) and so were visually compared in Figure 12.

Table 14: Statistical goodness-of-fit scores – VISION (weighted to KEYNOTE-024) – OS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	187.48	190.48	1	1
Weibull	188.52	194.51	3	3
Gompertz	189.21	195.20	4	4
Log-logistic	188.18	194.17	2	2
Log-normal **(Selected)**	189.35	195.34	5	5
Generalised gamma	190.30	199.29	6	6

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

All curves appeared to fit the data reasonably well apart from year 2 where the curves struggle to capture the large step in the KM which is likely driven by weighting of the VISION data, and resulting low patient numbers.

Clinicians expect that survival of tepotinib would be at least similar to that of patients treated with immunotherapy in the same population, and maybe even higher. As such, based on goodness of fit, visual fit and long-term plausibility, log-normal was selected to inform the base case OS as this closely aligned with the pembrolizumab estimates.

Figure 12: Parametric curve fits – VISION (weighted to KEYNOTE-024) – OS

Key: KM, Kaplan-Meier; OS, overall survival

Progression-free survival

The statistical goodness of fit scores are presented in Table 15. Based on AIC and BIC scores, the log-logistic and exponential distribution are the best fitting, respectively, however all models provide reasonably similar fits (within five points for AIC) and so were visually compared in Figure 13.

Table 15: Statistical goodness-of-fit scores – VISION (weighted to KEYNOTE-024) – PFS

Parameterisation	**AIC**	**BIC**	**Rank**	
			AIC	**BIC**
Exponential	210.01	213.01	2	1
Weibull	211.82	217.81	5	5
Gompertz	211.76	217.76	4	4
Log-logistic **(Selected)**	209.96	215.96	1	2
Log-normal	210.12	216.11	3	3
Generalised gamma	212.07	221.06	6	6

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

All curves appeared to fit the data well until around 1 year where the curves struggle to capture the large steps in the KM data, likely caused by the weighting of the tepotinib data. Given that log-logistic had the best AIC and visually fits the data best towards the end of the KM, log-logistic was selected to inform the base case PFS.

Figure 13: Parametric curve fits – VISION (weighted to KEYNOTE-024) – PFS

Key: KM, Kaplan-Meier; PFS, progression-free survival

Final curves

Figure 14 presents the final curves selected to inform the base case of tepotinib versus pembrolizumab.

Figure 14: Final base case – tepotinib versus pembrolizumab

Key: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival

Previously treated (vs docetaxel in wildtype NSCLC)

Docetaxel

To inform the efficacy of docetaxel and perform survival extrapolation, clinical trial data was digitised from the Fossella et al, 2000 publication, described in Appendix **2**.[5] Pseudo patient-level data was then created using the Guyot algorithm. PSMs were fitted to OS and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate over a life-time horizon. Visual fit, along with AIC/BIC score and clinical opinion of long-term estimates were then used to inform the most appropriate curve to take forward for the base case.

Overall survival

The statistical goodness of fit scores are presented in Table 16. Based on AIC and BIC scores, the log-normal distribution is the best fitting, closely followed by log-logistic and generalised gamma (within five points) and so were visually compared in Figure 15.

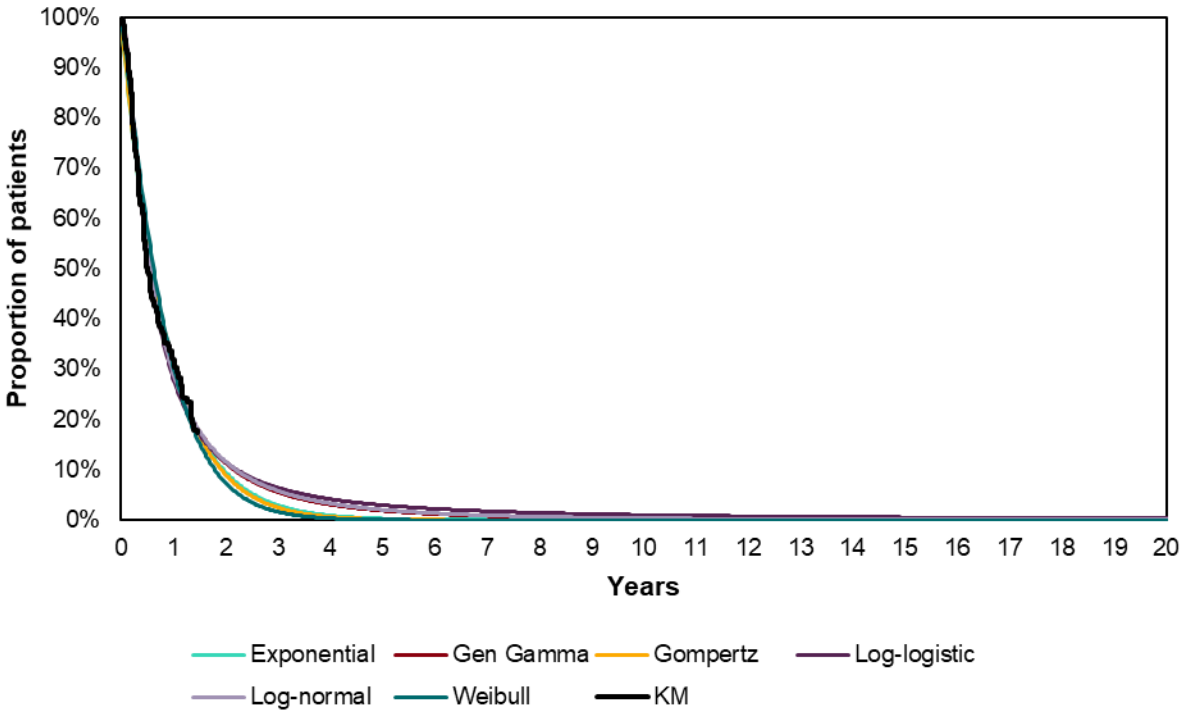
Table 16: Statistical goodness-of-fit scores – Fossella et al – OS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	686.36	689.19	5	4
Weibull	686.20	691.85	4	5
Gompertz	688.32	693.98	6	6
Log-logistic	679.71	685.36	2	2
Log-normal **(Selected)**	678.45	684.11	1	1
Generalised gamma	680.43	688.92	3	3

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

All curves appeared to fit the data well. Most clinicians expected that survival of patients with wild-type NSCLC treated with docetaxel would be around 1-3% at five-years and 0% by 10 year. Log-normal, log-logistic and generalised gamma sat the closest to this plausible range. As such, based on goodness of fit, visual fit and long-term plausibility, log-normal was selected to inform the base case OS.

Figure 15: Parametric curve fits – Fossella et al – OS



Key: KM, Kaplan-Meier; OS, overall survival

Progression-free survival

The statistical goodness of fit scores are presented in Table 17. Based on AIC and BIC scores, the log-normal distribution is the best fitting, closely followed by log-logistic and generalised gamma which had reasonably similar fits (within five points). Therefore the curves were visually compared in Figure 16.

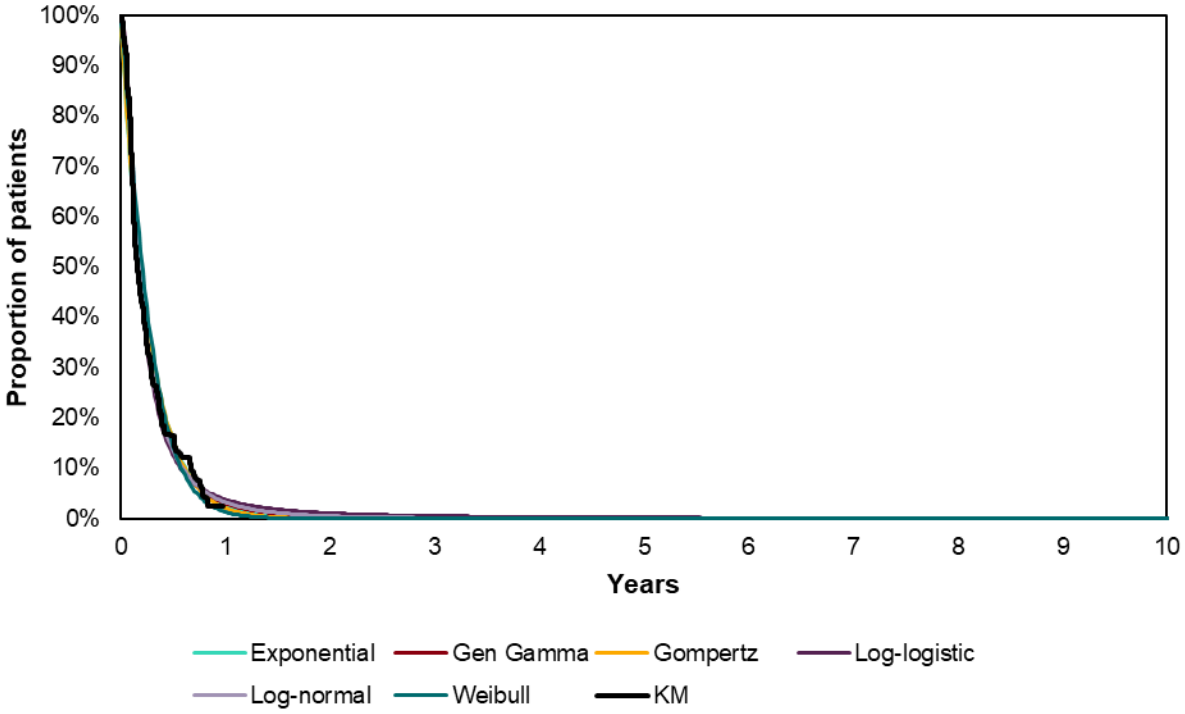
Table 17: Statistical goodness-of-fit scores – Fossella et al – PFS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	527.39	530.21	5	4
Weibull	525.14	530.78	4	5
Gompertz	529.26	534.90	6	6
Log-logistic **(Selected)**	513.39	519.03	2	2
Log-normal	512.14	517.78	1	1
Generaliszed gamma	514.04	522.50	3	3

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

All curves appeared to fit the data well. Clinicians expect that the proportion of wildtype NSCLC patients who remain PFS treated with docetaxel would be around 1-1.5% at five-years with all patients progressed or dead by 10 years. All curves apart from log-logistic estimated that all patients had progressed by 5 years. As such, based on goodness of fit, visual fit and long-term plausibility, log-logistic was selected to inform the base case PFS.

Figure 16: Parametric curve fits – Fossella et al – PFS



Key: KM, Kaplan-Meier; PFS, progression-free survival

Tepotinib

To inform the efficacy of tepotinib in comparison to docetaxel, previously treated VISION data (Cohort A+C) was matched to the Fossella et al trial. PSMs were fitted to weighted OS and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate over a life-time horizon. Visual fit, along with AIC/BIC score and plausibility of long-term estimates were then used to inform the most appropriate curve to take forward for the base case.

Overall survival

The statistical goodness of fit scores are presented in Table 18. Based on AIC and BIC scores, the log-normal and exponential distributions are the best fitting, however the other curves provide reasonably similar fits (within five points) and so were visually compared in Figure 17.

Table 18: Statistical goodness-of-fit scores – VISION (weighted to Fossella et al) – OS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential **(Selected)**	225.89	228.84	5	1
Weibull	225.49	231.40	4	4
Gompertz	227.03	232.94	6	5
Log-logistic	224.86	230.77	3	3
Log-normal	223.10	229.01	1	2
Generalised gamma	224.65	233.52	2	6

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

All curves appeared to fit the data well apart from the year 1 where the curves struggle to capture the large steps in the KM which is likely driven by weighting of the VISION data. Clinicians expect that patients treated with tepotinib would have substantially longer term OS than patients treated with docetaxel. As such, based on goodness of fit, visual fit and long-term plausibility, exponential was selected to inform the base case OS as this appeared to give more plausible long term estimates of tepotinib in comparison to docetaxel. Log-normal and log logistic were the other plausible options based on statistical fit and clinical plausibly, however clinical experts cautioned about introducing a too large long term survival benefit for tepotinib compared to docetaxel, and therefore exponential remained the choice.

Figure 17: Parametric curve fits – VISION (weighted to Fossella et al) – OS

Key: KM, Kaplan-Meier; OS, overall survival

Progression-free survival

The statistical goodness of fit scores are presented in Table 19. Based on AIC and BIC scores, the log-normal distribution is the best fitting, closely followed by log-logistic and generalised gamma which had reasonably similar fits (within five points). Therefore the curves were visually compared in Figure 18.

Table 19: Statistical goodness-of-fit scores – VISION (weighted to Fossella et al) – PFS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	279.33	282.29	5	4
Weibull	275.57	281.48	4	3
Gompertz	280.27	286.19	6	6
Log-logistic	273.95	279.87	2	2
Log-normal **(Selected)**	273.50	279.42	1	1
Generalised gamma	275.20	284.07	3	5

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

All curves appeared to fit the data reasonably well until year 1 where the curves slightly over estimate the PFS. Based on goodness of fit, visual fit and long-term plausibility, log-normal was selected to inform the base case PFS.

Figure 18: Parametric curve fits – VISION (weighted to Fossella et al) – PFS

Key: KM, Kaplan-Meier; PFS, progression-free survival

Final curves

Figure 19 presents the final curves selected to inform the base case of tepotinib versus docetaxel.

Figure 19: Final base case – tepotinib versus docetaxel

Key: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival

Previously treated (vs docetaxel + nintedanib in wildtype NSCLC)

Docetaxel + nintedanib

To inform the efficacy of docetaxel + nintedanib and perform survival extrapolation, trial data was digitised from the LUME-Lung 1 adenocarcinoma population, described in Appendix 2.[6] Pseudo patient-level data was then created using the Guyot algorithm. PSMs were fitted to OS and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate over a life-time horizon. Visual fit, along with AIC/BIC score and clinical opinion of long-term estimates were then used to inform the most appropriate curve to take forward for the base case.

Overall survival

The statistical goodness of fit scores are presented in Table 20. Based on AIC and BIC scores, the generalised gamma and log-normal distributions are the best fitting, respectively, closely followed by log-logistic and generalised gamma (within five points) and so were visually compared in Figure 20.

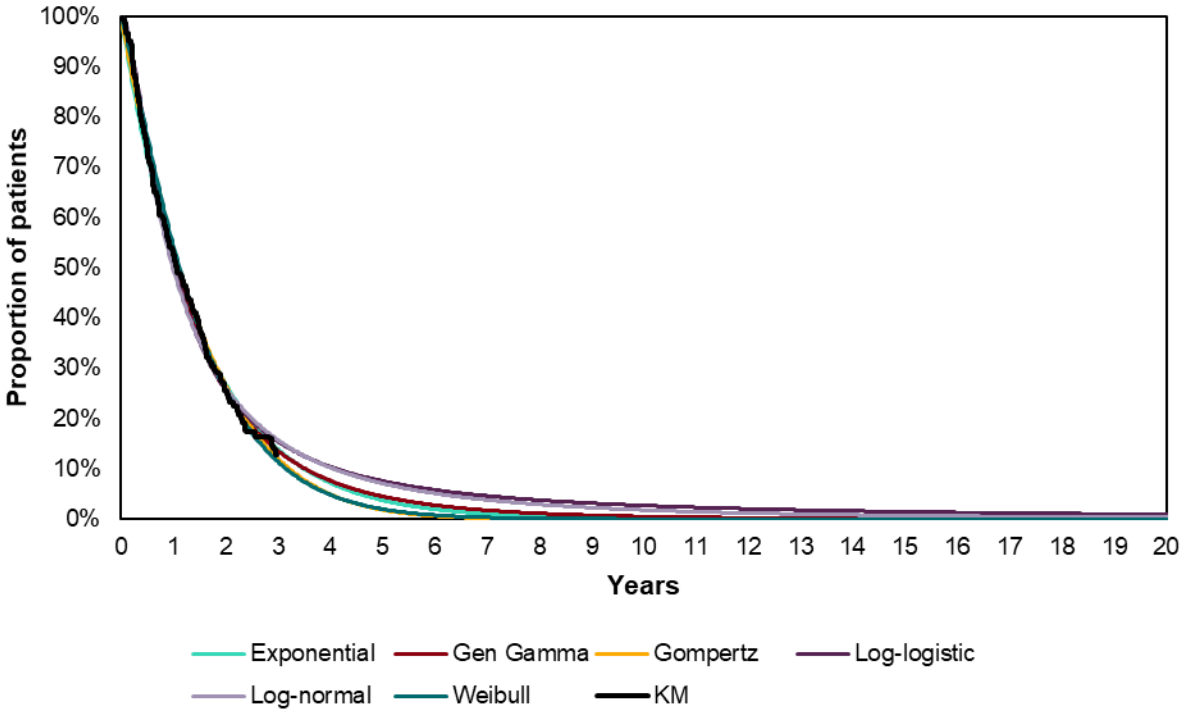
Table 20: Statistical goodness-of-fit scores – LUME-Lung – OS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	2008.41	2012.18	5	5
Weibull **(Selected)**	2002.77	2010.32	4	4
Gompertz	2008.50	2016.05	6	6
Log-logistic	2000.16	2007.70	3	2
Log-normal	1999.99	2007.54	2	1
Generalised gamma	1997.59	2008.91	1	3

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

All curves appeared to fit the data well. Most clinicians expected that survival of patients with wild-type NSCLC treated with docetaxel + nintedanib would be similar to docetaxel, at around 1-3% at five-years and 0% by 10 years. Exponential and Weibull sat within this plausible range with the other curves predicting much higher, unrealistic estimates for this population with a poor prognosis. As such, based on goodness of fit, visual fit and long-term plausibility, exponential was selected to inform the base case OS.

Figure 20: Parametric curve fits – LUME-Lung – OS



Key: KM, Kaplan-Meier; OS, overall survival

Progression-free survival

The statistical goodness of fit scores are presented in Table 21. Based on AIC and BIC scores, the log-normal distribution is the best fitting, closely followed by generalised gamma which had reasonably similar fits (within five points). Therefore the curves were visually compared in Figure 21.

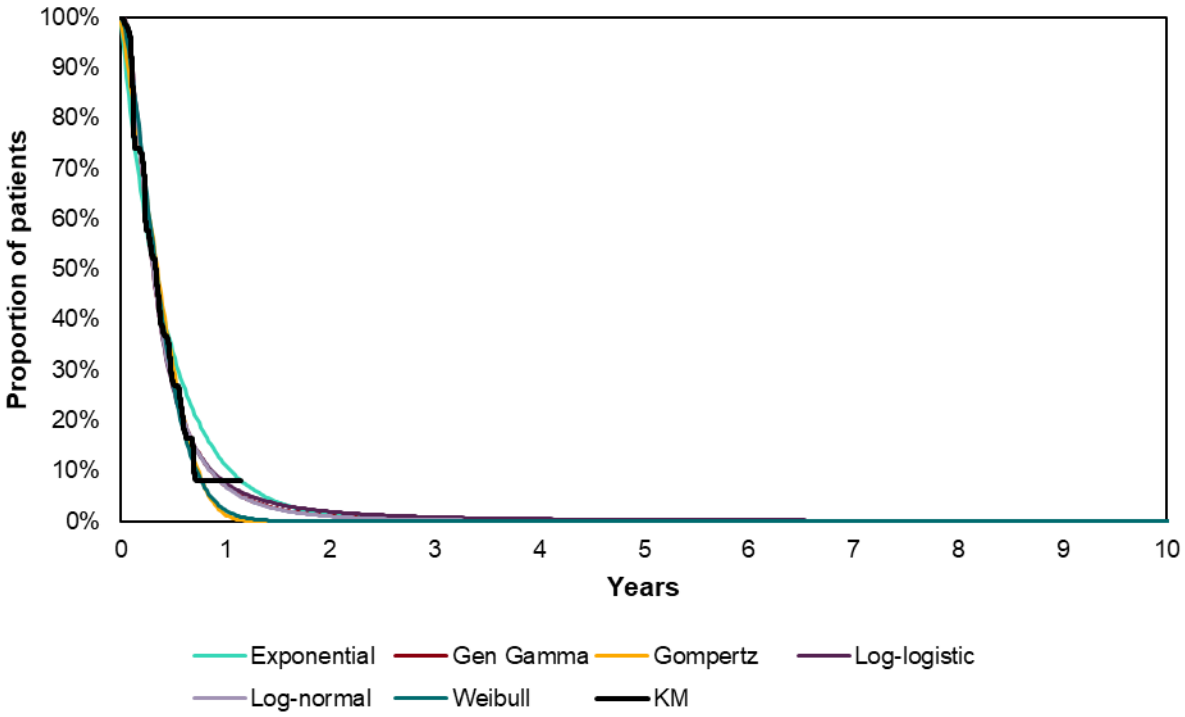
Table 21: Statistical goodness-of-fit scores – LUME-Lung 1 – PFS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	850.71	854.34	6	6
Weibull	808.12	815.37	4	4
Gompertz	830.06	837.30	5	5
Log-logistic **(Selected)**	801.16	808.41	3	3
Log-normal	794.21	801.46	1	1
Generalised gamma	796.21	807.08	2	2

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

All curves appeared to fit the data well. Clinicians expected that PFS of patients with wild-type NSCLC treated with docetaxel + nintedanib would be similar to that of docetaxel at around 1-1.5% at five-years with all patients progressed or dead by 10 years. All curves apart from log-logistic estimated that all patients had progressed by 5 years. As such, based on goodness of fit, visual fit and long-term plausibility, log-logistic was selected to inform the base case PFS.

Figure 21: Parametric curve fits – LUME-Lung – PFS



Key: KM, Kaplan-Meier; PFS, progression-free survival

Tepotinib

To inform the efficacy of tepotinib in comparison to docetaxel + nintedanib, previously treated VISION data (A+C cohort) was matched to the LUME-Lung 1 trial, described in Appendix 2. PSMs were fitted to weighted OS and PFS data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate over a life-time horizon. Visual fit, along with AIC/BIC score and plausibility of long-term estimates were then used to inform the most appropriate curve to take forward for the base case.

Overall survival

The statistical goodness of fit scores are presented in Table 22. Based on AIC and BIC scores, the log-normal and exponential distributions are the best fitting, however the other curves provide reasonably similar fits (within five points) and so were visually compared in Figure 22.

Table 22: Statistical goodness-of-fit scores – VISION (weighted to LUME-Lung) – OS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	158.71	161.67	4	1
Weibull	159.92	165.83	5	5
Gompertz	160.71	166.62	6	6
Log-logistic	158.12	164.04	3	3
Log-normal **(Selected)**	156.53	162.44	2	2
Generalised gamma	156.09	164.95	1	4

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

All curves appeared to fit the data reasonably well with the exception of generalised gamma. Clinicians expect that patients treated with tepotinib would have substantially longer OS than patients treated with docetaxel plus nintedanib. Log-normal, log logistic and generalised gamma sat within this plausible range. As such, based on goodness of fit, visual fit and long-term plausibility, log-normal was selected to inform the base case OS.

Figure 22: Parametric curve fits – VISION (weighted to LUME-Lung) – OS

Key: KM, Kaplan-Meier; OS, overall survival

Progression-free survival

The statistical goodness of fit scores are presented in Table 23. Based on AIC and BIC scores, the log-normal distribution is the best fitting, however all curves had reasonably similar fits (within five points). Therefore the curves were visually compared in Figure 23.

Table 23: Statistical goodness-of-fit scores – VISION (weighted to LUME-Lung) – PFS

Parameterisation	AIC	BIC	Rank	
			AIC	BIC
Exponential	192.55	195.51	5	3
Weibull	191.94	197.86	4	4
Gompertz	194.36	200.27	6	6
Log-logistic	189.57	195.49	2	2
Log-normal **(Selected)**	189.05	194.96	1	1
Generalised gamma	191.04	199.91	3	5

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression-free survival

All curves appeared to fit the data well apart from exponential which overestimated PFS from 6 months. Based on goodness of fit, visual fit and long-term plausibility, log-normal was selected to inform the base case PFS.

Figure 23: Parametric curve fits – VISION (weighted to LUME-Lung 1) – PFS

Key: KM, Kaplan-Meier; PFS, progression-free survival

Final curves

Figure 24 presents the final curves selected to inform the base case of tepotinib versus docetaxel + nintedanib.

Figure 24: Final base case – tepotinib versus docetaxel + nintedanib

Key: KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival

Appendix 1e: Supplementary analyses economic results

Results for supplementary analyses

Results for the supplementary comparisons are presented in Table 24.

Table 24: Base case results – tepotinib versus other comparators

Treatment	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Untreated PD-L1≥50% – tepotinib versus immunotherapy (using RWD)							
Tepotinib	[redacted]	2.94	[redacted]				
Immunotherapy	[redacted]	2.43	[redacted]	[redacted]	0.51	[redacted]	Dominant
Untreated PD-L1≥50% – tepotinib versus pembrolizumab (clinical trial)							
Tepotinib	[redacted]	4.73	[redacted]				
Pembrolizumab	[redacted]	5.22	[redacted]	[redacted]	-0.49	[redacted]	£151,609 (SW)
Previously treated, all PD-L1 subgroups – tepotinib versus docetaxel (clinical trial)*							
Tepotinib	[redacted]	2.21	[redacted]				
Docetaxel	[redacted]	1.00	[redacted]	[redacted]	1.21	[redacted]	£52,605
Previously treated – tepotinib versus docetaxel + nintedanib (clinical trial)*							
Tepotinib	[redacted]	2.55	[redacted]				
Docetaxel + nintedanib	[redacted]	1.53	[redacted]	[redacted]	1.02	[redacted]	£47,142

Key: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years; SW, South-West quadrant

*End of life criteria applies in these comparisons, see ACD response for further details.

For all comparisons, tepotinib remains cost-effective at the relevant £30,000 and £50,000 thresholds, with the exception of the docetaxel comparison which sits just above the relevant £50,000 end-of-life threshold. However, results presented do not account for confidential discounts for comparator treatments (just for tepotinib). The ICER for tepotinib compared to docetaxel is sensitive to any PAS for nintedanib specifically, as this is a subsequent treatment in the tepotinib arm in the previously-treated setting, based on clinical expert feedback. A small discount for nintedanib brings the docetaxel comparison to below the £50,000, as explored in confidential scenario analyses run by the company. Confidential discounts for the other treatments, including pembrolizumab, would of course alter the presented ICERs as well.

Scenario analyses

To address the key uncertainties regarding long-term estimates and subsequent treatments, scenarios were conducted, varying these individually (For the different parametric curve scenarios, bold indicates the clinically plausible curves, as indicated by clinical expert opinion for the realistic curves estimates for comparators, and their expectation of tepotinib OS/PFS in comparison. If there are not clinically plausible alternatives, the best fitting curves statistically are bolded, primarily for PFS. Please see the more detailed curve selection process in Appendix 1d and the clinical expert feedback in Appendix 1c for more details. '*' indicates the curve selected in the final economic model.

Table 25). Each parametric curve for tepotinib and comparator is varied in turn for OS and PFS. For subsequent treatments the following scenarios have been run:

- Assuming the proportion of patients who get docetaxel versus docetaxel + nintedanib is 50/50

- Assuming that 50% or 90% of patients go onto immunotherapy after tepotinib instead of 75%
- Varying the immunotherapy treatments received after tepotinib
- Assuming 50% of patients receive subsequent treatment after progressing

For the different parametric curve scenarios, bold indicates the clinically plausible curves, as indicated by clinical expert opinion for the realistic curves estimates for comparators, and their expectation of tepotinib OS/PFS in comparison. If there are not clinically plausible alternatives, the best fitting curves statistically are bolded, primarily for PFS. Please see the more detailed curve selection process in Appendix 1d and the clinical expert feedback in Appendix 1c for more details. '*' indicates the curve selected in the final economic model.

Table 25: Scenario results – supplementary analyses – tepotinib versus comparators

Parameter	Base case	Scenario	ICERs			
			Vs immunotherapy (vs RWD)	Vs pembrolizumab	Vs docetaxel	Vs docetaxel + nintedanib
OS - tepotinib	Various – see Appendix 1d	Exponential	£241,541	£42,090 (SW)	**£52,605***	£62,058
		Gen Gamma	£200,686	£37,650 (SW)	£32,329	**£19,753**
		Gompertz	£97,440	£31,428 (SW)	£73,552	£58,291
		Log-logistic	**Dominant***	**£65,838 (SW)**	**£44,921**	**£43,978**
		Log-normal	**Dominant**	**£151,609 (SW)***	**£46,756**	**£47,142***
		Weibull	£90,342	£32,355 (SW)	£71,956	£98,933
PFS - tepotinib	Various – see Appendix 1d	Exponential	Dominant	£118,327 (SW)	£52,732	£47,474
		Gen Gamma	**Dominant**	**£145,672 (SW)**	£53,080	**£47,023**
		Gompertz	**Dominant**	**£159,313 (SW)**	£53,236	**£47,823**
		Log-logistic	**Dominant**	**£151,609 (SW)***	**£52,220**	**£46,549**
		Log-normal	**Dominant***	**£158,915 (SW)**	**£52,605***	**£47,142***
		Weibull	Dominant	£113,804 (SW)	£53,474	**£48,126**
OS – comparator	Various – see Appendix 1d	Exponential	**Dominant**	Dominant	£48,773	**£47,142***
		Gen Gamma	**Dominant**	£635,838 (SW)	**£52,085**	£49,266
		Gompertz	Dominant	£174,716 (SW)	£48,457	£44,762
		Log-logistic	£45,348	**£144,760 (SW)**	**£55,551**	£68,495
		Log-normal	£40,209	**£151,609 (SW)***	**£52,605***	£59,251
		Weibull	Dominant	Dominant	£48,023	**£45,172**
PFS – comparator		Exponential	**Dominant**	£216,122 (SW)	£52,438	£45,470

Parameter	Base case	Scenario	ICERs			
			Vs immunotherapy (vs RWD)	Vs pembrolizumab	Vs docetaxel	Vs docetaxel + nintedanib
	Various – see Appendix 1d	Gen Gamma	Dominant	**£151,609 (SW)***	£52,459	£47,401
		Gompertz	Dominant	£130,391 (SW)	£52,419	£48,944
		Log-logistic	Dominant	£179,027 (SW)	**£52,605***	**£47,142***
		Log-normal	**Dominant**	£182,989 (SW)	£52,485	£47,469
		Weibull	**Dominant**	£201,500 (SW)	£52,359	£49,265
Subsequent treatments – tepotinib (untreated)	75% pembrolizumab; 75% platinum-based chemotherapy	50% pembrolizumab vs platinum chemotherapy	Dominant	£188,601 (SW)	NA	
		90% pembrolizumab vs platinum chemotherapy	Dominant		NA	NA
		75% immunotherapy split between pembrolizumab/ atezolizumab/nivolumab	Dominant	£129,414 (SW)	NA	NA
Subsequent treatments – tepotinib (previously treated)	20% pemetrexed + carboplatin; 80% docetaxel + nintedanib	50% pemetrexed + carboplatin; 50% docetaxel + nintedanib	NA	NA	£58,722	£55,616
Subsequent treatments	90% docetaxel + nintedanib; 10% docetaxel monotherapy	50% docetaxel + nintedanib; 50% docetaxel monotherapy	Dominant	£151,712 (SW)	£47,812	£40,501
Proportion receiving subsequent treatment	100%	Assuming 50% receive subsequent treatment after progressing	Dominant	£207,459 (SW)	£43,945	£35,145

Key: ICERs, incremental cost-effectiveness ratio; NA, not applicable; OS, overall survival; PFS, progression-free survival; QALYs, quality-adjusted life-years; SW, South-West

'*' indicates the curve selected in the final economic model. **Bold** indicates curves within the range deemed to be clinically plausible based on clinical expert interviews.

The plausible OS curve scenario analyses are explored in more detail below. PFS has not been explored in this level of detail for time constraints, although the PFS curve selection has smaller impact on the ICERs.

Summary of plausible OS curves in scenario analyses

- For the immunotherapy RWD OS, spline models were fit, which were not explored in scenario analyses here due to time constraints. The two best fitting parametric curves (exponential and generalised gamma), also resulted in a dominant ICER for tepotinib in scenario analyses. Please see the relevant section above in Appendix 1d for more details on why the other curves were deemed to be clinically implausible. For this comparison, the tepotinib OS was selected as log-logistic. The only other plausible alternative was log-normal, based on clinical feedback which expected at least similar long term OS compared to immunotherapy monotherapy in the METx14 skipping population, also aligned with ITC results.
- For the pembrolizumab clinical trial comparison (PD-L1≥50%), only log logistic and log normal were deemed to be clinically plausible for pembrolizumab by clinical experts for OS, based on long term survival estimates. Tepotinib remains cost-effective with these selections. For the tepotinib OS selection in this curve, only log normal and log logistic were deemed to be clinically plausible by clinical experts, based on expectations of similar OS between tepotinib and pembrolizumab in a matched population. Log normal was deemed to be the most plausible, based on the closest match to pembrolizumab OS, although in the scenario of log logistic, tepotinib remains cost-effective. Please see the relevant section above for more details on curve selection and clinically plausible estimates.
- For the docetaxel monotherapy comparison in the previously-treated setting for OS, log-normal, log-logistic and generalised gamma were deemed by experts to be the clinically plausible curves, where all report similar cost-effective results, around the £50,000 threshold. For tepotinib OS in this comparison, exponential, log normal and log logistic were deemed by experts to be the plausible ranges of OS for tepotinib, based on the expectation of large survival benefit, also seen in the ITC. The two curves not selected (log normal and log logistic) actually decrease the tepotinib ICER. Please see the relevant section above for more details on curve selection and clinically plausible estimates.
- For the docetaxel + nintedanib comparison in the previously treated setting, exponential and Weibull sat within the plausible ranges for survival given by clinical experts, with the other curves predicting much higher, unrealistic estimates for this population with a poor prognosis. In the other plausible curve not selected (exponential) tepotinib remains cost-effective. For the tepotinib OS curve, log-normal, log logistic and generalised gamma sat within the plausible range of estimating a large benefit for OS over docetaxel + nintedanib. In the other plausible curve not selected for tepotinib (log logistic) tepotinib is even more cost-effective. Please see the relevant section above for more details on curve selection and clinically plausible estimates.

Discussion

One-way sensitivity analyses and probabilistic sensitivity analyses are not presented for these supplementary comparisons, as due to time limitations in preparing the ACD response, the focus was placed on the most relevant comparison versus chemo-immunotherapy, presented in the ACD response document.

However, in the results presented for these supplementary analyses, and across the vast majority of scenarios explored, tepotinib is shown to be cost-effective against immunotherapy (using updated and validated METex14 skipping observational data in line with clinical expert opinion; untreated, PD-L1≥50%) as well as comparisons to clinical trial data, for pembrolizumab monotherapy (untreated, PD-L1≥50%) and docetaxel +/- nintedanib (previously-treated patients, regardless of PD-L1 expression), including for all clinically plausible scenario analyses, indicated by clinically expert opinion.

Of note for these supplementary comparisons, Merck consider the immunotherapy real-world data specific to the METex14 skipping NSCLC population more appropriate than the clinical trial data for pembrolizumab. METex14 skipping patients are known to respond worse to immunotherapy monotherapy, and so where validated data in this specific population is available, aligned to clinical expert opinion, the true ICERs are likely to be closer to these results, rather than the clinical trial data in the wildtype NSCLC population. This is discussed further in the ACD response and Appendix **2**.

Tepotinib is also shown to be cost-effective compared to docetaxel +/- nintedanib in the previously-treated setting, and in the ITC (Appendix 2) shows substantially greater OS and PFS, highlighting the large and important benefit tepotinib can offer patients in the previously treated setting, where currently only poorly tolerated chemotherapy options are available, with limited clinical benefit and a high unmet need. These comparisons are believed to be more appropriate than the analyses based on the METex14 skipping population previously provided, where the committee and clinical experts felt that the chemotherapy outcomes were substantially higher than expected in NHS practice.

Appendix 1f: VISION subsequent treatment data

Table 26. Subsequent treatment distributions from VISION – untreated and previously treated populations separately for Cohort A

		Untreated patients (n=69)		Previously treated patients (n=82)	
		n	Percent	n	Percent
Patients who received any subsequent treatment		[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
	Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]
	Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
	Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Platinum	Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
	Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
MET inhibitor	Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Other	Other chemo	[redacted]	[redacted]	[redacted]	[redacted]
	Other targeted	[redacted]	[redacted]	[redacted]	[redacted]
	Other MET	[redacted]	[redacted]	[redacted]	[redacted]
	Nintedanib	[redacted]	[redacted]	[redacted]	[redacted]
	Investigational	[redacted]	[redacted]	[redacted]	[redacted]

Table 27. Subsequent treatment distributions from VISION – untreated and previously treated populations separately for Cohort A+C

		Untreated patients (n=69)		Previously treated patients (n=82)	
		n	Percent	n	Percent
Patients who received any subsequent treatment		[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]
	Atezolizumab	[redacted]	[redacted]	[redacted]	[redacted]
	Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	Pemetrexed	[redacted]	[redacted]	[redacted]	[redacted]
	Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]
	Gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]
Platinum	Cisplatin	[redacted]	[redacted]	[redacted]	[redacted]
	Carboplatin	[redacted]	[redacted]	[redacted]	[redacted]
MET inhibitor	Crizotinib	[redacted]	[redacted]	[redacted]	[redacted]
Other	Other chemo	[redacted]	[redacted]	[redacted]	[redacted]
	Other targeted	[redacted]	[redacted]	[redacted]	[redacted]
	Other MET	[redacted]	[redacted]	[redacted]	[redacted]
	Nintedanib	[redacted]	[redacted]	[redacted]	[redacted]
	Investigational	[redacted]	[redacted]	[redacted]	[redacted]

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Supplementary analyses for tepotinib in advanced NSCLC: Appendix 2

Prepared as part of response to NICE Appraisal Consultation Document (ACD) for tepotinib in advanced NSCLC with MET gene alterations (ID3761)

Date: 23 February 2022

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1. INTRODUCTION

The original submission to NICE for tepotinib in the treatment of patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition (MET) exon 14 (ex14) skipping alterations (ID3761) centred around an indirect treatment comparison (ITC) between tepotinib and its comparators; immunotherapy and chemotherapy. This comparison was conducted using the latest data cut (1 February 2021) available from Cohort A of the pivotal phase II VISION study to inform the tepotinib data, and real-world data comprising of METex14 skipping NSCLC patients from four observational studies to inform the comparator data.

In the time since the original submission in July 2021, further data have become available. Firstly, Cohort C, the confirmatory cohort in VISION is now available for use. In addition, a further real-world dataset, the Group Francais de Pneumo-Cancérologie (GFPC) dataset, has been made available to Merck. The use of updated data for both arms of the study increases patient numbers, increasing confidence in the comparisons, extrapolations, and allowing further analysis than was previously possible – for example analysis by line, and by some individual agents.

Using the newly available data, updated comparisons are presented for tepotinib versus immunotherapy and for tepotinib versus chemotherapy for relevant line of therapy subgroups highlighted by clinical expert opinion as well as in the NICE Appraisal Consultation Document (ACD). Furthermore, additional exploration of the real-world cohort outcomes are presented, including why some of the outcomes are not always aligned to expectations of UK practice. Validation against other published studies in METex14 skipping is also conducted.

Finally, in addition to the real-world data comparison, feedback from the ACD indicated an interest in assessing tepotinib (indirectly) compared to the published outcomes of clinical trials in the general NSCLC population (i.e., wildtype NSCLC, not specifically METex14 skipping patients). Therefore, this report also includes indirect comparisons against published wildtype NSCLC data for the chemo-immunotherapy combination, immunotherapy monotherapy, and chemotherapy monotherapy.

2. ADDITIONAL DATA SOURCES IN METEX14 SKIPPING NSCLC

2.1. VISION Cohort A+C data

Summary: The NICE ACD expressed a preference for updating the ITC with the larger Cohort A+C dataset from VISION, using the latest data cut (February 2021). Therefore, this update has been carried out, for the updated real-world cohort ITC, as well as the new clinical trial comparison in wildtype NSCLC presented later on. This section describes the additional Cohort C patients added to the analysis, and demonstrates the similarities between the patient groups. The larger Cohort A+C provides more certainty in observed results and in the efficacy of tepotinib in METex14 skipping patients.

The confirmatory VISION C dataset provides data from an additional 139 patients in total, with similar patient characteristics observed compared to VISION Cohort A (per the original NICE submission), as shown in Table 1.

Table 1: Patient characteristics for VISION Cohort A versus VISION Cohort C

Characteristic		VISION A	VISION C	p-value	SMD
n					
Study	VISION A				
	VISION C				
Prior Treatment	Naïve (%)				
	Experienced (%)				
Age	Mean (SD)				
	% over 75				
Sex	Male (%)				
	Female (%)				
Smoking history	Yes (%)				
	No (%)				
Race	White (%)				
	Asian (%)				
	Black or African American (%)				
	Other (%)				
	Not available				
Stage	IIIB+				
	IV				
	Not available				
Advanced / Metastatic	Advanced				
	Metastatic				
Histology	Adenocarcinoma (%)				
	Squamous (%)				
	Sarcomatoid (%)				
	Other (%)				
	Not available				

Key: n, number; SD, standard deviation; SMD, standardised mean difference.

Figure 1 and Figure 2 present the progression-free survival (PFS) and overall survival (OS) Kaplan-Meier (KM) curves for Cohort A versus Cohort C. Outcomes between Cohorts are observed to be similar between groups, with the key difference being the degree of follow up between cohorts, with limited follow up available for Cohort C.

The full dataset of Cohort A+C (n=290) is marginally larger than from the 275 patients with at least 3 months of follow up, described previously in technical engagement and in the original company submission. Although the additional 15 patients add little for long-term extrapolation, they do further increase confidence in the short term results of tepotinib,

and there is no statistical reason for their exclusion when analysis is performed. Therefore, the full 290 patients have been included.

Figure 1: Investigator progression-free survival, VISION Cohort A versus VISION Cohort C

Figure 2: Overall survival, VISION Cohort A versus VISION Cohort C

Figure 3: Progression-free survival & Overall survival, VISION A+C pooled

2.2. GFPC data in METex14 skipping NSCLC

Summary: Recently a fifth real-world dataset for outcomes in advanced METex14 skipping NSCLC became available to Merck. This is an additional dataset from France known as the GFPC data set. This section introduces the additional data set and describes the process for including this data in the overall cohort analysis. Importantly, it is demonstrated that the results of the overall real-world cohort are not impacted by the addition or removal of a single data set, further supporting the validity of the METex14 skipping outcomes observed.

The GFPC dataset came from data collected during routine practice from a range of specialist centres in France, from 2013 to 2020. A range of patient characteristics were captured (age, smoking status, sex) as well as clinical characteristics (MET mutation status and histology). Outcome data included Time to Next Treatment or Death (TNTD), OS and response status, for chemotherapy, immunotherapy and MET inhibitors. The design and reporting was similar to the four other observational provided as part of the real-world cohort – please see Section B.2.9.1 of the company submission for a description of the other observational studies, and the wider ITC methodology.

Table 2 summarises the baseline characteristics (split by treatment line) of the patients in the GFPC dataset. The GFPC data contains 91 unique patients, followed through the majority of their treatment lines, with data on 190 treatment lines available in total.

Table 2: Patient characteristics of the GFPC dataset, split by treatment experience

Characteristic		Untreated	Previously treated
n	Unique individuals		
	Individuals with lines		
	Total treatment lines		
Age	Mean (SD)		
	Median		
Sex	Male		
	Female		
Smoking history	Yes		
	No		
Race	White		
	Asian		
	Black or African American		
	Other		
	Not Available		
Advanced / Metastatic	Advanced		
	Metastatic		
Histology	Adenocarcinoma		
	Squamous		
	Sarcomatoid		
	Other		
	Not available		

Abbreviations: n, number; SD, standard deviation.

Table 3 presents the treatments received by patients in the GFPC dataset. A variety of treatments were administered, with the majority of patients receiving crizotinib, immunotherapy (pembrolizumab and nivolumab), and various chemotherapy regimens.

Table 3: Treatments received by patients in the GFPC dataset

Regimen	Frequency
Crizotinib	
Carboplatin, pemetrexed	
Pembrolizumab	

Regimen	Frequency
Carboplatin, paclitaxel	[redacted]
Nivolumab	[redacted]
Cisplatin, pemetrexed	[redacted]
Capmatinib	[redacted]
Chemotherapy monotherapy	[redacted]
Bevacizumab, cisplatin, pemetrexed	[redacted]
Immunotherapy	[redacted]
Bevacizumab, carboplatin, pemetrexed	[redacted]
Bevacizumab, carboplatin, paclitaxel	[redacted]
Cabozanitib	[redacted]
Carboplatin, vinorelbine	[redacted]
Cisplatin, vinorelbine	[redacted]
Erlotinib	[redacted]
Unknown	[redacted]
Cisplatin, gemcitabine	[redacted]
Docetaxel	[redacted]
Gemcitabine, pemetrexed	[redacted]
Pemetrexed	[redacted]
Platinum	[redacted]

When combined, MET inhibitors and immunotherapy comprise the majority of treatments administered in the GFPC dataset in the treatment experienced setting. Another further observation was that patients generally change treatment class following each line, with only a few repeating a treatment class. This can be observed in the Sankey plot below (Figure 4).

Figure 4: Sankey plot of patient flow through treatment lines in the GFPC dataset

No PFS data are available from the GFPC data however, TTNTD data are included. In the absence of PFS, TTNTD is used as a proxy to inform this outcome, aligned with the approach taken in the other four real-world data studies used in the ITC.

To explore the impact of each real-world study upon the overall real-world cohort data PFS and OS KM curves, a 'leave one out' analysis was performed. In this analysis, each study is omitted in turn, with the remaining data reweighted to match the tepotinib data from VISION (thus holding patient characteristics constant). Kaplan-Meier curves are then re-

estimated, and plotted on the same axis for each omitted dataset. Figure 5 to Figure 8 present the results of this analysis for immunotherapy and chemotherapy for PFS and OS. In this analysis, should one study have an unusually large impact it will be apparent in the KM plot as the survival curve would appear noticeably different.

Figure 5: Leave one out analysis for immunotherapy Progression Free Survival

Figure 6: Leave one out analysis for immunotherapy Overall Survival

Figure 7: Leave one out analysis for chemotherapy Progression Free Survival

Figure 8: Leave one out analysis for chemotherapy Overall Survival

In both the immunotherapy and chemotherapy comparisons, all five datasets present similar outcomes. Specifically, the GFPC dataset appears to provide immunotherapy outcomes around the centre of the range seen with the original ITC studies, and provides amongst the most optimistic chemotherapy outcomes (likely a direct result of the high use of MET inhibitors as subsequent treatment).

2.3. Updated comparisons conducted and presented to NICE as part of ACD response

Summary: This section briefly describes the updated real-world data comparisons provided to NICE in this document as part of the ACD response, and the relevance of each for the committee's decision making.

As a result of the increased data availability, all of the comparisons for tepotinib compared to the METex14 skipping real world cohort for immunotherapy and/or chemotherapy can be updated with Cohort A+C and the additional real-world cohort dataset (GFPC), using the same methodology as in the original NICE submission (i.e., propensity scoring on observed characteristics).

Although updated comparisons for all comparators are possible, they are not all appropriate for the updated analysis provided to NICE as part of the ACD response. Firstly, the NICE committee have highlighted that they would prefer to see analysis by line of therapy subgroups separately, and so the line agnostic groups are not relevant and therefore not presented. Furthermore, clinical experts have highlighted not all treatments are appropriate at all lines of therapy in NHS practice for wildtype NSCLC. In particular, immunotherapy is given typically to untreated patients, and so there is next to no later line use for immunotherapy in NHS practice. Furthermore, very few patients receive

chemotherapy up front, and so chemotherapy is almost entirely given to previously-treated patients in NHS practice.

Therefore the updated comparisons using Cohort A+C and the updated real-world cohort data are described in Table 4. It is further highlighted which of these have been carried forward to the economic model.

Table 4. Real-world cohort ITC and economic model updates provided as part of ACD response

Comparator	Line of therapy	N	Updated MAIC presented here in Appendix 2?	Updated in economic model?
Immunotherapy (IO) monotherapy	Line agnostic	[redacted]	**No** – line agnostic not relevant as per ACD	**No**
	Untreated	[redacted]	**Yes** – relevant group for IO based on ACD and clinical expert feedback	**Yes** – to provide a more realistic alternative to using IO clinical trial data for cost-effective estimates
	Previously treated	[redacted]	**No** – not relevant subgroup for IO based on ACD and clinical expert feedback	**No**
Pembrolizumab monotherapy*	Line agnostic	[redacted]	**Yes** – to provide additional validation of IO outcomes as requested by ERG	**No** – line agnostic not relevant for cost-effective analysis as per ACD
Chemotherapy	Line agnostic	[redacted]	**No** – line agnostic not relevant as per ACD	**No**
	Untreated	[redacted]	**No** – not relevant subgroup for chemo based on ACD and clinical expert feedback	**No**
	Previously treated	[redacted]	**Yes** – relevant group for chemo based on ACD and clinical expert feedback	**No** – as the committee deemed chemotherapy outcomes to be unplausible for NHS practice. Clinical trial comparisons deemed to be more appropriate here
Chemo-immunotherapy	Untreated	[redacted]	**Yes -** to provide validation to chemo-IO outcomes in clinical trial comparison	**No** – too few patients available. Clinical trial comparison deemed to be more appropriate here

*The pembrolizumab-only comparison contains enough patients in the line agnostic cohort only. Although the line agnostic cohort is not relevant according to the ACD, this comparison has been provided to support validation of the larger immunotherapy group outcomes, whilst also complying with a request from the ERG at Technical Engagement.

As mentioned previously and in the ACD response, Merck believe the real-world cohort outcomes for immunotherapy in METex14 skipping NSCLC to be aligned with other published studies in METex14 skipping NSCLC, and clinical expectation versus wildtype NSCLC. Therefore, the focus of the update has been the updated immunotherapy outcomes in untreated patients, which has been carried through to the economic model in Appendix 1.

3. COMPARISONS OF TEPOTINIB TO REAL WORLD DATA

3.1. Comparison to immunotherapy monotherapy - Untreated population

Summary: The updated comparison to immunotherapy monotherapy in untreated patients, using the larger real-world cohort in METex14 skipping NSCLC patients, is reported here. In the ACD response, Merck demonstrate how the immunotherapy outcomes are in line with other published studies in METex14 skipping NSCLC in the relevant untreated population, and in line with clinical expectations compared to wildtype NSCLC. Further validation is presented later in this document, supporting the view that this comparison is still appropriate for decision making. In addition, a separate analysis is presented using only real-world pembrolizumab data, to support the outcomes seen in the larger immunotherapy cohort.

3.1.1. Comparison to immunotherapy monotherapy using METex14 skipping real-world cohort data

The comparison to immunotherapy presented for the untreated population in the original submission has been updated to include the additional data for both tepotinib (Cohort A+C), and the GFPC real-world data. Patient characteristics for immunotherapy before and after weighting and tepotinib are presented in Table 5.

Before weighting, the groups were reasonably well balanced statistically, with the largest difference observed in smoking history. Following the application of the propensity score weighting in the immunotherapy arm, the groups display an improved statistical balance with minimal loss of sample size, 32 reducing to 29, compared to the 148 untreated tepotinib patients across VISION A+C.

Table 5: Patient characteristics of the untreated immunotherapy sample compared to VISION Cohort A+C

Characteristic		Immunotherapy		VISION A+C	Unweighted		Weighted	
		Unweighted	Weighted		p-value	SMD	p-value	SMD
n								
WSS (ESS)								
Study	0015							
	0035							
	COTA							
	Wong et al.							
	GFPC							
	VISION A							
	VISION C							
Prior Treatment	Naïve (%)							
	Experienced (%)							
Age	Mean (SD)							
	% over 75							
Sex	Male (%)							
	Female (%)							
Smoking history	Yes (%)							
	No (%)							
Race	White (%)							
	Asian (%)							
	Black or African American (%)							
	Other (%)							
	Not available							
Stage	IIIB+							
	IV							
	Not available							
Advanced / Metastatic	Advanced							
	Metastatic							
Histology	Adenocarcinoma (%)							
	Squamous (%)							
	Sarcomatoid (%)							
	Other (%)							
	Not available							

Key: ESS, Effective Sample Size; n, Number; SD, standard deviation; SMD, standardised mean difference; WSS, Weighted Sample Size.

The treatments received, before and after weighting in the immunotherapy arm, are shown in the table below. As can be seen this is overwhelmingly pembrolizumab, aligned to NHS practice, and it is likely also that the unspecified immunotherapies are also pembrolizumab, based on the treatments available for untreated NSCLC in Canada (from the Wong et al dataset).

Table 6: Treatments received in the immunotherapy group

Treatment	Unweighted (n=32)	Weighted (n=139)
Pembrolizumab	[redacted]	[redacted]
Immunotherapy		
Ipilimumab, nivolumab		
Nivolumab		

Figure 9 shows the resulting weighted curves for OS and PFS. Tepotinib shows consistently greater PFS, with similar OS for the full time period, compared to immunotherapy monotherapy in untreated METex14 skipping patients.

Figure 9: PFS and OS for previously untreated immunotherapy compared to tepotinib, weighted

[redacted]

Outcomes in terms of survival milestones and restricted mean survival time (RMST) estimates are presented in Table 7. Tepotinib shows statistically longer PFS (Weighted Cox PH model p = 0.03, Weighted Log-rank test p=0.03). OS estimates cross (rendering point estimates unreliable), however the RMST estimates appear similar for OS throughout the observed period, with also similar median OS between groups. These outcomes are consistent to what was seen in the previous ITC (with Cohort A and without the GFPC dataset included).

Table 7: Kaplan-Meier and RMST estimates for previously untreated immunotherapy and tepotinib

	Percentage (%)			RMST (months)		
	Unweighted	Weighted	VISION A+C	Unweighted	Weighted	VISION A+C
Patients						
Progression-free survival						
Median						
95% CI						
Number of events						
30 months (max for RMST)						
3 months						
6 months						
9 months						
12 months						
24 months						
36 months						
Overall survival						
Median						
95% CI						
Number of events						
30 months (max for RMST)						
3 months						
6 months						
9 months						
12 months						
24 months						
36 months						

Key: CI, confidence interval; RMST, restricted mean survival time

The comparison of summary statistics in Table 7 demonstrate that the OS outcomes are similar between tepotinib and immunotherapy treatments in untreated METex14 skipping patients. However there is uncertainty in long term survival outcomes with comparisons likely confounded by subsequent treatment. However tepotinib also shows greatly improved PFS which is not confounded by subsequent treatments.

3.1.2. Comparison to pembrolizumab

Due to the increased patient numbers available from the GFPC dataset, it is possible to perform a comparison to the subset of patient receiving pembrolizumab specifically in the line agnostic cohort, as requested by the ERG at Technical Engagement. This provides a useful validation for the larger immunotherapy cohort. However, it should be noted that due to the limited number of patients available for the comparison (n=51) there is increased uncertainty for this comparison, and furthermore it can only be conducted in the overall patient population due to patient numbers.

Prior to weighting, the groups were reasonably well balanced, aside from smoking history, with a loss in effective sample size from weighting to 37.5 patients (reduced from 51), compared to the 290 tepotinib patients across VISION A and C.

Table 8: Patient characteristics for pembrolizumab compared to VISION Cohort A+C (line agnostic cohort)

Characteristic		Pembrolizumab		VISION A+C	Unweighted		Weighted	
		Unweighted	Weighted		p-value	SMD	p-value	SMD
n								
WSS (ESS)								
Study	0015							
	0035							
	COTA							
	Wong et al.							
	GFPC							
	VISION A							
	VISION C							
Prior Treatment	Naïve (%)							
	Experienced (%)							
Age	Mean (SD)							
	% over 75							
Sex	Male (%)							
	Female (%)							
Smoking history	Yes (%)							
	No (%)							
Race	White (%)							
	Asian (%)							
	Black or African American (%)							
	Other (%)							
	Not available							
Stage	IIIB+							
	IV							
	Not available							
Advanced / Metastatic	Advanced							
	Metastatic							
Histology	Adenocarcinoma (%)							
	Squamous (%)							
	Sarcomatoid (%)							
	Other (%)							
	Not available							

Key: ESS, Effective Sample Size; n, Number; SD, standard deviation; SMD, standardised mean difference; WSS, Weighted Sample Size.

Similarly to the immunotherapy monotherapy group, tepotinib shows significantly greater PFS (p=0.01 for both the weighted Cox PH, and weighted Log-rank test). OS is greater for tepotinib up to 15 months, whereafter OS is similar, and crosses at 18 months, as shown in Figure 10.

Figure 10: PFS and OS for pembrolizumab compared to tepotinib, weighted (line agnostic cohort)

Outcomes in terms of survival milestones and restricted mean survival time estimates are presented in Table 7.

Table 9: Kaplan-Meier and RMST estimates for previously treated pembrolizumab and tepotinib

	Percentage (%)			RMST		
	Unweighted	Weighted	VISION A+C	Unweighted	Weighted	VISION A+C
Patients	51	274.5	290	51	274.5	290
Progression-free survival						
Median						
95% CI						
Number of events						
30 months (max for RMST)						
3 months						
6 months						
9 months						
12 months						
24 months						
36 months						
48 months						
Overall survival						
Median						
95% CI						
Number of events						
30 months (max for RMST)						
3 months						
6 months						
9 months						
12 months						
24 months						
36 months						
48 months						

Key: CI, confidence interval; RMST, restricted mean survival time.

It should be noted that it is likely that patients treated with pembrolizumab could have been excluded from this comparison due to their treatment being recorded as 'immunotherapy', where this treatment is expected to be pembrolizumab in the majority of cases anyway. As such, this comparison should be interpreted in the context of validation, with the overall immunotherapy comparison likely to represent the most relevant comparison, especially with the increase patient numbers available – and thus, ability to analyse by line of therapy. This pembrolizumab-only comparison provides useful validation of the outcomes seen in the larger immunotherapy cohort, further supporting the certainty of the real-world cohort analysis in METex14 skipping NSCLC.

3.2. Comparison to chemotherapy in previously treated patients

Summary: As a part of the NICE submission process, clinical experts highlighted that the most appropriate comparison in the previously-treated patient population was chemotherapy (docetaxel +/- nintedanib, or platinum base chemotherapy, primarily carboplatin + pemetrexed, according to clinical expert opinion). The real-world cohort analysis was therefore updated for chemotherapy patients in the previously-treated setting. Merck acknowledge that the feedback from the ACD that the chemotherapy outcomes were overstated in the initial company submission. As such, Merck believe the clinical trial comparison in previously-treated patients is more relevant and aligned with NHS practice, therefore this is what has been carried forward to the economic model. However the real-world cohort comparison is updated for completeness and transparency. The likely reasons for the overstated outcomes are also explored.

Before weighting, the groups were reasonably balanced statistically. After weighting the similarity between characteristics improves, with some loss of sample size resulting in 45.1 (reduced from 56) in the chemotherapy arm, compared to the 142 previously treated tepotinib patients across VISION A and C.

Table 10: Patient characteristics of chemotherapy compared to VISION Cohort A+C

Characteristic		Chemotherapy		VISION A+C	Unweighted		Weighted	
		Unweighted	Weighted		p-value	SMD	p-value	SMD
n								
WSS (ESS)								
Study	0015							
	0035							
	COTA							
	Wong et al.							
	GFPC							
	VISION A							
	VISION C							
Prior Treatment	Naïve (%)							
	Experienced (%)							
Age	Mean (SD)							
	% over 75							
Sex	Male (%)							
	Female (%)							
Smoking history	Yes (%)							
	No (%)							
Race	White (%)							
	Asian (%)							
	Black or African American (%)							
	Other (%)							
	Not available							
Stage	IIIB+							
	IV							
	Not available							
Advanced / Metastatic	Advanced							
	Metastatic							
Histology	Adenocarcinoma (%)							
	Squamous (%)							
	Sarcomatoid (%)							
	Other (%)							
	Not available							

Key: ESS, Effective Sample Size; n, Number; SD, standard deviation; SMD, standardised mean difference; WSS, Weighted Sample Size.

The treatments received in the chemotherapy arm are shown below, with platinum based chemotherapy the most commonly received intervention across all treatment patterns

Table 11: Treatments received in the chemotherapy group

Treatment	Unweighted (n=56)	Weighted (n=143.7)
Carboplatin, pemetrexed		
Pemetrexed		
Docetaxel		
Gemcitabine		
Platinum doublet		
Bevacizumab, carboplatin, pemetrexed		
Bevacizumab, pemetrexed		
Carboplatin, paclitaxel		
Bevacizumab, carboplatin, paclitaxel		
Bevacizumab, docetaxel		
Carboplatin		
Carboplatin, docetaxel		
Cisplatin, docetaxel		
Cisplatin, pemetrexed		
Docetaxel, gemcitabine		
Everolimus		
Gemcitabine, pemetrexed		
Gemcitabine, vinorelbine		
Vinorelbine		

Figure 12 presents the PFS and OS for tepotinib compared to weighted chemotherapy in the previously treated population. Tepotinib appears to offer a markedly increased PFS, with a gain in OS observed in the short term (up to 21 months). This gain reduces over time as there appears to be a turning point in the shape of the chemotherapy OS hazard at around 12 months.

Figure 11: PFS and OS for chemotherapy compared to tepotinib in the previously treated population, weighted

The patterns observed in Figure 11 are also seen in Table 12, where the OS RMST gain for tepotinib versus chemotherapy is 1 month at 12 months, but by 36 months is equal after weighting.

Table 12: Kaplan-Meier and RMST estimates for chemotherapy and tepotinib in the previously treated population

	Percentage (%)			RMST		
	Unweighted	Weighted	VISION A+C	Unweighted	Weighted	VISION A+C
Patients	56	143.7	142	56	143.7	142
Progression-free survival						
Median						
95% CI						
Number of events						
45 months (max for RMST)						
3 months						
6 months						
9 months						
12 months						
24 months						
36 months						
48 months						
Overall survival						
Median						
95% CI						
Number of events						
50 months (max for RMST)						
3 months						
6 months						
9 months						
12 months						
24 months						
36 months						
48 months						
60 months						

Key: CI, confidence interval; RMST, restricted mean survival time.

During the first NICE committee meeting, the OS chemotherapy estimates in the longer term were noted to be an unrealistic representation of NHS practice, with estimates stated to be too optimistic. This observation has prompted further investigation into the reason for the increased OS estimated for the real-world chemotherapy compared to clinical practice, with the expectation that this is likely a result of the treatments received at subsequent lines following chemotherapy.

When investigating the chemotherapy group, weighted patients go on to receive a mean of 0.89 further lines of treatment, including 0.23 lines of MET inhibitor, and 0.14 lines of immunotherapy (results presented as means, as some patients will receive more than 1 subsequent line). As such, the comparison should be viewed as a comparison to a chemotherapy treatment *strategy* including treatments that are not considered standard practice for NICE. This reflects that across the world, patients will be treated with such agents as a part of standard practice (nivolumab, chemotherapy), off label (crizotinib), or as a part of clinical studies (capmatinib, cabozantinib).

The impact of subsequent treatments can be seen in the post-progression survival times for the chemotherapy patients, presented in Figure 12.

Figure 12: Post-progression survival time by subsequent treatment for weighted chemotherapy patients

While it is not possible to construct an unbiased comparison of tepotinib and chemotherapy unconfounded by subsequent treatments, comparisons using Matching Adjusted Indirect Comparisons (MAICs) to published trials of chemotherapy are included in this report instead, as requested by NICE.

4. COMPARISON TO PUBLISHED DATA (WILDTYPE NSCLC)

Summary: Given the uncertainty in the comparisons to real world data in the METex14 skipping population, and acting on feedback from the ACD, new ITCs have been developed, comparing tepotinib (VISION Cohort A+C) to clinical trials in wildtype NSCLC, for the key comparators to tepotinib in NSCLC. The relevant comparators and clinical trials were agreed with the NICE technical team as part of the ACD response. This section reports the methodology and results of these additional comparisons.

4.1. Methodology

In order to compare to published studies, Matching Adjusted Indirect Comparison (MAIC) was performed. MAIC reweights the patient level data which is available, to match that of published data (Signorovitch *et al.*, 2010), as such it could be considered to be propensity score weighting to aggregate patient characteristics.

The methods works by weighting all patients in the individual patient data, such that the (selected) aggregate characteristics match between groups. The assumption implicit being that should patients be identical in observed characteristics, the outcomes should be comparable, provided all important characteristics are matched on.

MAIC was selected as the preferred methodology, as it allows for consistency with the approached used in the comparisons made using patient level data, with groups balanced on all characteristics available from the list provided by clinicians for the original submission, which is reproduced below:

- Percentage of patients previously untreated
- ECOG (where available i.e., clinical trials)
- Age (in published studies this is given variously as mean, median, % over 65)
- Sex
- Adenocarcinoma
- Smoking
- Metastatic vs advanced

MAICs were implemented using the 'maic' R package, matching on all characteristics available. ECOG was sparsely collected in the real-world data therefore could not be included in the IPD ITC performed for the original submission however, was included when reweighting the tepotinib data in the MAICs due to availability in the clinical trial data.

MAIC was preferred to other methods (namely Simulated Treatment Comparison, STC) due to consistency with other weighting approaches, ease of interpretation, and by avoiding the need to specify a regression model. Were STC used, a survival fit would need to be specified for the tepotinib data e.g., Weibull, and used in the resampling. This would be a further strong assumption which we wished to avoid. MAIC was also selected over a naïve comparison, as the patient populations between VISION and wildtype NSCLC are substantially different in a number of prognostic characteristics like age and ECOG. A naïve comparison would not account for these differences.

4.2. Chemo-immunotherapy MAIC – Untreated population

4.2.1. Comparator and trial selection

The ACD noted that pembrolizumab + pemetrexed + platinum is the most relevant comparator to tepotinib, for the untreated non-squamous population, where tepotinib is most likely to be used. This is across all PD-L1 subgroups, as per the MHRA label for tepotinib, as well as the relevant NICE guidance and label for pembrolizumab + pemetrexed + platinum.

The relevant clinical trial was deemed to be KEYNOTE-189, based on the pivotal clinical trial described in TA683 (Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer), which was confirmed by three clinical experts.

KEYNOTE-189 is a Phase III randomised controlled trial comparing the first-line treatment of pembrolizumab in combination with platinum-based chemotherapy versus pemetrexed with platinum in patients with advanced NSCLC. The publication selected was Rodriguez-Abreu et al., which reported the protocol-specified final analysis from KEYNOTE-189 (Rodríguez-Abreu *et al.*, 2021).

Eligible patients were randomized 2:1 to receive pembrolizumab 200 mg (n = 410) or placebo (n = 206) every 3 weeks (for up to 35 cycles, ~2 years) plus four cycles of pemetrexed (500 mg/m2) and investigators' choice of cisplatin (75 mg/m2) or carboplatin (area under the curve 5 mg/min/ml) every 3 weeks, followed by pemetrexed until progression. Patients assigned to placebo plus pemetrexed–platinum could cross over to pembrolizumab upon progression if eligibility criteria were met. The primary endpoints were OS and PFS. This publication reported results after a median follow-up of 31.0 months, and landmark 3-year survival outcomes reported.

4.2.2. Patient characteristics and results

When comparing the patient characteristics from VISION Cohort A+C data to the KEYNOTE-189 clinical study there are large differences between the patient populations. These differences are present across characteristics, but are particularly prominent in age (median of 65 versus 74 in VISION), sex (62% vs 50% male), ECOG 0 (45% vs 28%, smoking history (88% vs 54%) and adenocarcinoma (96% vs 79%). As a result, a large quantity of sample size is lost when reweighting. There are also differences in MET status (not measured in KEYNOTE-189, though unlikely to be present in many patients at all, as only present in 3% of NSCLC patients in total), and PD-L1 (not collected in the VISION study).

Patient characteristics before and after weighting are presented in Table 13, with the MAIC conducted using untreated VISION patients. Due to the differences in study population, there is a large loss in sample size (approximately 70% of the total).

Table 13: Patient characteristics before and after MAIC to KEYNOTE-189

Intervention	VISION A+C unweighted	VISION A+C weighted	KEYNOTE-189
N/ESS	[redacted]	[redacted]	410
Percentage previously treated	[redacted]	[redacted]	0.0
Age (mean)	[redacted]	[redacted]	
Age (median)	[redacted]	[redacted]	65.0
Percentage over 65	[redacted]	[redacted]	
Percentage male	[redacted]	[redacted]	62.0
Percentage ECOG 0	[redacted]	[redacted]	45.1
Percentage smoking	[redacted]	[redacted]	88.3
Percentage adenocarcinoma	[redacted]	[redacted]	96.1
Percentage with metastatic/stage 4 disease	[redacted]	[redacted]	99.5

Key: ECOG, Eastern Cooperative Oncology Group; ESS, Effective Sample Size; n, Number.

The outcomes of this comparison are presented in Figure 13, and tabulated in Table 14.

Figure 13: MAIC outcomes comparing VISION A+C to KEYNOTE-189 in the untreated population

Table 14: Outcomes of the MAIC comparing VISION A+C to KEYNOTE-189 in the untreated population

	VISION A+C Unweighted	VISION A+C Weighted	KEYNOTE-189
n/ESS	148	38.7	410
Progression-free survival			
Median	[redacted]	[redacted]	9.2
95% CI	[redacted]	[redacted]	(8.4 - 10.9)
24-month RMST	[redacted]	[redacted]	11.9
Cox PH	[redacted]	[redacted]	
95% CI	[redacted]	[redacted]	
p-value	[redacted]	[redacted]	
Overall survival			
Median	[redacted]	[redacted]	22.3
95% CI	[redacted]	[redacted]	(19.9 - 25.1)
24-month RMST	[redacted]	[redacted]	17.3
Cox PH	[redacted]	[redacted]	
95% CI	[redacted]	[redacted]	
p-value	[redacted]	[redacted]	

Key: CI, confidence interval; ESSS, effective sample size; n, number; PH, proportional hazard; RMST, restricted mean survival time.

Before weighting tepotinib has similar results to KEYNOTE-189, however after weighting both PFS and OS are markedly increased for tepotinib, with numerically superior median OS and median PFS to pembrolizumab + pemetrexed + platinum. PFS is consistent greater for tepotinib, and median PFS is nearly at the 5% significance threshold, despite the low effective sample size (ESS). OS is greater for tepotinib for the first 2 years, where it is similar afterwards, likely driven by the low ESS.

Although only very limited data are available in the real world dataset for chemo-immunotherapy, 6 patient lines are available (1 previously untreated, 5 previously treated). A Kaplan-Meier plot comparing these outcomes to VISION is given below, though the limitations of the small sample size prevent any weighting or conclusions from being drawn.

Figure 14: PFS and OS for immunotherapy + chemotherapy compared to tepotinib, unweighted

4.3. Immunotherapy monotherapy MAIC – untreated population (PD-L1≥50%)

4.3.1. Comparator and trial selection

The NICE ACD noted immunotherapy monotherapy as the other relevant comparator to tepotinib in the untreated, non-squamous population, specifically for patients with PD-L1≥50%. However it was deemed to be less relevant than the chemo-immunotherapy comparison, as patients with METex14 skipping NSCLC are likely to not be treated with immunotherapy monotherapy, due to the poor responses seen in this population, confirmed by clinical experts. Furthermore, even in wildtype NSCLC, the clinical experts noted that vast majority of patients receive chemo-immunotherapy, even some patients who are PD-L1≥50% (which is only 30% of the population) regardless. The ACD also noted that pembrolizumab monotherapy specifically would be the relevant comparator in this immunotherapy monotherapy treatment class, rather than another immunotherapy, again confirmed by clinical experts and NICE.

KEYNOTE-024 was selected as the relevant clinical trial, based on the pivotal trial highlighted in TA531 (Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer) and confirmed by clinical experts. KEYNOTE-024 (ClinicalTrials.gov identifier: NCT02142738) is an open-label, randomized controlled trial of pembrolizumab compared with platinum-based chemotherapy in patients with previously untreated NSCLC with a PD-L1 tumour proportion score of at least 50% and no sensitising EGFR or ALK alterations. Three hundred and five patients were randomly assigned: 154 to pembrolizumab and 151 to chemotherapy.

Reck et al. was selected as the most recent publication for KEYNOTE-024, reporting 5-year outcomes (Reck *et al.*, 2021).

4.3.2. Patient characteristics and results

When comparing tepotinib Cohort A+C data to the KEYNOTE-024 clinical study, there are large differences observed between patient populations. As with the chemo-immunotherapy comparison these are seen in age, sex and smoking. As a result, a large amount of sample size is lost when reweighting the tepotinib data. There are also differences in METex14 skipping status (not measured in KEYNOTE-024, though likely to be present in only very few patients, if any), and PD-L1 (not measured in the VISION study).

Patient characteristics before and after weighting are presented in Table 15, with the MAIC conducted using untreated VISION Cohort A+C patients. Due to the differences in the study populations there is a large loss in sample size (approximately 70% of the total).

Table 15: Patient characteristics before and after MAIC to KEYNOTE-024

Intervention	VISION A+C unweighted	VISION A+C weighted	KEYNOTE-024
N/ESS	[redacted]	[redacted]	154
Percentage previously treated	[redacted]	[redacted]	0.0
Age (mean)	[redacted]	[redacted]	
Age (median)	[redacted]	[redacted]	64.5
Percentage over 65	[redacted]	[redacted]	
Percentage male	[redacted]	[redacted]	59.7
Percentage ECOG 0	[redacted]	[redacted]	35.1
Percentage smoking	[redacted]	[redacted]	96.8
Percentage adenocarcinoma	[redacted]	[redacted]	
Percentage with metastatic/stage 4 disease	[redacted]	[redacted]	100.0

Key: ECOG, Eastern Cooperative Oncology Group; ESS, Effective Sample Size; n, Number.

The outcomes of this comparison are presented in Figure 15, and tabulated in Table 16.

Figure 15: MAIC outcomes comparing VISION A+C to KEYNOTE-024 in the untreated population

[redacted]

Table 16: Outcomes of the MAIC comparing VISION A+C to KEYNOTE-024 in the untreated population

	VISION A+C Unweighted	VISION A+C Weighted	KEYNOTE-024
n/ESS	148	40.5	154
Progression-free survival			
Median	[redacted]	[redacted]	8.3
95% CI	[redacted]	[redacted]	(6.2 - 12.5)
24-month RMST	[redacted]	[redacted]	11.6
Cox PH	[redacted]	[redacted]	
95% CI	[redacted]	[redacted]	
p-value	[redacted]	[redacted]	
Overall survival			
Median	[redacted]	[redacted]	26.0
95% CI	[redacted]	[redacted]	(19.6 - 41.9)
24-month RMST	[redacted]	[redacted]	17.2
Cox PH	[redacted]	[redacted]	
95% CI	[redacted]	[redacted]	
p-value	[redacted]	[redacted]	

Key: CI, confidence interval; ESSS, effective sample size; n, number; PH, proportional hazard; RMST, restricted mean survival time.

Though the uncertainty in this comparison should be noted, tepotinib appears to offer improved PFS consistently in the time period, with the point estimate of median PFS substantially greater for tepotinib ([redacted] months). Tepotinib appears to offer greater OS up to around 24 months, with similar median OS, with a Cox HR <1, and higher RMST.

4.3.3. Validation of immunotherapy outcomes compared to METex14 skipping real-world cohort data

The results of this comparison can also be validated, by using the identical methodology to weight the untreated immunotherapy real world cohort data (described in Section 3), to match the pembrolizumab clinical study (KEYNOTE-024). Given the vast majority of patients received immunotherapy, we would anticipate that if the populations are similar, and the MAIC conducted using appropriate characteristics, the results would be similar, albeit slightly lower in the METex14 skipping cohort, which is what the clinical experts suggested.

For brevity full MAIC results (characteristics, tabulated outcomes) are not presented here. Figure 16 presents the KM plot, which shows that the real-world data reweighted to match pembrolizumab from KEYNOTE-024 in wildtype NSCLC does appear to produce more similar outcomes, accounting for the differences in age, histology, ECOG etc. The outcomes for KEYNOTE-024 however are still substantially better than seen in the METex14 population, which is unsurprising given the expectation from clinical experts, as well as in previous studies in METex14 skipping NSCLC, which show that immunotherapy performs worse in METex14 skipping patients, even after accounting for other characteristics like age and ECOG.

Figure 16: Outcomes of the MAIC comparing untreated immunotherapy real-world data patients to KEYNOTE-024

4.4. Chemotherapy MAIC – Previously treated population

4.4.1. Comparison to docetaxel + nintedanib

Comparator and trial selection

Clinical expert opinion given to the company stated that most NSCLC patients with adenocarcinoma (non-squamous) histology who go on to second-line plus treatment are given docetaxel + nintedanib. Therefore, docetaxel + nintedanib is the main comparator for tepotinib in the previously-treated setting.

LUME Lung 1 was selected as the key clinical trial in wildtype NSCLC, as the pivotal trial reported in TA347 (Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer). Patients from 211 centres in 27 countries with stage IIIB/IV recurrent NSCLC progressing after first-line chemotherapy, were allocated to receive docetaxel 75 mg/m2 by intravenous infusion on day 1 plus either nintedanib 200 mg orally twice daily or matching placebo on days 2–21, every 3 weeks until unacceptable adverse events or disease progression. The adenocarcinoma cohort from the trial was selected as the relevant comparison, in line with the NICE recommendation and label. Reck et al. was selected as the appropriate and most recent publication for LUME Lung 1 which reported all relevant outcomes (Reck *et al.*, 2014).

Patient characteristics and results

When comparing VISION to the docetaxel + nintedanib adenocarcinoma patients in the LUME-1 clinical study, there are large differences between patient populations, resulting in a large amount of sample size lost when reweighting for the MAIC. As with the

immunotherapy comparisons, the differences between METex14 skipping patients and wildtype patients appear to be in age, sex, and smoking history. There are also differences in MET status (not measured in LUME Lung 1, though likely to be rare).

Patient characteristics before and after weighting are presented in Table 17, with the MAIC conducted using untreated VISION patients. Due to the differences in study population there is a large loss in sample size (approximately 80% of the total). The loss in patient numbers appears to be primarily due to the age difference, with patients in LUME Lung 1 over 10 years younger on average.

Table 17: Patient characteristics before and after MAIC to LUME Lung 1 (docetaxel + nintedanib)

Intervention	VISION A+C unweighted	VISION A+C weighted	LUME-1
N/ESS			322
Percentage previously treated			100.0
Age (mean)			58.5
Age (median)			
Percentage over 65			
Percentage male			63.0
Percentage ECOG 0			29.8
Percentage smoking			64.3
Percentage adenocarcinoma			100.0
Percentage with metastatic/stage 4 disease			

Key: ECOG, Eastern Cooperative Oncology Group; ESS, Effective Sample Size; n, Number.

The outcomes of this comparison are presented in Figure 17 and Figure 18, and tabulated in Table 18. Unweighted outcomes are also presented for this comparison, to demonstrate the even greater OS improvement for tepotinib in a naïve comparison.

Figure 17: Outcomes of the MAIC comparing VISION A+C to LUME Lung 1 in the previously treated population (docetaxel + nintedanib) – weighted

Figure 18. Outcomes of the MAIC comparing VISION A+C to LUME Lung 1 in the previously treated population (docetaxel + nintedanib) – unweighted

Table 18: Outcomes of the MAIC comparing VISION A+C to LUME-1 in the previously treated population (docetaxel + nintedanib)

	VISION A+C Unweighted	VISION A+C Weighted	LUME-1
n/ESS	142	28.2	322
Progression-free survival			
Median	[redacted]	[redacted]	4.1
95% CI	[redacted]	[redacted]	(3.2 - 4.4)
24 month RMST	[redacted]	[redacted]	5.6
Cox PH	[redacted]	[redacted]	
95% CI	[redacted]	[redacted]	
p-value	[redacted]	[redacted]	
Overall survival			
Median	[redacted]	[redacted]	12.9
95% CI	[redacted]	[redacted]	(11.2 - 15.6)
24 month RMST	[redacted]	[redacted]	13.6
Cox PH	[redacted]	[redacted]	
95% CI	[redacted]	[redacted]	
p-value	[redacted]	[redacted]	

Key: CI, confidence interval; ESSS, effective sample size; n, number; PH, proportional hazard; RMST, restricted mean survival time.

As per the other MAIC results, the uncertainty in this comparison should be noted however, tepotinib appears to offer substantially improved outcomes compared to docetaxel + nintedanib, with point estimates of PFS and OS being greater ([redacted] months and [redacted] months respectively), and consistent PFS and OS benefit observed in the KM graphs.

4.4.2. Comparison to docetaxel monotherapy

Comparator and trial selection

The other relevant comparator to tepotinib in the previous-treated setting highlighted by clinical experts and agreed with NICE is docetaxel monotherapy. It is worth highlighting that the clinical experts interviewed stated that 80-100% of non-squamous NSCLC patients are given docetaxel + nintedanib, so docetaxel alone is not as relevant a comparison. However this comparison is provided for completeness.

There is no appropriate Technology Appraisal (TA) for docetaxel alone, however docetaxel often appears as a comparator arm in previously-treated trials in advanced NSCLC. From a targeted literature review, five docetaxel trials were identified which could be used in the MAIC.

- KEYNOTE-010 is a randomised open-label Phase 2/3 randomised controlled trial of pembrolizumab for patients with previously treated, PD-L1 positive (>1%) advanced NSCLC versus docetaxel monotherapy (Herbst *et al.*, 2016)
- CheckMate 017 and CheckMate 057 are Phase III randomised open label trials for previously treated advanced squamous and non-squamous patients, respectively, comparing nivolumab to docetaxel. Five-year outcomes have been combined for these two trials and published (Borghaei *et al.*, 2021)
- REVEL NSCLC is a multicentre, double-blind, randomised phase 3 trial which enrolled patients with squamous or non-squamous NSCLC who had progressed during or after a first-line platinum-based chemotherapy regimen, and aimed to assess the efficacy and safety of treatment with docetaxel plus ramucirumab or placebo as second-line treatment for patients with stage IV NSCLC after platinum-based therapy (Garon *et al.*, 2014)
- TAX320: a registrational study for docetaxel, which is randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced NSCLC

previously treated with platinum-containing chemotherapy regimens (Fossella *et al.*, 2003)

Other trials were identified, such as PROFILE-01007, however these were often not in wildtype NSCLC, but instead in NSCLC with other driver mutations (ALK in this instance).

Clinical experts interviewed stated that any docetaxel trial could be used. However they noted that in KEYNOTE-010 and CheckMate-17/57, there were high proportions of immunotherapy crossover. In clinical practice, patients would not receive immunotherapy after docetaxel, and so these trials were not considered for this crossover outside of NHS practice. Furthermore, in KEYNOTE-010, patients were PD-L1 positive (≥1%) which is not the marketing authorisation for docetaxel or in the NICE guidelines. Therefore, the choice was between REVEL NSCLC and TAX320, where either could have been feasibly used. Due to the substantial time limitations, and the fact that docetaxel monotherapy is not the main comparator in the previously-treated setting, it was decided to go with just one comparison for the updated MAIC and economic model (TAX320) as the effective sample size was larger (29.7 vs 26.4), though a plot of weighted outcomes compared to REVEL is provided for completeness.

The paper by Fossella et al. was identified for TAX320, which was published in 2003 (Fossella *et al.*, 2003).

Results

When comparing to the Fossella et al., population, there are large differences between patient characteristics – again in age, sex, and on this occasion, adenocarcinoma. As a result, a large amount of sample size is lost when reweighting, reducing patient numbers from 142 to 29.7. There are also differences in MET status (not measured in Fossella et al., though unlikely to be common).

Patient characteristics before and after weighting are presented in Table 19, with the MAIC conducted using previously treated VISION patients. Due to the differences in study population there is a large loss in sample size (approximately 80% of the total). The differences in patient characteristics exist across several categories including age, sex and histology.

Table 19: Patient characteristics before and after MAIC to Fossella et al. (docetaxel monotherapy)

Intervention	VISION A+C unweighted	VISION A+C weighted	Fossella et al.
N/ESS	[redacted]	[redacted]	125
Percentage previously treated	[redacted]	[redacted]	100.0
Age (mean)	[redacted]	[redacted]	
Age (median)	[redacted]	[redacted]	59.0
Percentage over 65	[redacted]	[redacted]	
Percentage male	[redacted]	[redacted]	65.6
Percentage ECOG 0	[redacted]	[redacted]	
Percentage smoking	[redacted]	[redacted]	
Percentage adenocarcinoma	[redacted]	[redacted]	56.0
Percentage with metastatic/stage 4 disease	[redacted]	[redacted]	90.0

Key: ECOG, Eastern Cooperative Oncology Group; ESS, Effective Sample Size; n, Number.

The outcomes of this comparison are presented in Figure 19, and tabulated in Table 20.

Figure 19: Outcomes of the MAIC comparing VISION A+C to Fossella et al. in the previously treated population (docetaxel monotherapy)

Table 20: Outcomes of the MAIC comparing VISION A+C to Fossella et al. in the previously treated population (docetaxel monotherapy)

	Unweighted Weighted	VISION A+C Unweighted	Fossella et al.
n/ESS	142	29.7	125
Progression-free survival			
Median			2.0
95% CI			(1.6 - 2.6)
24-month RMST			3.4
Cox PH			
95% CI			
p-value			
Overall survival			
Median			6.0
95% CI			(5.3 - 8.4)
24-month RMST			9.5
Cox PH			
95% CI			
p-value			

Key: CI, confidence interval; ESSS, effective sample size; n, number; PH, proportional hazard; RMST, restricted mean survival time.

When compared to docetaxel (where contemporary subsequent treatments such as immunotherapy are not available) tepotinib appears to offer substantial gains in both PFS, and OS with statistically significant differences detected for both endpoints. Median PFS with tepotinib (8.3 months, both unweighted and weighted) is longer than median OS in Fossella et al.

For completeness a comparison is presented below for VISION A+C compared to REVEL NSCLC. The outcomes for docetaxel appear similar to those seen in Fossella et al., and thus the (substantial) gains for tepotinib compared to docetaxel are clear.

Figure 20: Outcomes of the MAIC comparing VISION A+C to REVEL NSCLC. in the previously treated population (docetaxel monotherapy)

5. VALIDATION OF METEX14 SKIPPING OUTCOMES: MAICS TO PUBLISHED STUDIES IN METEX14 SKIPPING NSCLC

Summary: In the original company submission, Merck provided additional MAICs comparing tepotinib to other published studies in METex14 skipping NSCLC for immunotherapy. These MAICs have now been updated with Cohort A+C and provide additional validation of the clinical benefit seen with tepotinib compared to immunotherapy in METex14 skipping NSCLC

In addition to the comparison with published pembrolizumab data, two publications studying immunotherapies are available in the literature for the METex14 skipping population, by Guisier et al. (2020), and Sabari et al. (2018), previously reported in the original company submission. Comparisons to these publications allow for validation of the results seen with the Merck real-world data ITC (originally submitted to NICE), in METex14 skipping specific populations.

5.1.1. Guisier et al. (2020)

Due to Guisier et al. enrolling a mixed untreated and previously treated population, the combined line agnostic VISION A+C and real-world data populations are used in the reweighting (with the percentage of untreated patients included in the MAIC).

For brevity, outcomes are only shown as Kaplan-Meier plots for reweighted VISION A+C data in Figure 21, and weighted real-world immunotherapy data in Figure 22.

Figure 21: Outcomes of the MAIC comparing VISION A+C patients to Guisier et al., overall population

Figure 22: Outcomes of the MAIC comparing weighted immunotherapy real-world data patients to Guisier et al., overall population

The results of this comparison show that VISION A+C patients experienced longer PFS and OS than those included in the Guisier et al. publication treated with immunotherapy, further validating the OS benefit of tepotinib compared to immunotherapy monotherapy in the specific METex14 skipping population.

When comparing outcomes in separate source of METex14 skipping immunotherapy treated patients (real-world cohort presented versus Guisier et al.), both PFS and OS are near identical regardless of whether treated in the real world data, or Guisier et al. Given the similarities in the 'leave on out' analysis, this again is supportive of the results of the real world data being generalisable to the wider METex14 skipping population for immunotherapy.

5.1.2. Sabari et al. (2018)

As with the paper by Guisier et al. the Sabari et al. paper presented a mixed untreated and previously treated population. Therefore, the combined line agnostic VISION A+C, and real-world data populations are used for reweighting (with the percentage of untreated patients included in the MAIC).

For brevity, outcomes are only shown as Kaplan-Meier plots, for reweighted VISION A+C data in Figure 23. Due to the degree of imbalance in the patient populations (and limited patient numbers), it was not possible for the real-world data to be reweighted to match Sabari et al.

Figure 23: Outcomes of the MAIC comparing VISION A+C patients to Sabari et al.

The results of this comparison provide supportive evidence that tepotinib patients experienced longer PFS than those treated with immunotherapy in the Sabari et al. publication. Similar OS is observed however, this may be confounded by the subsequent treatments received.

6. DISCUSSION

Updated ITC using real-world cohort and VISION Cohort A+C

The additional data now available for the real world comparisons (both the larger cohort from VISION and the GFPC dataset) further supports the generalisability of the findings to wider the METex14 skipping population (as previously shown in the original company submission) as well as increases patient numbers and reliability of the ITC outputs. Although there are limitations associated with the analysis, there is greater PFS consistently seen with tepotinib compared to immunotherapy in METex14 skipping patients. Furthermore, OS is seen to be at least similar, and greater in some comparisons. The real-world cohort underwent extensive validation, showing that the immunotherapy outcomes specifically are aligned to other published studies in METex14 skipping NSCLC, as well as for clinical expert expectations compared to wildtype NSCLC. Finally, the similarity of outcomes across datasets seen in the 'leave one out' analysis demonstrates the consistency seen in outcomes across observational datasets taken from different settings. In conclusion, Merck still believe the immunotherapy outcomes seen in the real-world cohort are valid, clinically plausible and aligned to expectations in this METex14 skipping NSCLC population.

New ITC comparing tepotinib to using clinical trial data in wildtype NSCLC

Although there remain limitations in the MAIC performed for tepotinib compared to wildtype NSCLC, specifically the methodology (namely the reliance on observable characteristics to account for differences across studies), in all comparisons, tepotinib compares favourably to existing therapeutic options. In nearly all cases tepotinib shows statistically improved PFS, with OS results being numerically better in many cases, or at worst, similar (generally with better RMST). These results are all in line with clinical expert expectations of the benefit of tepotinib over the comparators.

There are clear differences in the populations between METex14 skipping NSCLC (VISION) and wildtype NSCLC (clinical trial populations), with METex14 skipping patients appearing to be older, with lower smoking rates, and worse ECOG. Despite this, after weighting tepotinib appears shows greater PFS than chemo-immunotherapy and immunotherapy for PFS, and at least similar OS. When comparing to chemotherapy (docetaxel +/- nintedanib) in wildtype NSCLC, although tepotinib patients have worse patient characteristics, whether before or after weighting, there are substantial gains in PFS and OS, which are statistically significant for both outcomes.

Validation using published studies in METex14 skipping NSCLC

The results of the different immunotherapy ITCs conducted are able to be validated and replicated in the METex14 skipping population, using the publications of Guisier et al., and Sabari et al., where again the OS and PFS benefit of tepotinib compared to immunotherapy in the METex14 skipping population is demonstrated. Furthermore, reweighting the immunotherapy real world data to the Guisier et al. publication demonstrates an excellent match in characteristics and outcomes, again validating the conclusions drawn and supporting the external validation of the real-world cohort study conducted by Merck, specifically for immunotherapy. Across all of the studies and approaches, consistent clinical benefit is shown for tepotinib.

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NICE National Institute for Health and Care Excellence

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [ID3761]

Consultation on the appraisal consultation document – deadline for comments 5pm on **23 February 2022**. Please submit via NICE Docs.

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Roy Castle Lung Cancer Foundation
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	We are disappointed that the Appraisal Committee Decision is not to recommend this therapy in this indication. As acknowledged in the ACD, this is a small segmented group of lung cancer patients, with poorer prognosis and obvious unmet need. Whilst other target therapy options are available, this would be the first for patients with MET gene alterations. We would urge re-consideration that Tepotinib be available through the Cancer Drugs Fund at this time, as data matures. Or that, on discussion with the manufacturer, review is considered earlier than the three years, as suggested in paragraph 4.1.

Insert extra rows as needed

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Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [ID3761] – ERG critique of ACD response

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Nigel Armstrong acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness and economic evaluation methods and evidence and contributed to the writing of the report. Stephen Rice acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Hosein Shabaninejad and Steve Ryder acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Robert Wolff and Pawel Posadzki acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Lisa Stirk critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

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We would like to thank Luke Vale, Professor of Health Economics, Newcastle University, for his expert advice.

Abbreviations

ADC	Antibody-drug conjugate
AE	Adverse events
AIC	Akaike Information Criterion
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCS	Best case scenario
BI	Budget impact
BIC	Bayesian information criterion
BOR	Best overall response
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central nervous system
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
CT	Computerised tomography
CTR	Clinical trial results
DDFS	Distant disease-free survival
DFS	Disease-free survival
DOR	Duration of response
DRFI	Distant recurrence-free interval
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FAS	Full analysis set
FAD	Final appraisal document
FDA	Food and Drug Administration
GHS	Global health status
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health technology assessment
IC	Indirect comparison
ICD	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental cost effectiveness ratio
IDFS	Invasive disease-free survival
IPW	Inverse probability weighting
ITC	Indirect treatment comparison
ITT	Intention to treat

IV	Intravenous
KSR	Kleijnen Systematic Reviews
LVEF	Left ventricular ejection fraction
LYs	Life years
LYG	Life years gained
MAIC	Match-adjusted indirect comparison
MeSH	Medical subject headings
MET	Mesenchymal–epithelial transition
MHRA	Medicines and Healthcare Products Regulatory Agency
MOS SF-36	Medical Outcomes Study Short Form Survey
MTA	Multiple technology appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NCRI	National Cancer Research Institute
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OS	Overall survival
ORR	Objective response rate
PAS	Patient access scheme
pCR	Pathological complete response
PFS	Progression-free survival
PH	Proportional hazards
PLD	Patient level data
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTC	Pertuzumab + trastuzumab + chemotherapy
Q3W	Every three weeks
QALY	Quality adjusted life year
QLQ-C30	Quality of Life Questionnaire
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RID	Residual invasive disease
RR	Relative risk; Risk ratio
SAE	Serious adverse events
SC	Subcutaneous
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SoC	Standard of care

STA	Single technology appraisal
STEEP	Standardised definitions for efficacy endpoints
TA	Technology assessment
TEAE	Treatment emergent adverse events
ToT	Time on treatment
tpCR	Total pathological complete response
TTO	Time trade-off
TTOT	Time-to-off treatment
TTP	Time to progression
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
WHO	World Health Organization
WTP	Willingness-to-pay

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Overview

The company response to the Appraisal Committee Document (ACD) included a new economic model with 5 new analyses, 4 of which had comparators that were not considered in the company submission (CS), as summarised in the ERG report.[1, 2] New subsequent treatment distributions were elicited from clinical experts for these comparators, which therefore differ considerably from the subsequent treatment distributions used in the CS. Five new indirect treatment comparisons (ITCs) were conducted, all of which included evidence which was not included in the ITC used in the economic model in the CS. Four of these ITCs used the match-adjusted indirect comparison method (MAIC) in order to incorporate summary trial data (without access to individual patient data). That summary trial data were required to enable a cost-effectiveness analysis of tepotinib compared to specific comparators instead of the blended ones, referred to as immunotherapy, chemotherapy or chemo-immunotherapy, as these trials included greater numbers of patients. The MAIC method adjusts the VISION trial population to better match the comparator population. This contrasts with the propensity score method used in the CS, which adjusts the comparator trial population to better match the VISION trial population. The ERG had very little time to review this evidence, and so this document is intended to focus on the most important aspects of the company response and the key differences from the CS.

1. ***Line of therapy subgroups ACD Section 3.2, page 5-6: Untreated and treated subgroups should be considered separately***

The company have implemented this.

ERG comment: Nothing to add.

2. ***Relevant subgroups ACD Section 3.3, page 6-7: The appraisal should focus on untreated non-squamous NSCLC with METex14 skipping alterations***

The company have provided analyses for this subgroup, but also included analyses of previously treated patients.

ERG comment: The ERG would like to point out, notwithstanding the judgement made in previous appraisals cited by the company, that it is unclear how effective tepotinib would be in the squamous population given the low proportion of patients ([redacted]%) with this histology in the VISION trial and the lack of a separate analysis for these patients.

3. ***Chemo-immunotherapy comparisons ACD Section 3.4: Chemo-immunotherapy is the most relevant comparator for tepotinib***

The company have provided an updated ITC in the form of a matching adjusted indirect comparison (MAIC) comparing tepotinib to pembrolizumab with pemetrexed and platinum, using clinical trial data from NSCLC without specific oncogenic biomarkers (wildtype NSCLC), as reported in Appendix 2,[3] as well as an updated economic model to reflect this comparison.

ERG comment: This is in addition to the naïve comparison included in the original company submission, as described in the ERG report.[2]

4. ***VISION generalisability ACD Section 3.5, page 7–8: The clinical evidence for tepotinib is uncertain because it is based on 1 single-arm study that may not be generalisable to NHS practice***

The company argues that the single arm design was "…the most feasible and appropriate method…" (p.7)

The company also presented in Appendix 1 some data on UK patients treated with tepotinib based on the Early Access to Medicines Scheme (EAMS) and compassionate use requests.[4] The company stated they were reflective of what is expected for the METex14 skipping population, and what is observed in the VISION trial, specifically older age and predominantly non-squamous histology. They also stated that "*Tepotinib was also observed to be clinically effective in this UK-specific population."* (p. 7)[1]

Finally, the company presented a breakdown of subsequent treatments in VISION and clinical expert feedback on subsequent treatments in Appendix 1.[4]

ERG comment: The ERG would still argue that an RCT should be conducted given the uncertainty of treatment effect because of the high risk of bias, which continues despite any kind of adjustment for confounding implemented using the MAIC (See comment 6.), as described in TSD 18.[5]

The ERG can confirm that the sample of UK patients was of similar age and histology to VISION, although the percentage who were of adenocarcinoma histology was even higher (93% vs. 81%), with only one UK patient being of squamous histology. There did appear to be similarity in effectiveness, albeit based only on response and on a very small sample (n=15 (10 treatment naïve)), e.g. no complete responders and partial response in 46.7% in both the UK patients and VISION, although of the UK partial responders were treatment naïve.[4]

5. ***Cohort A+C Section 3.6 page 8: Using the data from cohort A plus cohort C has little effect on the results, but would be preferable***

The company have implemented this, including all 290 Cohort A+C patients in the updated ITC.

ERG comment: Nothing to add.

6. ***Indirect treatment comparison ACD Section 3.7 page 9–11: The indirect treatment comparisons results are highly uncertain***

Real-world data analyses

The company provided further clinical trial evidence to validate the original ITC using pooled patient data with chemotherapy and immunotherapy monotherapy (Real-world cohort). This real-world cohort was updated by the addition of French data in the METex14 population, referred to as the GFPC data set, which was used in updated ITCs which also included the Cohort A+C of the VISION trial.[3] The method used i.e. propensity score weighting to estimate the average treatment effect in the treated (ATT) by adjusting only the comparator data was as described in the ERG report.[2]

Untreated population

Although a little lower than the [redacted] months in the original analysis in the CS in the previously treated population, median overall survival (OS) was [redacted] for any immunotherapy: [redacted] versus [redacted] months. As with the original analysis in the CS, in the previously treated, median progression free survival (PFS) was [redacted] for any immunotherapy:

[redacted] versus [redacted] months. An additional analysis in a line-agnostic population versus pembrolizumab only showed that median OS was [redacted] for tepotinib: [redacted] versus [redacted] months with [redacted] in comparison to any immunotherapy in the untreated.

Previously treated population

Updating the real-world data from the original CS, for chemotherapy, OS [redacted] to [redacted] months. Although the value for tepotinib also [redacted] by using Cohort A+C instead of only Cohort A, the change was [redacted], from [redacted] to [redacted] months. Therefore, median OS remained [redacted] for tepotinib, although with a [redacted] in the treatment effect from [redacted] months.

MAICs

The company conducted a set of MAICs for various comparators and populations, reported in Appendix 2.[3]

Untreated population

In contrast to comparison with the blended immunotherapy comparator in the real-world cohort analysis, the company also provided two MAICs in the untreated population, one for comparison with pembrolizumab monotherapy using the KEYNOTE-24 trial in the PD-L1 ≥50% subgroup, notwithstanding the lack of PD-L1 status data in the VISION trial. The other MAIC was for comparison with pembrolizumab plus pemetrexed and platinum using KEYNOTE 189. Neither comparator trial recorded METex 14 status and therefore, given a prevalence of the mutations about 3% in NSCLC, could be regarded as being in a wild-type population.

Both OS and PFS appeared [redacted] for tepotinib versus pembrolizumab plus pemetrexed and platinum pre-adjustment using the MAIC. Both OS and PFS appeared [redacted] for tepotinib versus pembrolizumab plus pemetrexed and platinum post-adjustment with an OS of [redacted] versus 22.3 (19.9 - 25.1) months. This implies a treatment effect of [redacted] months, and the HR was [redacted]

In the PD-L1 ≥50% subgroup, post-adjustment, median OS was improved for tepotinib from [redacted] to [redacted] months, [redacted] 26.0 (19.6 - 41.9) months for pembrolizumab, although the point estimate for the HR [redacted] PFS [redacted] for tepotinib than pembrolizumab according to both median PFS and the point estimate of the hazard ratio (HR).

Previously treated population

In contrast to comparison with the blended chemotherapy comparator in the real-world cohort analysis, the company also provided two MAICs in the untreated population, one for comparison with docetaxel monotherapy using the TAX320 trial. The company stated that clinical experts stated that any docetaxel trial could be used. However, this trial was chosen for the following reasons:

- KEYNOTE-010 and CheckMate-17/57 had high proportions of immunotherapy crossover,
- KEYNOTE-010 patients were PD-L1 positive (≥1%) which is not the marketing authorisation for docetaxel or in the NICE guidelines
- the effective sample size was larger for TAX320 than for REVEL (29.7 vs 26.4)

- substantial time limitations, and the fact that docetaxel monotherapy is not the main comparator

A Kaplan-Meier (KM) plot of weighted outcomes with no summary statistics compared to REVEL was provided.

The other MAIC was for a comparison with docetaxel + nintedanib, using the LUME Lung 1 trial.

None of the comparator trials recorded METex 14 status, and so, given a prevalence of the mutations about 3% in NSCLC, could be regarded as being in a wild-type population.

Versus docetaxel monotherapy or + nintedanib, tepotinib was more effective in terms of PFS and OS, both before and after MAIC adjustment. After adjustment, versus docetaxel monotherapy, OS was: [redacted] versus 6.0 (5.3 - 8.4) months, thus producing a treatment effect of [redacted] months. After adjustment, versus docetaxel + nintedanib, OS was: [redacted]) versus 12.9 (11.2 - 15.6) months, thus producing a treatment effect of [redacted] months.

ERG comment: As argued in the original ERG report, the ERG considers that any MAIC is prone to substantial remaining risk of bias, particularly given the risk of not adjusting sufficiently for all prognostic variables as well as treatment effect modifiers, as described in TSD 18.[5] There is also the risk of lack of generalisability given that the adjustment is of the intervention cohort, in this case VISION, which is probably more likely to be applicable to UK clinical practice, not least because of the presence of the METex 14 skipping mutations, the comparator cohort largely lacking this (present in only about 3% of NSCLC). Therefore, the ERG stated a preference for the real-world data analysis, in line with the company preference and as supported by TSD 17 and 18 and set out in the ERG report.[2, 5, 6] Of course, the disadvantage of the real-world data approach is the lack of comparison with chemo-immunotherapy, as well as with specific types of monotherapies due to limited data. By contrast, the MAICs permit these specific comparisons. Also, in the untreated population, the results of the MAIC for pembrolizumab plus pemetrexed and platinum also seem counterintuitive when compared to those for pembrolizumab. This is because, although subject to much uncertainty, tepotinib [redacted] with the former despite the former being considered to be the most appropriate comparator. Indeed, the company stated: *"Furthermore, clinical experts highlighted that as patients with METex14 skipping NSCLC are known to respond poorly to immunotherapy monotherapy, even if a patient had PD-L1≥50%, they would mostly be given chemo-immunotherapy over immunotherapy monotherapy in the absence of a targeted therapy."* (p.6)[1] There is also consistency between the MAIC and the real-world data analysis for immunotherapy in the margin of advantage for median OS. In the previously treated population, the [redacted] in median OS was quite a lot larger when compared to specific agents using the MAIC than when compared to chemotherapy using the real-world data. There are also some questions regarding the choice of trial for comparison with docetaxel monotherapy in that it appears that REVEL could have been used, but only the KM curves were presented.

In conclusion, all of the methods employed by the company represent a reasonable means of adjusting for confounding in the absence of a controlled trial in the METex14 skipping NSCLC population. No method seems to be unequivocally better than another. The ERG preferred the real-world data analysis given that it is the only one in the correct population and because of its superiority how it adjusts for confounding. However, it does not permit a comparison with chemo-immunotherapy and does not discriminate between specific treatments by line of therapy. Therefore, the results of both the real-world cohort ITC and the MAIC highlight the uncertainty in outcomes, especially OS, when comparing tepotinib to any treatment in the METex14 population.

7. ***Economic model update: survival extrapolation ACD Section 3.9, page 12–23: <u>The comparator overall survival extrapolations are implausible, particularly for chemotherapy and chemo-immunotherapy</u>***

The company provided new OS and PFS extrapolations for the populations and comparators listed in Table 1. The company focused their reporting and commentary on analysis (1). The survival data used for survival extrapolation came from the ITC analyses, as was done in the original CS.

Table 1: The populations, comparators and trial data for which progression-free and overall survival analyses were conducted for comparators

Analysis	Population	Comparator	Trial data/analysis type for comparator
1	Untreated, wildtype NSCLC	Pembrolizumab + pemetrexed + platinum	KEYNOTE-189/MAIC
2	Untreated, PD-L1≥50%	Immunotherapy monotherapy	Real-world cohort data was updated to include the French, GFPC data set
3	Untreated, wildtype NSCLC, PD-L1≥50%	Pembrolizumab	KEYNOTE-024 /MAIC
4	Previously treated, wildtype NSCLC	Docetaxel	TAX320/MAIC
5	Previously treated, wildtype NSCLC	Docetaxel + nintedanib	LUME-Lung 1 adenocarcinoma population/MAIC

The fitting of the survival curves followed the same procedures as those used in the original CS. Curves were fit independently for tepotinib and the comparator; different types of survival models were fit based on a procedure; and AIC and BIC statistics as well as visual inspection and clinical expert opinion were used to select the survival model for use in the economic analysis.

The company reported that the opinion of clinical experts was that survival of patients with wildtype NSCLC treated with chemo-immunotherapy would be around 15-20% at five-years and around 5-10% at 10 years.

The OS curves for pembrolizumab + pemetrexed + platinum and for tepotinib are presented in Figures 1 and 2, respectively. The PFS curves for pembrolizumab + pemetrexed + platinum and for tepotinib are presented in Figures 3 and 4, respectively. For tepotinib, the curve were fitted to the VISION data weighted to KEYNOTE-189. All of the survival curve modelling graphs were presented in ACD response Appendix 1.

The selected models for analysis 1 are presented in Table 2.

Table 2: Survival models for analysis 1 (Pembrolizumab + pemetrexed + platinum)

Intervention	Outcome	Survival model
Pembrolizumab + pemetrexed + platinum	Overall survival	Log-logistic
	Progression-free survival	Log-logistic
Tepotinib	Overall survival	Log-logistic

Intervention	Outcome	Survival model
	Progression-free survival	Log-logistic

Figure 1: Pembrolizumab + pemetrexed + platinum overall survival (Figure 3, ACD response)

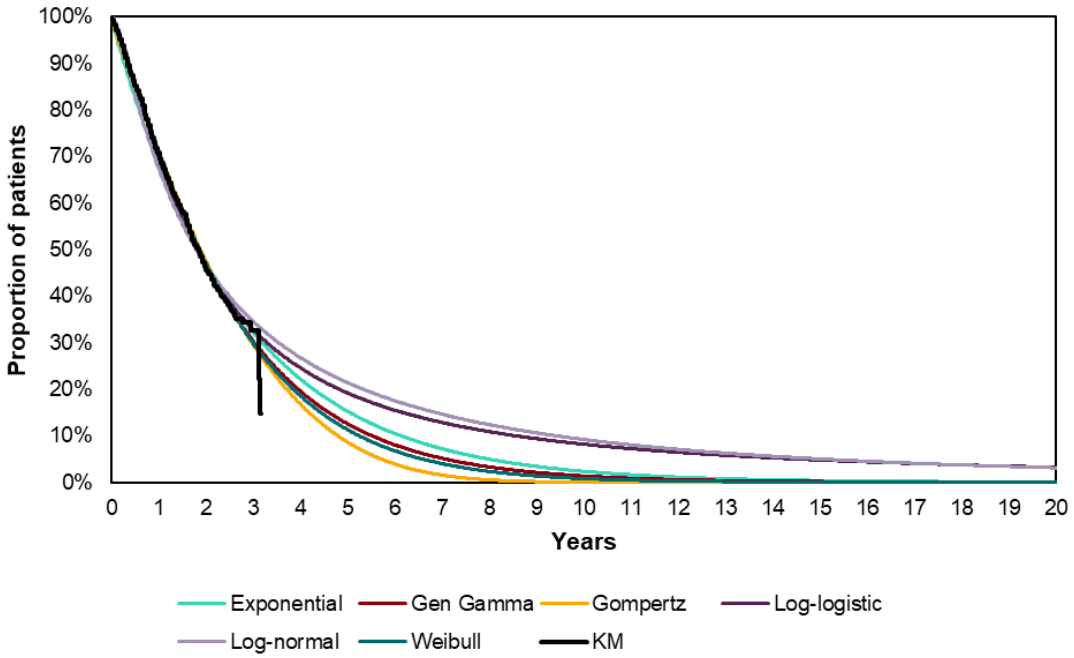

Figure 2: Tepotinib overall survival (Figure 5, ACD response)

[redacted]

Figure 3: Pembrolizumab + pemetrexed + platinum progression-free survival (Figure 4, ACD response)

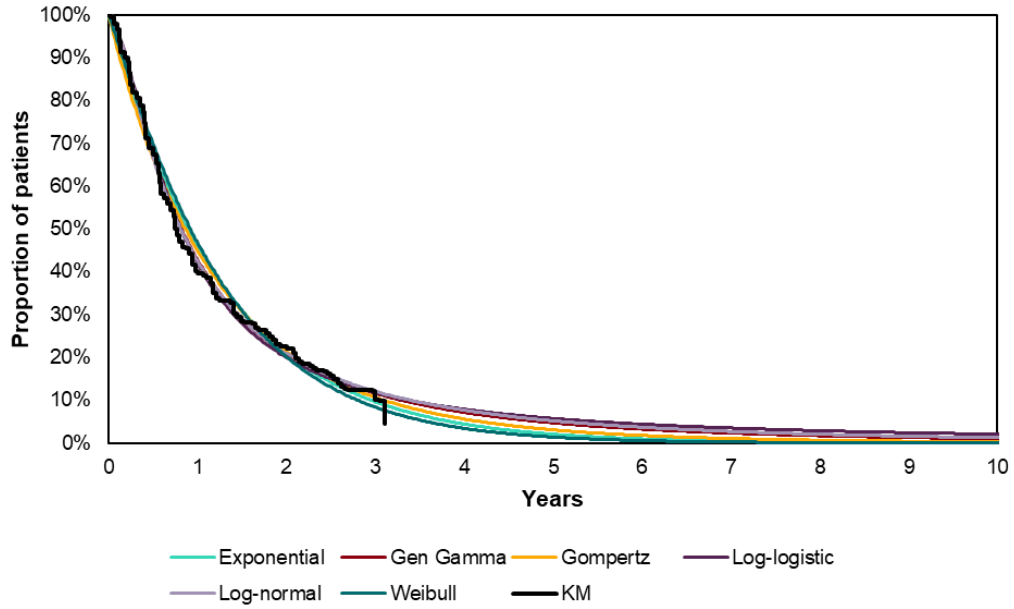

Figure 4: Tepotinib progression-free survival (Figure 6, ACD response)

ERG comment: The ERG still considers it would be preferable to jointly estimate survival for both tepotinib and the comparator using the pseudo-patient level data generated. However, in the case of pembrolizumab + pemetrexed + platinum (analysis 1), the clinical experts selected one of the survival models for OS with the greatest survival estimates. In addition, the same survival model was selected for tepotinib for OS. The same survival models were also selected for both interventions for PFS. It should be noted that the data are very immature for tepotinib in particular, and that a considerable range of survival models could be fit to the data. A sharp increase in mortality is observed at 3 years for

pembrolizumab + pemetrexed + platinum and at 2 years for tepotinib increasing the difficulty in fitting curves.

The ERG would not select alternative survival models based on the information provided.

8. ***Economic model update: subsequent treatment <u>ACD Section 3.10, page 13–14: Separate subsequent treatment distributions based on prior treatment status, and for people having chemo-immunotherapy, are needed</u>***

The company has elicited opinion from 3 clinical experts on subsequent treatment distributions according to prior treatment status. The subsequent treatment distributions are summarised in Table 3. These were used in the additional economic analyses conducted.

Table 3: The subsequent treatment distributions for the intervention and comparators for each population

Analysis	Population	Intervention/ comparator	Subsequent treatment distribution*
1	Untreated, wildtype NSCLC	Pembrolizumab + pemetrexed + platinum	100%: Docetaxel +/- nintedanib (90% with nintedanib)
2	Untreated, PD-L1≥50%	Immunotherapy monotherapy	Not stated- same as in the CS?
3	Untreated, wildtype NSCLC, PD-L1≥50%	Pembrolizumab	<u>Second-line treatment:</u> 100%: Platinum-based chemotherapy, specifically carboplatin + pemetrexed, <u>Last-line treatment:</u> 100%: Docetaxel +/- nintedanib (90% with nintedanib)
4	Previously treated, wildtype NSCLC	Docetaxel	No subsequent treatment
5	Previously treated, wildtype NSCLC	Docetaxel + nintedanib	No subsequent treatment
1-3	Untreated	Tepotinib	<u>Second-line treatment</u>: 75%: Immunotherapy monotherapy (all pembrolizumab) 25%: Platinum-based chemotherapy (all carboplatin + pemetrexed) <u>Last-line treatment:</u> 100%: docetaxel +/- nintedanib (90% with nintedanib)
4-5	Previously treated	Tepotinib	<u>For those with 1L chemo-IO (80% of total):</u>

Analysis	Population	Intervention/ comparator	Subsequent treatment distribution*
			Docetaxel +/- nintedanib (90% with nintedanib) as last line after tepotinib For those with 1L IO (20% of total): Platinum-based chemotherapy, specifically carboplatin + pemetrexed, then docetaxel +/- nintedanib (90% of these patients with nintedanib) as last line after tepotinib
*Source: Table 11, Appendix 1 to company ACD response			

ERG comment: The subsequent treatment distributions for the comparators in Analyses 1,3,4 and 5 are very different to those in the CS because the comparators in these analyses are specific, whereas the comparators are treatment classes in the CS. These subsequent treatment distributions were elicited from expert opinion. This is reasonable if there is no published evidence on this, but the ERG was not able to consult a clinical expert to review the plausibility of the subsequent treatment distributions.

If treatment is sometimes given subsequent to second-line docetaxel then an assumption of no subsequent treatment following docetaxel is conservative with respect to tepotinib; it favours the comparator.

9. Economic model update: ToT extrapolation ACD Section 3.11, page 14: There is uncertainty about the most appropriate time-on-treatment model for tepotinib, but the company's base case is likely appropriate

The company reiterated its approach in the CS. In the CS, the generalised gamma distribution was used, as it is here in the new economic analyses.

ERG comment: Nothing to add.

10. End of life criteria: life expectancy ACD Section 3.12, page 14–15: Life expectancy for people with METex14 skipping NSCLC is likely to be less than 2 years in the overall population

The company agreed with the ACD that survival estimates are likely to be less than 2 years for both the untreated and treated populations. The company noted that the additional survival estimates for tepotinib and comparators had been provided for untreated and previously treated populations in the company technical engagement response. The company stated in the text of the ACD response that it reported new survival estimates for a previously treated population based on the ITC data in Tables 12-14. In Tables 12-13 of the ACD response, the company reported survival estimates based on the MAIC

data for analyses 4 and 5. In Table 14, the company reported survival estimates based on the ITC data for real-world cohort comparisons. It is not clear to what that refers.

The MAICs cannot be used to provide evidence on life expectancy because the comparator data are in populations that can be largely regarded as wild-type. In the untreated population, median survival was about [redacted] with immunotherapy in the updated real-world data analysis, [redacted] than the [redacted] in the original CS (See Comment 6.) In the previously treated population, median survival with chemotherapy was about [redacted], [redacted] [redacted] in the original CS. Mean survival from the model was 12 months for docetaxel and 17.6 months for docetaxel for docetaxel + nintedanib. Mean survival from the model for immunotherapy was not reported.

ERG comment: No survival estimates were reported for analyses 1-3. It is noted that in the response to Comment 7, the company stated that "Clinical expects consulted as part of the response to the ACD expected that survival of patients with wildtype NSCLC treated with chemo-immunotherapy would be around 15-20% at five-years and around 5-10% at 10 years," which appears to be greater survival than expected in the overall population receiving chemotherapy treatment.

11. ***End of life criteria: survival gain ACD Section 3.13, page 15–16: It is uncertain whether tepotinib extends life by more than 3 months, so it does not meet the end-of-life criteria***

The company provided survival gain estimates from the model only for analyses 4 and 5. For analysis 4 (docetaxel in the previously-treated group), the mean OS gain was [redacted] in comparison to a gain in the medians of [redacted] months (see Comment 6.) for tepotinib. For analysis 5 (docetaxel + nintedanib in the previously-treated group), the mean OS gain was [redacted] in comparison to a gain in the medians of [redacted] months (see Comment 6.) for tepotinib. Based on the real-world data analysis the gain in the medians was [redacted] months. For the untreated population, based on the real-world data, median OS was higher for immunotherapy and, based on the MAICs, it was higher for pembrolizumab monotherapy in the PD-L1 ≥50% subgroup and [redacted] months higher than pembrolizumab plus pemetrexed and platinum.

ERG comment: The company did not provide model derived mean survival gain estimates for the untreated populations and the relevant comparators. It is surprising that the estimated survival gain should be [redacted] when tepotinib is compared to docetaxel + nintedanib than to docetaxel. The reported estimates also differ from those the ERG found in the ACD response and the Excel model (see Table 4). For the untreated population, as mentioned in relation to Comment 6., it seems counterintuitive that the tepotinib should do better in terms of median OS versus pembrolizumab plus pemetrexed and platinum than pembrolizumab monotherapy.

Table 4: The mean months of life for tepotinib and the comparator and the life months gained by analysis (from Excel model)

Analysis	Tepotinib Mean Life Months	Comparator Mean Life Months	Life months gain
4	[redacted]	12	[redacted]
5	[redacted]	18.4	[redacted]
*Source: ACD response Excel model			

12. ***Economic model results ACD Section 3.14, page 16: A plausible ICER could not be determined because of problems with the company's modelling approach and uncertainty in the model parameters, so tepotinib is not recommended for routine use***

The company conducted economic analyses for the 5 analyses listed in Table 1.

The economic models incorporated the following changes:

- New ITC evidence based on
  - VISION Cohort A+C data
  - Trial data specific to the comparator (see Table 1)
- Survival extrapolations based on the new ITC evidence (see Issue 7)
- New subsequent treatment distributions for each analysis (see Table 2)
- Updated patient characteristics to reflect the source clinical trial
- Updated utility and adverse event data to reflect Cohort A+C for tepotinib
- Removal of testing costs for squamous patients to reflect the relevant non-squamous population highlighted in the ACD response
- A larger PAS for tepotinib has been submitted to PASLU (now [redacted] off the list price). The model and all results have been updated to reflect this new PAS

When reporting the results, the company focused on analysis 1 (pembrolizumab + pemetrexed + platinum in the untreated, wildtype NSCLC population). The deterministic cost-effectiveness results are presented in Table 4. The company reported probabilistic sensitivity analysis, results, a Tornado diagram for the parameters with greatest impact on the ICER, and scenario analyses. The results for the other 4 analyses were also reported in the ACD response Appendix 1. These are reproduced here in Table 5. Tepotinib was dominant compared to pembrolizumab + pemetrexed + platinum; that is, it was less costly and more effective. The probability of being cost-effective was 100% at a cost-effectiveness threshold of £30,000/QALY. The company also presented several sensitivity and scenario analyses.

Table 5: Deterministic incremental cost-effectiveness results for Analysis 1 (adapted from Table 15, ACD response)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	Life years	QALYs	Costs (£)	Life years	QALYs	
Tepotinib	[redacted]	4.26	[redacted]				Dominant
Pembrolizumab + pemetrexed + platinum	[redacted]	3.65	[redacted]	[redacted]	-0.62	[redacted]	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 6: Deterministic incremental cost-effectiveness results for analyses 2-4 (adapted from Table 24, ACD response Appendix 1)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	Life years	QALYs	Costs (£)	Life years	QALYs	
Untreated PD-L1≥50% – tepotinib versus immunotherapy (using RWD)							
Tepotinib	[redacted]	2.94	[redacted]				Dominant
Immunotherapy	[redacted]	2.43	[redacted]	[redacted]	-0.51	[redacted]	Dominated
Untreated PD-L1≥50% – tepotinib versus pembrolizumab (clinical trial)							
Tepotinib	[redacted]	4.73	[redacted]				-
Pembrolizumab	[redacted]	5.22	[redacted]	[redacted]	0.49	[redacted]	151,609
Previously treated, all PD-L1 subgroups – tepotinib versus docetaxel (clinical trial)							
Docetaxel	[redacted]	1.00	[redacted]				-

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	Life years	QALYs	Costs (£)	Life years	QALYs	
Tepotinib	[redacted]	2.21	[redacted]	[redacted]	1.21	[redacted]	52,605
Previously treated – tepotinib versus docetaxel + nintedanib (clinical trial)							
Docetaxel + nintedanib	[redacted]	1.53	[redacted]				-
Tepotinib	[redacted]	2.55	[redacted]	[redacted]	1.02	[redacted]	47,142
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

ERG comment:

In the CS, the company ICER for tepotinib in the untreated population was £23,354/QALY and the ERG alternative was tepotinib was dominated. These results were derived from full incremental analysis of all comparators and the next most cost-effective comparator was chemotherapy and only then chemo-immunotherapy. In the CS, while combination treatment was associated with an additional [redacted] QALYs, it was also associated with an additional [redacted] compared to tepotinib. In contrast, in this analysis combination therapy is associated with [redacted] fewer QALYs compared to tepotinib and an additional [redacted].

The difference in cost between this ACD response model and the CS model is related to the less costly comparator and subsequent treatments included. The difference in QALY gain estimates is due to the different effectiveness evidence used in the models. In the CS, the hazard ratio of survival for combination therapy compared to chemotherapy was multiplied by the hazard rate of survival for chemotherapy at each time point. The same method was used for PFS. The hazard ratios were obtained from KEYNOTE-189, the trial used to provide the survival data for the MAIC conducted to populate the economic model in the company ACD response model for analysis 1.

The ERG did not have time to look in detail at the uncertainty in the ICERs. However, the ERG considers the greatest uncertainty to lie in the ITC/MAIC effectiveness evidence.

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