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:

Consultees and commentators can **find the final scope and final stakeholder list** on the NICE website.

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9. **Evidence Review Group critique of company response to technical engagement** prepared by Kleijnen Systematic Reviews (KSR):
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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 [ID3761]

Document B

Company evidence submission

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Abbreviations

AE	adverse event
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
ATP	adenosine triphosphate
BOR	best overall response
BRAF	v-raf murine sarcoma viral oncogene homolog B1
BSL	baseline
CAAX	cysteine; Aliphatic Amino acid, any amino acid (X)
CRUK	Cancer Research UK
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DNA	deoxyribosenucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EORTC-QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
EORTC	European Organization for Research and Treatment of Cancer,
EOT	end of trial
EQ5D5L	EuroQol Five Dimension Five Level Scale
ESMO	European Society of Medical Oncology
FGR1	fibroblast growth factor receptor 1 gene
FISH	Fluorescence In Situ Hybridization
GHS	global health status
HER2	human epidermal receptor 2 gene
HGF	hepatocyte growth factor
HRQL	health-related quality of life
IAP	interim analysis plan
ICER	incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
ILD	interstitial lung disease

IMP	investigational medicinal product
INV	investigator
IRC	Independent Review Committee
ITT	intention to treat
KRAS	ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LBx	liquid biopsy
LCSS	Lung Cancer Symptom Scale
LYG	life years gained
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epithelial transition
MHLW	Ministry of Health Labour and Welfare
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	mixed model repeated measures
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NF1	neurofibromin 1 gene
NGS	next generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NRG1	neuregulin 1 gene
NSCLC	non-small cell lung cancer
NTRK1	neurotrophic receptor tyrosine kinase 1 gene
ORR	overall response rate
OR	objective response
OS	overall survival
PCR	polymerase chain reaction
PFS	progression free survival
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene
PRO	patient reported outcome
PT	preferred term
QALY	quality-adjusted life year
RAS	rat sarcoma
RCT	randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RET	rearranged during transfection proto-oncogene
RIT1	RAS like without CAAX 1 gene
RNA	ribose nucleic acid
ROS1	c-ros oncogene 1

SAF	safety analysis set
SCLC	small cell lung cancer
SEM	Standard error of mean
SLR	systematic literature review
SOC	standard of care
TBx	tissue biopsy
TEAE	treatment emergent adverse event
TNM	tumour (T) nodes (N) metastasis (M)
TRAE	treatment related adverse event
UICC	Union for International Cancer Control
VAS	visual analogue scale

B.1. Decision problem, description of the technology and clinical care pathway

Executive summary

- Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for 88.6% of lung cancers in England and Wales in 2018. NSCLC may be further divided into histological subtypes, including adenocarcinoma and squamous cell carcinoma.
- Patients with METex14 skipping alterations are a distinct population within NSCLC and differ in terms of multiple characteristics compared to wildtype NSCLC (without oncogenic driver mutations) or NSCLC with other genetic driver mutations. Compared to wildtype NSCLC, patients with METex14 skipping alterations are typically older, with adenocarcinoma histology, although an increased frequency of tumours with sarcomatoid features has also been observed.
- Patients with tumours that have METex14 skipping alterations have a poor prognosis compared to NSCLC without METex14 skipping alterations, as well as poor responses to immunotherapy. This makes treatment of this population clinically challenging, further impacted due to their older age, comorbidities, and overall frailty, which limit the use of currently available non-targeted treatment options.
- ESMO guidelines state the importance of METex14 as an emerging treatment target, and the updated ESMO Precision Medicine Working Group guidance on recommendations for next generation sequencing (NGS) recommends testing for METex14 as a level IB alteration (meaning the match of a genetic alteration and a drug has been validated in clinical trials, and should drive treatment decision in daily practice). The NCCN 2021 guidelines recommend testing for METex14 skipping alterations after the recent accelerated US approvals of MET inhibitors. [redacted].
- There are currently no EMA or MHRA approved treatments in the UK specifically targeting NSCLC with METex14 skipping alterations. This is despite predictive biomarkers being used to inform treatment decisions in advanced NSCLC, and activating mutations with NICE-recommended treatments that are currently tested for include EGFR, ALK and ROS1. In the absence of specific MET-targeted therapies, treatments currently used for patients without any identifiable biomarkers in advanced NSCLC make up the current NHS standard of care (SoC), including immunotherapies and/or chemotherapy.
- There is currently a significant unmet need for advanced NSCLC patients with METex14 skipping alterations in whom prognosis is particularly poor and for whom there is currently no approved targeted treatment.

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication: for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations. Please see Table 1 below for a summary of the National Institute for Health and Care Excellence (NICE) decision problem.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with advanced non-small cell lung cancer (NSCLC) with mesenchymal–epithelial transition (MET) exon 14 skipping mutations	Adults with advanced non-small cell lung cancer (NSCLC) with mesenchymal–epithelial transition (MET) exon 14 skipping mutations	Population aligned with the NICE final scope
Intervention	Tepotinib	Tepotinib	Intervention aligned with NICE final scope
Comparator(s)			
Untreated disease:			
For people with non-squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score:	• Pembrolizumab monotherapy • Pembrolizumab combination with pemetrexed and platinum chemotherapy • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) • Atezolizumab monotherapy	• Pembrolizumab monotherapy • Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab monotherapy	Aligned with NICE scope except for the omission of: • Pembrolizumab with carboplatin and paclitaxel for people with squamous NSCLC - *this is because it is only available via the Cancer Drugs Fund.* • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) – *not recommended by time of submission* • Best supportive care (BSC) – *not considered a comparator, as patients with NSCLC harbouring METex14 skipping alterations who would receive tepotinib are highly unlikely to receive BSC instead of active treatment. In addition, there is no data available for BSC in the METex14 skipping alterations population either, therefore a comparison was not possible.* Please see Section B.2.9 for further details on how comparators are grouped by treatment class in the indirect comparisons and economic model.
For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%:	• Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) ○ with or without pemetrexed maintenance treatment • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)	• Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) ○ with or without pemetrexed maintenance treatment	
For people with adenocarcinoma or large-cell carcinoma whose tumours express PD-L1 with a tumour	• Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) ○ with (following cisplatin-containing regimens only) or without	• Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) ○ with (following cisplatin-containing regimens only) or without	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
proportion score below 50%	pemetrexed maintenance treatment	pemetrexed maintenance treatment	
For people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score	• Pembrolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel • Atezolizumab monotherapy • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)	• Pembrolizumab monotherapy	
For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%	• Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab with carboplatin and paclitaxel (subject to ongoing appraisal ID1683) • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)	• Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab with carboplatin and paclitaxel (subject to ongoing appraisal ID1683)	
Previously treated disease			
People with squamous NSCLC PD-L1 ≥50%	• Platinum doublet • Pemetrexed with carboplatin • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care	• Platinum doublet • Pemetrexed with carboplatin • Docetaxel, with (for adenocarcinoma histology) or without nintedanib	
People with squamous NSCLC PD-L1 <50%	• Atezolizumab monotherapy • Nivolumab monotherapy • Pembrolizumab monotherapy • Docetaxel with (for adenocarcinoma histology) or without nintedanib • Best supportive care	• Atezolizumab monotherapy • Pembrolizumab monotherapy • Nivolumab monotherapy • Docetaxel, with (for adenocarcinoma histology) or without nintedanib	
People with squamous NSCLC PD-L1 >50%	• Gemcitabine with carboplatin or cisplatin • Vinorelbine with carboplatin or cisplatin • Docetaxel • Best supportive care	• Gemcitabine with carboplatin or cisplatin • Vinorelbine with carboplatin or cisplatin • Docetaxel	

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	Outcomes were aligned with the NICE final scope
Subgroups to be considered	If evidence allows, subgroup analysis by: • previous therapy • tumour histology (squamous or non-squamous) • level of PD-L1 expression (strong positive or weak positive), The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Subgroup analysis presented by: • previous therapy	Sub-group data by PD-L1 expression was not collected as part of the VISION trial, so sub-group analysis could not be conducted. There were only [redacted] patients ([redacted]%) in VISION Cohort A (1 Feb 2021 data cut-off) who were of squamous histology, and [redacted] ([redacted]%) who were sarcomatoid, so full sub-group analysis by histology was not possible. However, in Appendix E subgroup analysis for ORR by histology is reported.
Special considerations including issues related to equity or equality	None specified	No special considerations including issues related to equity or equality were specified in the final scope.	Not applicable

B.1.2. Description of the technology being appraised

The draft of the summary of product characteristics (SmPC) has been included in Appendix C.

The technology being appraised (tepotinib) is described in Table 2.

Table 2. Technology being appraised

UK approved name and brand name	Tepotinib
Mechanism of action	Tepotinib is a highly selective, potent, reversible, Type Ib ATP-competitive small-molecule inhibitor of MET (c-N-methyl-N′-nitroso-guanidine) tyrosine kinase (the receptor of hepatocyte growth factor), which is encoded by the MET proto-oncogene.[1] Tepotinib has few off-target effects compared with type Ia and II MET inhibitors.[2] Tepotinib is thought to inhibit hepatocyte growth factor-dependent and independent MET signalling by blocking MET phosphorylation and downstream signalling in a dose-dependent manner and has shown antitumour activity in multiple tumour models derived from diverse cancer types. In pre-clinical studies, the antitumour activity of tepotinib was noted in tumours with oncogenic alterations of MET, such as METex14 skipping alterations (i.e., MET gene with a skipped exon 14) and high-level MET gene amplification (defined as a MET gene copy number >10).[3]
Marketing authorisation/CE mark status	The MHRA regulatory submission was made in [redacted] and marketing authorisation is expected in [redacted]. Tepotinib was approved in Japan in March 2020 for the treatment of advanced NSCLC with METex14 skipping alterations,[4] having previously been granted SAKIGAKE 'fast-track' designation and Orphan Drug Designation by the MHLW. In February 2021, the Food and Drug Administration granted accelerated approval to tepotinib, after previously granting the medicine Breakthrough Therapy Designation as well as Orphan Drug Designation.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Tepotinib is under investigation for the treatment of adult patients with advanced NSCLC harbouring METex14 skipping alterations.
Method of administration and dosage	Each film-coated tablet contains 225 mg tepotinib (equivalent to 250 mg tepotinib hydrochloride hydrate).

	The recommended dose is 450 mg tepotinib (2 tablets) taken once daily (equivalent to 500 mg tepotinib hydrochloride hydrate). Tepotinib is administered until progression of the disease or undue toxicity.
Additional tests or investigations	METex14 skipping alterations should be confirmed by a validated test method, using nucleic acids isolated from plasma or tumour specimens. [redacted].
List price and average cost of a course of treatment	List price: [redacted]* for 60 250 mg tablets
Patient access scheme (if applicable)	A simple PAS discount of [redacted] applied to the list price of tepotinib*

† [redacted]

B.1.3. Health condition and position of the technology in the treatment pathway

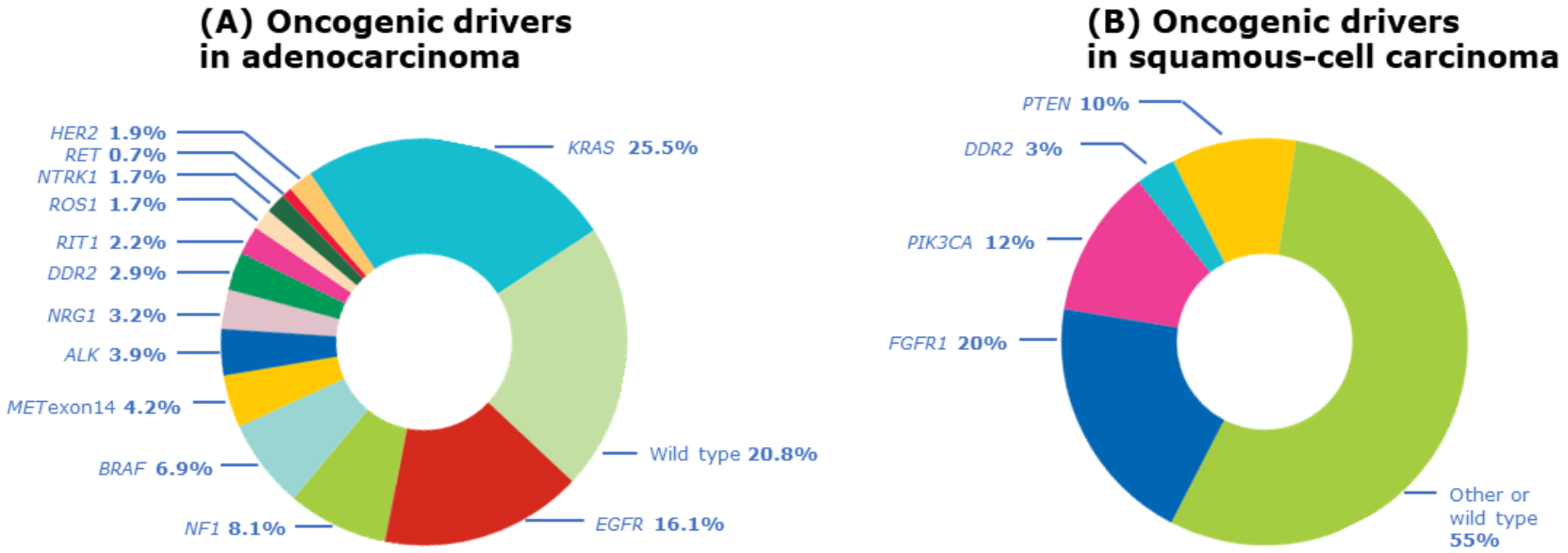
B.1.3.1. NSCLC disease overview

In the UK approximately 47,800 new lung cancer cases are diagnosed ever year, which is the equivalent of 130 cases every day (2015–2017). Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases (2017),[5] and resulting in 35,300 lung cancer deaths in the UK every year (2015-2017).[5] Lung cancer is the most common cause of cancer death, accounting for 21% of all cancer deaths (2017).[5]

The majority of lung cancers fall into two major classes, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[6,7] NSCLC is the most common type of lung cancer, accounting for 88.6% of lung cancers in England and Wales in 2018.[8] NSCLC may be further divided into histological subtypes, including adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[9] Approximately 40% of NSCLC are adenocarcinoma, 25% are squamous cell carcinoma, 10% are large cell carcinomas, and the remaining 25% is comprised of a mix of rarer histological subtypes including sarcomatoid.[9-12] Adenocarcinoma and large-cell carcinoma are classified as non-squamous histological subtypes of NSCLC.

NSCLC is genomically very diverse and offers the potential to define molecular subsets of patients treated with personalised therapies.[13-15] Up to 60% of patients with adenocarcinoma and up to 80% of patients with squamous cell carcinoma have known oncogenic driver mutations;[16] i.e. mutations that are responsible for both the initiation and maintenance of the cancer. These mutations are often found in genes that encode for signalling proteins that are critical for maintaining normal cellular proliferation and survival.[17] Most adenocarcinomas can be classified based on molecular testing for predictive biomarkers in oncogenic drivers such as epidermal growth factor receptor (EGFR), ROS proto-oncogene 1 (ROS1), anaplastic lymphoma kinase (ALK), B-raf murine sarcoma homolog B gene (BRAF), Kirsten rat sarcoma viral oncogene homolog (KRAS) and mesenchymal-epithelial transition (MET) (Figure 1).[18]

Figure 1. Molecular profile of adenocarcinoma and squamous cell carcinoma lung cancer



Source: Rosell and Karachaliou [18]

Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, B-raf murine sarcoma homolog B gene; DDR2, discoidin domain receptor tyrosine kinase 2 gene; EGFR, epidermal growth factor receptor gene; FGFR1 fibroblast growth factor receptor 1 gene; HER2, human epidermal receptor 2 gene; METexon14, mesenchymal-epithelial transition gene exon 14; NF1, neurofibromin 1 gene; NRG1, neuregulin 1 gene; NSCLC, non-small cell lung cancer; NTRK1, neurotrophic receptor tyrosine kinase 1 gene; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha gene; KRAS, kirsten rat sarcoma viral oncogene homolog; RET, rearranged during transfection proto-oncogene; RIT1, RAS like without CAAX 1 gene; ROS1, ROS proto-oncogene 1

The most widely used staging system in NSCLC is the tumour, node and metastasis (TNM) system developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) (8th edition).[19,20] The TNM staging system uses the extent of the primary tumour (T), regional lymph nodes (N), and distant metastases (M) as the basis for staging.[20] Tumour stage is then determined by a composite of these factors.[20] Additionally, NSCLC may be categorised as localised (Stage I), locally advanced (Stage II-IIIA), advanced, or metastatic (Stage IIIB-IV).[19,20] Around three-quarters of lung cancer cases are diagnosed at a late stage (Stages III and IV) in England (2014), Scotland (2014-2015) and Northern Ireland (2010-2014).[21-23]

B.1.3.1.1. Clinical burden

The most prevalent symptoms in patients with NSCLC are coughing (phlegm, mucus or blood), dyspnoea, fatigue, insomnia, and pain.[24] Additional symptoms include a change in colour or volume of sputum, shortness of breath, changes in the voice, recurrent bronchitis or pneumonia, loss of appetite, weight loss, cachexia, bone fractures, memory loss, gait instability, swelling, bleeding and blood clots.

That said, patients with early stage lung cancer often experience non-specific symptoms, therefore in most situations, disease recognition comes at an advanced stage.[25] Therefore, as mentioned, around 75% of patients with lung cancer have Stage III or IV disease at the time of diagnosis, excluding them from potentially curative surgery.[26] As a result, lung cancer is recognised to carry a high burden to patients, with some studies suggesting that a higher burden of lung cancer-related symptoms negatively affects the response to treatment and overall survival (OS) in NSCLC patients.[27,28]

Furthermore, the clinical presentation of NSCLC is generally concordant for patients with or without METex14 skipping alterations, and further molecular testing is required to determine METex14 status and tumour mutation burden, described in later sections.[29-36]

B.1.3.1.2. Humanistic burden

Using the Lung Cancer Symptom Scale (LCSS), the most frequent symptoms in patients with advanced NSCLC were found to be fatigue (100%), loss of appetite (97%), shortness of breath (95%), cough (93%), pain (93%) and blood in sputum (63%). The correlation between these symptoms and HRQL was noted to be significant for loss of appetite ($\beta = -0.204$; $p<0.001$), cough ($\beta = -0.145$; $p<0.01$), pain ($\beta = -0.265$; $p<0.001$), and shortness of breath ($\beta = -0.145$; $p<0.01$).[37]

Fatigue, dyspnoea, cough and pain have been found to reduce the emotional dimension of HRQL, while sleep deprivation had the greatest effect on cognitive function.[38] In a study conducted using the European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire (EORTC-QLQ-C30), the most common symptoms in patients with advanced NSCLC were cough, dyspnoea, fatigue, insomnia and pain (Table 4).[24] Multivariate analyses revealed that significant ($p<0.05$) reductions in cognitive, physical and emotional functioning, in addition to significant ($p<0.05$) increases in diarrhoea, insomnia, and dyspnoea were present in patients with advanced NSCLC (as assessed by EORTC QLQ-C30), demonstrating the notable impact of NSCLC on HRQL.[24] A separate study also using the EORTC QLQ-C30 and LC13 largely corroborated these findings in NSCLC patients, while also noting detriments in role function and social function and significant impacts of current treatments, respiratory comorbidities and level of financial income on HRQL (Table 4).[24] These studies, using multiple instruments, all conclude that the symptoms associated with NSCLC are a significant burden to patients' HRQL.

Table 3. Most prevalent symptoms and factors that impact HRQL in patients with advanced NSCLC

Most prevalent symptoms (EORTC score*)		**Functions/symptoms with significant impact on HRQL (p-value)****	
Silvoniemi 2016	**Hechtner 2019**	**Silvoniemi 2016**	**Hechtner 2019**
Dyspnoea (33.9)	Dyspnoea (41)	Physical functioning (0.013)	Higher physical activity (<0.01)
Fatigue (31.9)	Role function (33)	Cognitive functioning (0.003)	Mental distress (<0.001)
Insomnia (30.3)	Fatigue (27)	Emotional functioning (0.041)	Current treatment (<0.01)
Pain (21.8)	Social function (27)	Insomnia (0.037)	Respiratory comorbidity (<0.01)
Appetite loss (19.3)	Physical function (24)	Diarrhoea (0.020)	Living on disability pension (<0.01)
Constipation (16.0)	Insomnia (21)	Dyspnoea (0.0002)	High income (<0.01)

Source: Ripamonti ,1997[36]; Hechtner , 2019[39]

Abbreviations: EORTC=European Organisation for Research and Treatment of Cancer; HRQL=health-related quality of life

Note: * Scale of 0 to 100; higher score represents more prevalent symptom; **Based on LC13 module results

B.1.3.2. NSCLC harbouring METex14 skipping alterations

Alterations to the MET oncogene, such as METex14 skipping alterations and MET amplification, have been identified as primary oncogenic drivers in NSCLC.[40,41] The MET

receptor tyrosine kinase is a cell surface receptor capable of mediating pleiotropic effects, including cell migration, survival, and proliferation.[42-44] Mutations in MET that cause skipping of exon 14 in the mRNA transcript leads to a more stable protein and overactivity of MET mediated cell signalling and is thought to contribute to cell proliferation, survival, invasion, and metastasis.[45]

B.1.3.2.1. Epidemiology of METex14 skipping alterations

The prevalence of METex14 skipping alterations in NSCLC varies by histology and has been previously reported to account for approximately 3% of NSCLC cases in total; however, it is notable that rates vary according to histological subtype and source, with 3–4% of adenocarcinomas and 8–30% of sarcomatoid carcinomas presenting with METex14 skipping alterations.[10,18,29,45,46]

To assess epidemiological evidence in NSCLC with METex14 skipping alterations, a comprehensive systematic literature review (SLR) of published evidence in this population was conducted.[47] In total, 40 studies were identified that reported prevalence data for METex14 in NSCLC patients; no studies were identified that reported incidence data.

The prevalence of METex14 skipping alterations, as reported in individual studies, ranged from 0.6% to 6.6%. When looking at geographical subgroups, the prevalence ranged from 0.6% to 6.6% in Asia, 1.4% to 3.0% in Europe, and 2.3% to 5.1% in North America.[47]

Notably, some studies on the low- or high end of the prevalence included relatively small numbers of patients and relatively high numbers of adenocarcinoma histology types. The observed heterogeneity in the prevalence of METex14 mutation skipping in NSCLC may be related to the differences in the number of patients sampled in studies, included histology types, study design, and geographical origin. Furthermore, various genetic testing methods were used in different studies.[47]

A recent oral abstract presented at the British Thoracic Oncology Group (BTOG) 19th Annual Conference 2021 reported on the detection of tier 1 variants with circulating tumour (ct) DNA next generation sequencing (NGS) in the UK for NSCLC patients, including for METex14 skipping alterations. Of the 103 patients tested, 3.9% (n=4) were positive for METex14 skipping alterations.[48]

B.1.3.2.2. Patient characteristics with METex14 skipping alterations

Compared to wildtype NSCLC, patients with primary METex14 skipping alterations are more commonly older individuals with adenocarcinoma histology, although an increased frequency of tumours with sarcomatoid features has also been observed. Based on findings of the recently conducted SLR, 27 studies reported median age ranging from 64 to 80.5 years of age in NSCLC patients with METex14 skipping alterations, with a median of 72 years.[47] Among the studies that reported gender distribution, median female inclusion was 56%; median male inclusion was 45%.[47] The most common histology that was reported among NSCLC patients with METex14 skipping was adenocarcinoma (79%), followed by pulmonary sarcomatoid carcinoma (3%) and squamous histology (3%).[47]

Compared to other driver mutations in NSCLC, such as EGFR- and ALK-positive mutations, which primarily occur in never smokers, findings regarding METex14 skipping alterations are less pronounced. Although some studies suggest that the majority (i.e., 59%–65%) of NSCLC with METex14 skipping alterations occur in smokers, other research points to a higher occurrence among older female non-smokers.[49-52] Included studies in the SLR demonstrated a higher inclusion rate for ever-smokers (median 56%) than for never-smokers (median 43%).[47]

Furthermore, patients with NSCLC harbouring METex14 skipping alterations are more likely to be PD-L1 positive.[51] According to one study, PD-L1 expression of 0%, 1-49%, and ≥50% in METex14-altered lung cancers were 37%, 22%, and 41%, respectively. Further analysis showed that patients with sarcomatoid histology had a higher PD-L1 expression, compared with adenocarcinoma (p=0.021).[51]

Similar patient characteristics have been observed in clinical trial populations, where patients with NSCLC harbouring METex14 skipping alteration were found to be older and more predominantly with non-squamous histology.[1,53] In conclusion, patients with METex14 skipping alterations are therefore a distinct population within NSCLC with different patient characteristics to wildtype NSCLC or NSCLC with other oncogenic driver mutations.

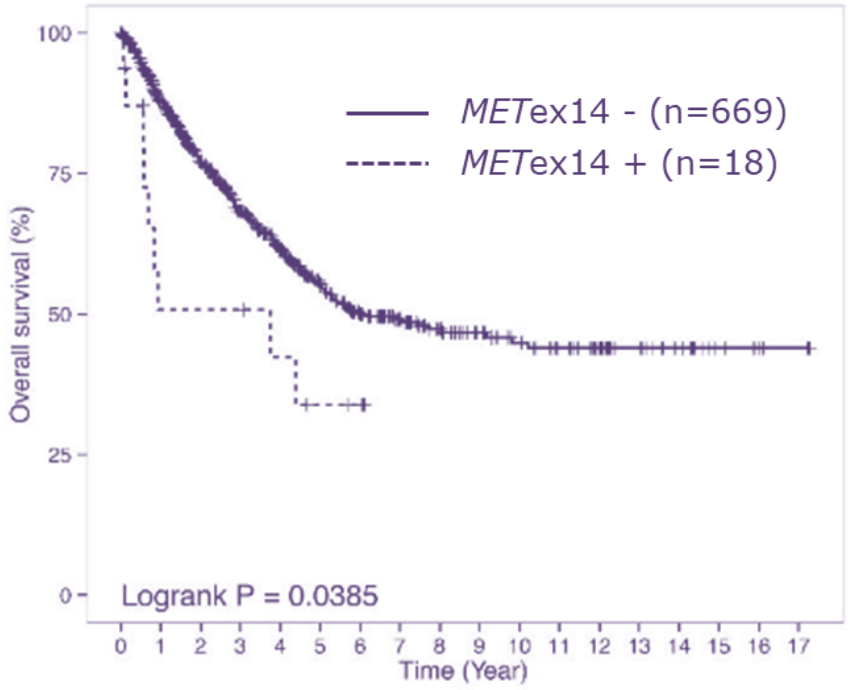
B.1.3.2.3. Disease prognosis and risk factors of METex14 slipping alterations

In general, patients with tumours that have MET alterations (including METex14 skipping alterations) have poor prognosis compared to NSCLC patients without MET alterations.[49,54-56] In a recent study of patients with advanced NSCLC harbouring METex14 skipping

alterations (N=148), OS measured since the timepoint of diagnosis of Stage IV was only 8.1 months for patients treated with therapies that did not target MET (N=34) (Awad 2019).[49] The target patient population with NSCLC harbouring METex14 skipping alterations tends to be older than other oncogenic driven NSCLC subpopulations. This makes treatment of this population clinically challenging, further impacted by comorbidities and overall frailty, which limit the use of currently available non-targeted treatment options, ultimately impacting on the prognosis of this subset of patients.

In a retrospective study conducted by Tong et al. in patients diagnosed with NSCLC between 1995 and 2011 in Hong Kong, a multivariable analysis of patients with NSCLC demonstrated that in addition to stage (p<0.001), METex14 skipping alterations (HR, 2.156; 95% CI, 1.096–4.242; Figure 2) and high-level MET amplification (HR, 3.444; 95% CI, 1.398–8.482) were independent poor prognostic factors for NSCLC patients (Figure 2).[57] It should be noted that this study is based on a small number of patients with METex14 skipping alterations (N=18); future studies will be needed to confirm this finding.

Figure 2. Presence of METex14 skipping alterations and correlations with poor outcome



Source: Tong et al., 2016[57]
Abbreviations: METex14, mesenchymal-epithelial transition gene exon 14

Section B.1.3.3.2 also discusses the poor response to immunotherapy seen in the METex14 skipping alterations population, contributing to the poor prognosis seen in these patients.

B.1.3.3. Current management and unmet need

B.1.3.3.1. Molecular testing for predictive biomarkers including METex14

After diagnosis and tumour staging, the next consideration should be therapy-predictive biomarker testing, as predictive biomarkers are used to inform treatment decisions in locally advanced and metastatic NSCLC.[58] It has been recognised that there are different molecular subtypes of lung cancer, and that there is a shift towards practicing precision medicine with the availability of targeted therapies which can treat specific molecular subtypes of cancer. Targeted therapies are now the standard of care for patients with EGFR-mutant, ALK positive or ROS1 positive advanced NSCLC. Advanced NSCLC with METex14 skipping alterations is now considered to represent another group of patients who would benefit from a targeted treatment option.

Current clinical guidelines from the European Society for Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and American Society of Clinical Oncology (ASCO) strongly recommend performing molecular testing prior to the initiation of a treatment for advanced disease.[58-61] If a predictive oncogenic marker such as EGFR, ALK, ROS1, RET or METex14 skipping alterations is identified in a NSCLC patient, initiation of targeted treatment with the respective approved agent is to be applied whenever possible, due to their known beneficial effects. A characteristic of these oncogenic drivers is their apparent mutual exclusivity, which has also been shown for METex14 skipping alterations.[29,62] Activating mutations in EGFR, ALK, and ROS1 are detected by real-time PCR, next generation sequencing (NGS), Sanger sequencing, or fluorescence in situ hybridisation (FISH).[58,63,64]

In Europe, the ESMO guidelines re-iterate the importance of METex14 skipping alterations as an emerging treatment target. Currently, NICE guidelines do not recommend testing for METex14 skipping alterations, as a standard of care, despite the testing of other targets, such as EGFR, ALK and ROS1, where targeted treatments are already available.[65,66] However, the updated ESMO Precision Medicine Working Group guidance on recommendations for NGS has noted METex14 skipping alterations as a molecular target of interest and recommends testing for METex14 skipping alterations as a level IB alteration (meaning the match of a genetic alteration and a drug has been validated in clinical trials, and should drive treatment decision in daily practice).[62] The NCCN 2021 guidelines clearly recommend testing for METex14 after very recent accelerated approval of the MET inhibitors tepotinib and capmatinib.[58]

Assays for determining the presence of METex14 skipping alterations in patients with NSCLC are available, including real-time quantitative reverse transcription-polymerase chain reaction (qRT-PCR), Sanger sequencing, and next-generation sequencing (NGS; hybrid-capture targeted DNA/RNA sequencing).[67] In 2019, a study was conducted which compared the sensitivity and specificity of these respective assays in patients with NSCLC; it was determined that qRT-PCR has greater sensitivity but worse specificity for METex14 than Sanger sequencing.[67] NGS was found to be the most appropriate assay for multiplex testing in clinical practice.[67] Based on clinical expert feedback (N=4), the majority of centres in England are moving towards using NGS, or already use NGS, for detection of mutations in NSCLC.

[redacted].

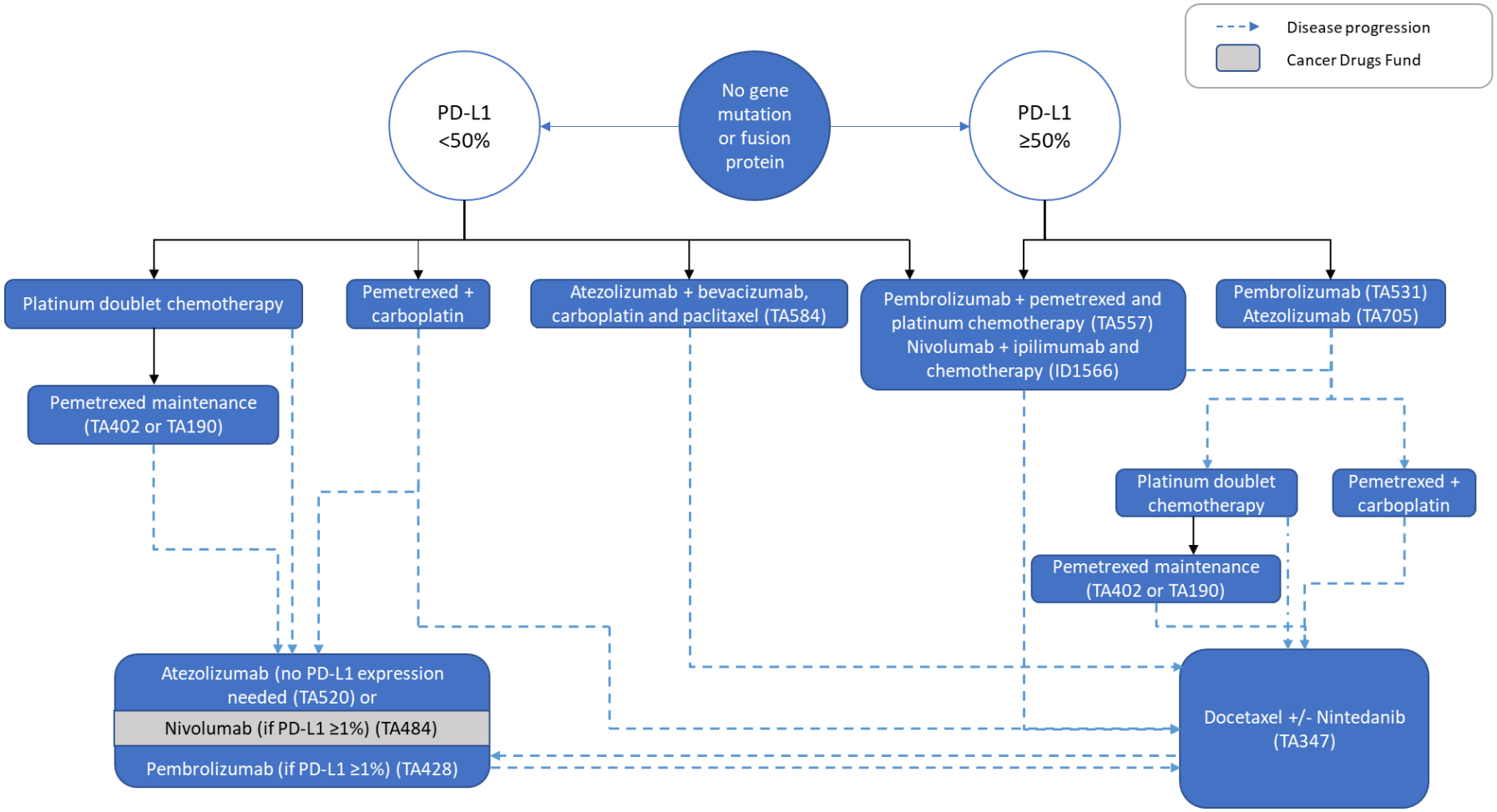
B.1.3.3.2. Treatment options for advanced NSCLC

The primary objective of treating advanced, recurrent, or metastatic NSCLC (Stage IIIb-IV) is to extend survival and improve the quality of life.[68] The choice of treatment depends on the disease stage, tumour characteristics revealed by histology, prior treatment, biomarker testing in metastatic NSCLC (mutation status and PD-L1), and the patient's performance status.[58,69]

As discussed, predictive biomarkers are used to inform treatment decisions in advanced NSCLC. Activating mutations currently tested for with specifically NICE-approved treatments include EGFR, ALK and ROS1.[70] However, there are currently no EMA or MHRA approved treatments specifically targeting NSCLC with METex14 skipping alterations. In the absence of specific MET-targeted therapies, treatments currently used for patients without any identifiable biomarkers in advanced NSCLC make up the current NHS standard of care (SoC), including immunotherapies and/or chemotherapy.[70] The sections below also highlight the poor response seen to immunotherapy in the METex14 skipping alterations population.

The NICE treatment algorithms are reported below for advanced NSCLC without driver mutations (Figure 3 [non-squamous] Figure 4 [squamous]) as well as for targeted treatments (Figure 5).[70]

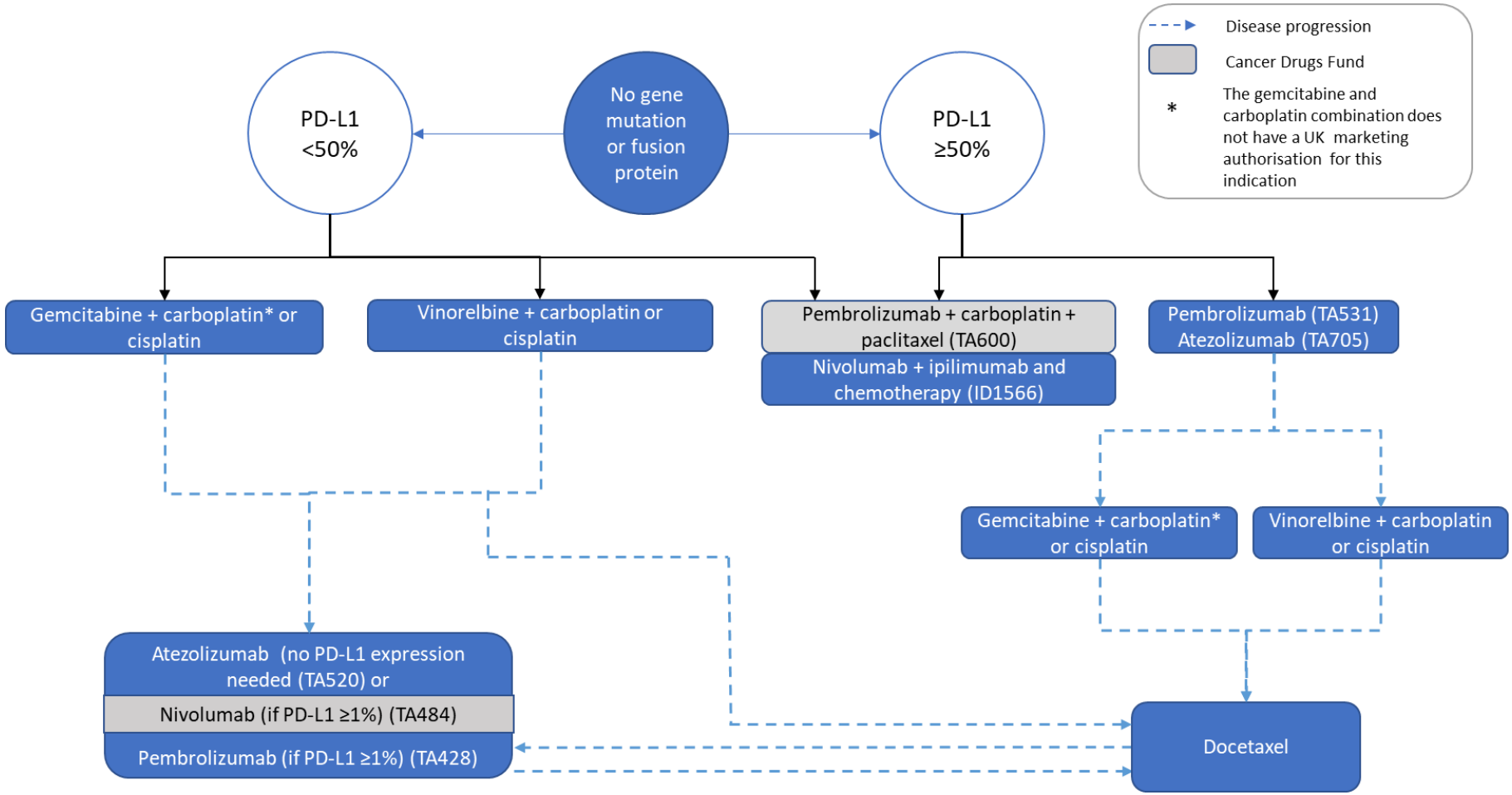
Figure 3. NICE guidelines – Lung cancer: Systemic anti-cancer therapy for patients with no gene mutation or fusion protein, management options for people with non-squamous advanced NSCLC



Abbreviations = PD-L1, programmed death ligand 1; TA = technology appraisal

Source = NICE Guidelines NG122;[70] NICE TA190;[71] NICE TA347;[72] NICE TA402;[73] NICE TA428;[74] NICE TA484;[75] NICE TA520;[76] NICE TA531;[77] NICE TA557;[78] NICE TA584;[79] NICE TA705;[80] NICE Guidance in Development Nivolumab + Ipilimumab + chemotherapy (ID1566)[81]

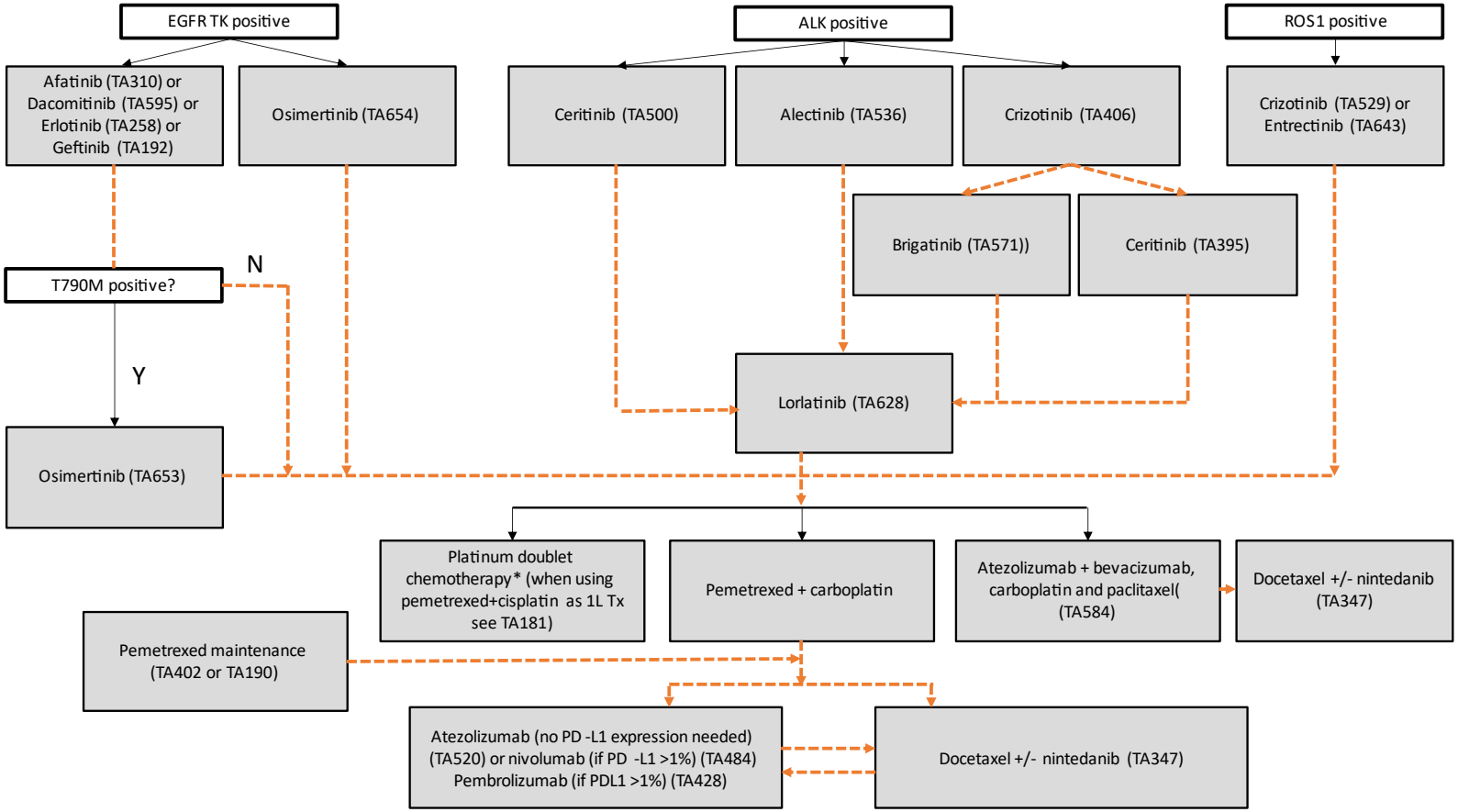
Figure 4. NICE guidelines – Lung cancer: Systemic anti-cancer therapy for patients with no gene mutation or fusion protein, management options for people with squamous advanced NSCLC



Abbreviations = PD-L1 = programmed death ligand 1; TA = technology appraisal

Source = NICE Guidelines NG122;[70] NICE TA428;[74] NICE TA484;[75] NICE TA520;[76] NICE TA531;[77] NICE TA600;[82] NICE TA705;[80] NICE Guidance in Development Nivolumab + Ipilimumab + chemotherapy (ID1566)[81]

Figure 5. NICE guidelines – Lung cancer: Systemic anti-cancer therapy: management options for people with non-squamous (adenocarcinoma, large cell undifferentiated) carcinoma and non-small-cell carcinoma (non-otherwise specified) – December 2020 Update



Source = NICE Guidelines NG122;[70] NICE TA190;[71] NICE TA347;[72] NICE TA402;[73] NICE TA428;[74] NICE TA484;[75]

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; PD-L1, programmed death ligand 1; ROS1, c-ros oncogene 1; TA, technology appraisal; TK, tyrosine kinase

Notes:

Crizotinib TA529[83] = Cancer Drugs Fund

* This combination/some of these combinations of drugs do not have a UK marketing authorisation for 1 or more indications

Immunotherapy

NICE Guidelines recommend testing for PD-L1 expression before first time treatment in all patients with metastatic NSCLC, if clinically feasible. PD-1 and PD-L1 immune checkpoint inhibitors (ICIs) (single agent or as a combination with chemotherapy) are treatment options in patients with advanced or metastatic NSCLC and negative results for the driver mutations (EGFR, ALK and ROS1).[58]

Recent studies have shown that patients with METex14 skipping alterations tend to have poor response to immunotherapy specifically, particularly for response rates and PFS. In 2018, a study reported the tumour mutational burden and response to immunotherapy for patients diagnosed with METex14 skipping alterations NSCLC between 2014 and 2017. In total, 24 patients were identified with these inclusion criteria; of these, 11 patients received first-line therapy, six received second-line therapy, and seven received third-line therapy. Of the total study population, 63% of patients assessed had tumours that were PD-L1 positive (≥1%). The results demonstrated that the overall response rate (ORR) for these patients was 17%, median OS was 18.2 months, and the median progression-free survival (PFS) was 1.9 months, despite the PD-L1 expression status of the patients.[51]

In a separate study from the IMMUNOTARGET registry, which included a retrospective analysis of 551 patients, treated in 24 centres from 10 countries (France, US, Switzerland, UK, Spain, Australia, The Netherlands, Israel, Italy, Germany), with driver mutations who were treated with immunotherapy, the ORR and PFS for patients with MET alterations was similar to results reported for patients expressing other mutation tumours in this setting (Table 4).[84] This provides further supporting evidence for the limited efficacy of immunotherapies in patients with specific driver mutations, including MET alterations.

Table 4: Efficacy of immunotherapy in patients with driver mutations (IMMUNOTARGET registry)

	N	ORR, %	Median PFS, months	6-month PFS, n	12-month PFS, n
KRAS	271	26%	3.2	37.9	25.6
EGFR	125	12%	2.1	18.4	6.4
BRAF	43	24%	2.5	32.1	18.0
MET	36	16%	3.4	36.5	23.4
HER2	29	7%	2.1	22.7	13.6
ALK	23	0%	3.1	11.8	5.9
RET	16	6%	2.1	14.1	7.0

	N	ORR, %	Median PFS, months	6-month PFS, n	12-month PFS, n
ROS1	7	17%	-	-	-

Source: Mazieres et al. 2019[84]

Abbreviations: ALK: Anaplastic lymphoma kinase; BRAF: B-Raf proto-oncogene; EGFR: Epidermal growth factor receptor; HER2, human epidermal receptor 2 gene; KRAS, kirsten rat sarcoma viral oncogene homolog; MET, mesenchymal-epithelial transition gene; NSCLC: Non-small cell lung cancer; PFS: Progression-free survival; ORR: Objective response rate; RET, rearranged during transfection proto-oncogene; ROS1: ROS proto-oncogene-1

In qualitative interviews (N=2) and an advisory board (N=4), clinical experts agreed with and supported the published evidence that patients with advanced NSCLC harbouring METex14 skipping alterations are more likely to respond poorly to immunotherapy, particularly in terms of lower responses rates and lower PFS than expected for immunotherapy. This was based on their experience when patients at specific centres have received a MET test, as well as experience with other driver mutations where similar responses are seen. One clinical expert stated that this reduced response is not seen in all patients, however a general trend of poor responses is often still seen.

A retrospective, multicentre study in ICI-treated BRAF-, HER2-, MET- or RET-NSCLCs, analysed clinical characteristics and outcomes.[85] Before ICI, patients had received a median of one treatment line. The response rate for patients with MET mutations was 36%, median PFS was 4.9 months, 12-month PFS was 22.2%, median OS was 13.4 months and 12-month OS was 59.0%.[85]

The management of adverse events associated with immunotherapies is complex, and requires a multidisciplinary approach involving not only oncologists, but also other internal medicine specialists, to ensure prompt diagnosis and optimal management of these complications.[86] This is of relevance for the targeted METex14 skipping alterations NSCLC population, mainly comprising elderly patients who may experience low benefit with the current non-targeted available therapies, and who are often unable to tolerate the adverse reactions and demanding infusions linked to chemotherapy or immune checkpoint inhibitors.

Chemotherapy

Chemotherapy is used for patients with metastatic disease that is negative for driver mutations (EGFR, ALK and ROS1), and where the patient is contraindicated to immunotherapy.[58,59,69,87] Chemotherapy options are also used as second-line and beyond treatments when a patient has received immunotherapy (monotherapy or combination) at first line. NICE recommended and commonly used regimens include cisplatin-based doublets (such as cisplatin and pemetrexed [non squamous alone]) and carboplatin-based

doublets (such as carboplatin and paclitaxel).[58,59,69,87] The choice of chemotherapy regimen can be dependent on histological subtype (non-squamous vs. squamous). Platinum-based chemotherapy in fit patients, prolongs survival, improves symptom control, and yields superior quality of life compared with best supportive care in patients with advanced NSCLC.[58,59,69,87]

However, platinum-based chemotherapy combinations also show limited responses in patients with advanced NSCLC harbouring METex14 skipping alterations. Responses to platinum-based chemotherapy were assessed in Hur et al 2020, a retrospective, single-centre observational study in South Korea, where patients were identified between 2015 and 2017 (n=20). The median PFS in these patients was 4.0 months (95% CI:2.8-14.1) and the median OS was 9.5 months (95%CI:6.5-23.1). In 12 patients treated with pemetrexed-based chemotherapy, the ORR was 33.3% (4/12).

Common AEs experienced with chemotherapy include nausea/vomiting, neutropenia/anaemia/pancytopaenia, alopecia, constipation/diarrhoea, and fatigue/tiredness.[88] This is of relevance for the targeted METex14 skipping alterations NSCLC population, mainly comprising elderly patients who may experience low benefit with the current non-targeted available therapies, and who are often unable to tolerate the adverse reactions and demanding infusions linked to chemotherapy or immune checkpoint inhibitors.

Unmet medical need

Unlike for patients with EGFR, ALK or ROS1 mutations, patients in the UK with advanced NSCLC harbouring METex14 skipping alterations do not currently benefit from a targeted treatment, and as demonstrated, the available non-targeted therapies are considered unsatisfactory with limited clinical benefit and a clear unmet need exists for these patients. As such, a therapy that targets this specific alteration and prevents or delays the need for subsequent-line treatment, and the associated adverse events (AEs) of chemotherapies, represents a significant unmet need.

Positioning of tepotinib relative to the current treatment pathway

Tepotinib is being investigated in patients with advanced (locally advanced or metastatic) NSCLC with METex14 skipping alterations as detected by a liquid and /or tissue biopsy, and so would be available for suitable patients with a METex14 skipping alteration regardless of line of therapy and histology.

The expectation is that tepotinib would replace non-targeted therapies (immunotherapies and/or chemotherapies) for patients with METex14 skipping alterations in all lines of treatment, in line with past recommendations for targeted treatments in EGFR, ALK and ROS1 NSCLC.

B.1.4. Equality considerations

There are no anticipated equality issues relating to the use of tepotinib in patients with advanced NSCLC with METex14 alterations.

B.2. Clinical effectiveness

Executive summary

- VISION is an ongoing, single-arm, open-label, Phase II study designed to assess the antitumour activity and tolerability of tepotinib in patients with advanced NSCLC harbouring METex14 skipping alterations. The study population in Cohort A is representative of the METex14 skipping alterations NSCLC population based on reported disease history.
- VISION is the largest study in patients with NSCLC harbouring MET alterations to prospectively enrol patients using tissue biopsy as well as liquid biopsy, allowing for maximum accessibility to patients and physicians. Liquid biopsies are an accessible alternative, especially when tissue biopsy is not an option, although tissue biopsy remains the standard of care
- Tepotinib had durable antitumour activity in patients with advanced NSCLC with METex14 skipping alterations with consistent activity across treatment lines (1L and 2L+) and promising activity in patients with brain metastases.
- ORR by the independent review committee (IRC) was [redacted]% (95% CI: [redacted]); onset of response was mostly within six weeks with a long median DOR of up to [redacted] months (95% CI: [redacted]). The response rate was higher in the 1L population ([redacted]%) versus the 2L+ population ([redacted]%) and was consistent across the tissue biopsy and liquid biopsy groups, as well as across other baseline characteristics.
- The median PFS based on IRC in Cohort A was [redacted] months (95% CI: [redacted]), and the median OS was [redacted] months (95% CI: [redacted]). Consistent results were observed between 1L and 2L+ patients.
- Tepotinib penetrates the blood-brain barrier at therapeutic levels. The response to tepotinib was consistent in patients with stable brain metastases at baseline (determined by RECIST v1.1; n=[redacted]). IRC-assessed ORR was [redacted]% (95% CI: [redacted]), and median DOR was [redacted] months (95% CI: [redacted]). IRC-assessed median PFS was [redacted] months (95% CI: [redacted]).[89]
- Tepotinib demonstrates and confirms a favourable and well-tolerated safety profile, with the most common AEs being Grade 1 or 2. In this elderly patient population, there was a low proportion of Grade ≥3 treatment-related AEs ([redacted]%), and a low frequency of treatment discontinuation due to treatment-related AEs ([redacted]%).
- Patients' quality of life was maintained during treatment with tepotinib; dyspnoea symptoms were stable, whereas cough symptoms were reduced.
- The first HRQL analysis results were consistent across different PRO tools, such as QLQ-LC13, EORT QLQ-30, and EQ-5D VAS, suggesting stability in HRQL over time, as well as an improvement in coughing symptoms.
- EORTC QLQ-LC13 symptom scores revealed mean changes from baseline indicated a meaningful improvement in coughing, with a median time to improvement ([redacted] months) paralleling the onset of objective response (within the first three months) and a numerical improvement in dyspnoea ([redacted] at Week 12) and chest pain ([redacted] at Week 12).
- QLQ-C30 global health values remained stable over the treatment period, as did EQ-5D-5L VAS scores (higher=better): mean (standard deviation, SD) change from baseline score ([redacted]) was [redacted] at Week 6 and [redacted] at Week 12.

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

A systematic literature review (SLR) was performed to identify randomised controlled trials (RCTs), non-randomised clinical trials, single arm studies and retrospective real-world studies that evaluated survival, response, safety and patient-reported outcomes for patients with advanced NSCLC harbouring METex14 skipping alterations.

A total of 143 publications were included in the review (refer to Appendix D, Appendix G Appendix H, and Appendix I). Of the total publications identified, 38 publications reported clinical outcomes associated with treatments for patients with NSCLC harbouring METex14 skipping alterations (16 full-text and 22 abstracts/conference posters) (refer to Table 5).

Table 5. Identified clinical effectiveness evidence

Intervention	Trial	N	Publications
Tepotinib	VISION NCT02864992	8	Mazieres et al. 2020;[90] Mazieres et al. 2021;[91] Park et al. 2019;[92] Paik et al. 2020 (full text);[1] Paik et al. 2021;[93] Veillon et al. 2021[94] Viteri et al. 2020;[95] Yang et al. 2020[96]
Capmatinib	GEOMETRY NCT02414139	11	Goodwin et al. 2021a;[97] Goodwin et al. 2021b;[98] Groen et al. 2020;[99] Han et al. 2021;[100] Heist et al. 2021a;[101] Heist et al. 2021b;[102] Schuler et al. 2020 (full text);[103] Vansteenkiste et al. 2020;[104] Wolf et al. 2019;[53] Wolf et al. 2020a (full text);[105] Wolf et al. 2021[106]
Crizotinib	NCT02499614 NCT02034981	3	Drilon et al. 2020 (full text);[107] Landi et al. 2019 (full text);[108] Moro-Sibilot et al. 2019 (full text)[109]
Savolitinib	NCT02897479	2	Lu et al. 2019;[110] Lu et al. 2020[111]
Tyrosine kinase inhibitors (crizotinib, capmatinib, cabozantinib)		1	Lau et al. 2021[112]
Chemotherapy (1L) PD-1 inhibition monotherapy (1L+) Crizotinib (1L)		1	Pruis et al. 2020 (full text)[113]
Pemetrexed-based chemotherapy (1L+) , crizotinib (2L+)		1	Hur et al. 2020 (full text)[114]
Immune checkpoint inhibitors (pembrolizumab,		5	Guisier et al 2021 (full text);[85] Kato et al 2021 (full text);[115] Kauffmann-Guerrero et al. 2020 (full text);[116] Mazieres et al.

Intervention	Trial	N	Publications
nivolumab, atezolizumab)			2019 (full text);[84] Sabari et al. 2018 (full text)[51]
Standard treatments (RWE)		1	Wolf et al. 2020b[105]
Sym015 (MET antibody mixture)		3	Camidge et al 2019;[117] Camidge et al. 2020;[118] Castiglione et al 2019 (full text)[119]
Various (No MET inhibitor; 1L+ and/or 2L+)		2	Awad et al 2019 (full text);[49] Gow et al. 2017[120]
Total		**38**	

Abbreviations: 1L, firstline; 1L+ firstline or subsequent line; 2L, secondline; 2L+ secondline or subsequent; MET, mesenchymal-epithelial transition; RWE, real world evidence

B.2.2. List of relevant clinical effectiveness evidence

The clinical evidence used to support the marketing authorisation and reimbursement of tepotinib comes from the VISION study, which is an ongoing Phase II single-arm study that investigates tepotinib in patients with locally advanced or metastatic NSCLC harbouring METex14 skipping alterations or MET amplification (Table 6, Section B.2.3).

Table 6. Clinical effectiveness evidence

Study	VISION (NCT02864992)
Study design	Single arm, open-label, Phase II study
Population	The study included adult male and female patients ≥ 18 years of age with measurable disease according to RECIST 1.1 and an ECOG PS of 0 or 1. Patients had to have histologically or cytologically confirmed locally advanced or metastatic NSCLC (all types including squamous and sarcomatoid) and be either untreated (for 1L therapy) or previously treated with no more than 2 lines of prior therapy. Patients needed to have MET alterations to be eligible, as detailed below: 1) METex14 skipping alterations in plasma and/or tissue, determined by the central laboratory or by an assay with appropriate regulatory status; for these patients, sufficient tumour tissue and/or plasma was requested to allow additional testing; 2) MET amplification only in plasma defined by a positive liquid biopsy (LBx) test, as determined by the central laboratory or by an assay with appropriate regulatory status; 3) Based on the outcome of the interim analysis in 12 LBx selected patients: MET amplification only in tissue defined by a positive tissue biopsy (TBx) with a gain of at least 4 copies of the MET gene, as determined by the central laboratory or by an assay with appropriate regulatory status. Patients with characterised EGFR activating mutations that predict sensitivity to anti-EGFR therapy and patients with characterised ALK rearrangements that predict sensitivity to anti-ALK therapy were excluded from the study.

<table>
<tr><td>Intervention(s)</td><td colspan="5">Patients took 450 mg tepotinib (equivalent to 500 mg tepotinib hydrochloride hydrate) orally once daily during each 21-day cycle until progression of disease (as assessed according to RECIST 1.1), withdrawal of consent, AE leading to discontinuation, or death.</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Not applicable as single arm study</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">VISION is the pivotal trial for tepotinib in the population directly relevant to the decision problem.</td></tr>
<tr><td>Reported outcomes specified in the decision problem (outcomes highlighted in bold are outcomes used in the economic model)</td><td colspan="5">ORR (confirmed complete response or partial response) as per IRC determined according to RECIST 1.1
ORR as per Investigator determined according to RECIST 1.1
DOR as per IRC
DOR as per investigator
Objective disease control as per IRC
PFS as per IRC
PFS as per investigator assessment
OS
EQ-5D-5L
EORTC QLQ-C30
EORTC QLQ-LC13
Safety</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">Plasma pharmacokinetic parameters of tepotinib and metabolites
Exploratory biomarkers including biomarkers that may correlate with antitumour activity, including, but not limited to, markers of MET pathway activation (e.g., HGF levels and MET mutations) and other relevant oncogenic pathways
QT/QTc interval concentration relationship based on Cycle 1, Day 1 and Cycle 2, Day 1 data
Associations between exposure, predictive biomarker candidates, and efficacy and/or safety</td></tr>
</table>

Abbreviations: DOR=duration of response, ECOG=Eastern Cooperative Oncology Group, EORTC=European Organization for Research and Treatment of Cancer, EORTC QLQ-C30=EORTC Quality of Life Questionnaire Core 30, EQ5D5L=EuroQol Five Dimension Five Level Scale, HRQL=health-related quality of life, IRC=independent review committee, ORR=objective response, OS=overall survival, PFS=progression-free survival, PROs=patient-reported outcomes, PS=performance status, QLQLC13=Quality of Life Questionnaire Lung Cancer 13, RECIST=Response Evaluation Criteria in Solid Tumours

Non-interventional studies investigating patient characteristics, treatment patterns and effectiveness outcomes in patients with advanced NSCLC harbouring METex14 skipping alterations were also conducted and included in the indirect comparisons and cost-effectiveness analysis to inform the comparator efficacy data (Table 7). For further detail please see Section B.2.9 and the indirect treatment comparison report (Appendix L) provided separately.

Table 7. Summary of non-interventional studies in patients with advanced NSCLC harbouring METex14 skipping alterations used in the indirect treatment comparison

Study	0015	0035	COTA	Wong et al
Country	USA	Israel, The Netherlands, Taiwan, USA	USA and Canada	Canada
Study type	Non-interventional real world retrospective cohort study based on EMR data	Non-interventional real world retrospective cohort study, based on EMR data	Data source based on EMR data sourced from COTA Healthcare	Non-interventional real world retrospective review
Study period	01 Jan 2004 to 30 Sept 2019	01 Jan 2010 to 30 Sept 2018	15 Aug 2008 to 10 Feb 2020	Jan 2016 to Sept 2019
N (before application of inclusion criteria)	39 with MET alterations	86 with MET alterations	202	41[a]
Treatment lines	76	165	680	NR

Abbreviations: NR, not reported; OS, overall survival; PFS, progression free survival; RR, response rate; ToT, time on treatment; TTNTD, time to next treatment or death

Notes:

a Data was available for 41 patients, though not all received treatment

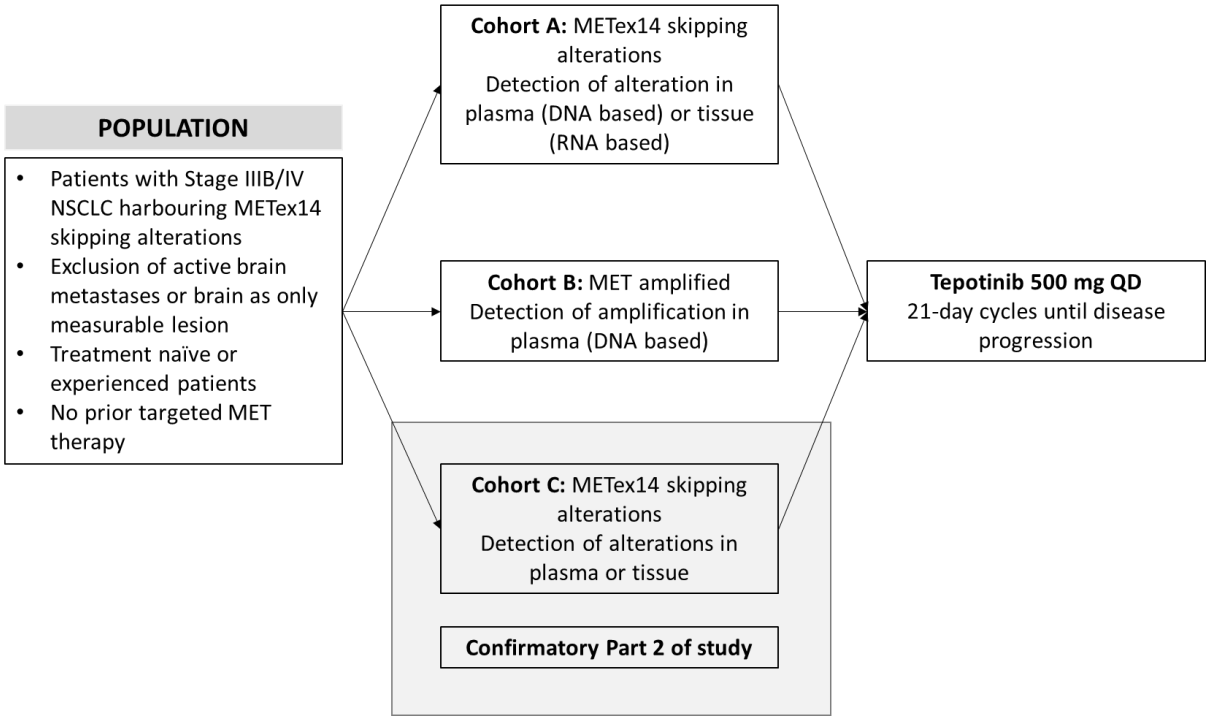
B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. VISION Study

VISION (NCT02864992) is an ongoing, single-arm, open-label, Phase II study designed to assess the antitumour activity and tolerability of tepotinib 500 mg (equivalent to 450 mg free form tepotinib), a highly selective small-molecule inhibitor of MET in patients with advanced (locally advanced or metastatic) NSCLC harbouring METex14 skipping alterations or MET amplification. Patients were selected based on defined MET alterations or MET amplification identified in tumour tissue and/or in circulating tumour DNA (ctDNA) derived from plasma, and then subdivided into three cohorts (Figure 6):

- **Cohort A:** Tepotinib 500 mg for METex14 skipping alterations
- **Cohort B:** Tepotinib 500 mg for MET amplification
- **Cohort C:** Confirmatory part for tepotinib 500 mg for METex14 skipping alterations

Figure 6: Schematic overview of Cohort A and Cohort C in the VISION trial design



Source: Data on File: VISION Clinical Study Report 2020[121]
Abbreviations: NSCLC, non-small cell lung cancer; QD, once daily.

The study was divided into two parts: Part 1 included the pivotal Cohort A and Cohort B. Part 2 included the new confirmatory part, Cohort C. Additional patients were needed to extend and confirm the existing results for Cohort A (METex14 skipping alterations), so to expand the METex14 population in this study, a new confirmatory cohort was subsequently added (Cohort C). Cohort C was started following the completion of the subject accrual for Cohort A. The eligibility criteria and schedule of assessments for Cohort C were the same as those for enrolment into Cohort A.

The key VISION data considered in this submission are from Cohort A and included data from two different cut-off dates (Table 8).

- Data cut-off 1 February 2021: The total patient set for Cohort A. All patients who received a dose of tepotinib in Cohort A, all before 01 November 2020, using the 1 February 2021 cut-off date (N=152) (Figure 8).

- Data cut-off 1 July 2020: ITT analysis set restricted to patients who received the first dose of tepotinib before 02 October 2019 (this approach ensured that the latest enrolled subject had a follow-up of at least nine months, expected to provide six months of follow-up beyond a possible onset of response), using the 1 July 2020 cut-off date (N=146) (Figure 7).

The cost-effectiveness analysis is based on the 1 February 2021 data cut and therefore is the focus of the text in the clinical effectiveness results (Section B.2.6). However, results are presented for both data cuts in the data tables to ensure full transparency and comprehensive reporting of data.

The dossier also presents efficacy outcomes supporting the activity of tepotinib in brain metastases from patients enrolled in VISION. Exclusion criteria for this subset were: brain metastasis as the only measurable lesions, leptomeningeal disease and neurologically unstable symptomatic brain metastases requiring an increase in steroid dose within two weeks and/or have received prior stereotactic radiosurgery/gamma knife within two weeks and/or other prior treatment for brain metastases within four weeks prior to the start of therapy.

In Appendix R, additional efficacy results are also reported from Cohort A+C, using the 1 February 2021 cut-off (i.e., pooled METex14 skipping alteration cohorts), to confirm the efficacy of tepotinib in a larger population of patients with METex14 skipping alterations.

The safety data from VISION are summarised for patients in Cohorts A+C (Table 9): SAF-1 July 2020: The safety analysis set (SAF) for Cohorts A+C included 255 subjects. A total of 152 patients were enrolled and were administered at least one dose of tepotinib in Cohort A; 103 patients were enrolled and were administered at least one dose of tepotinib in Cohort C (Figure 7), based on 1 July 2020 cut-off.

In Appendix R, summary safety data from the latest 1 February 2021 data cut for Cohort A+C are also reported (N=291) (Figure 8).

Table 8: VISION data synopsis presented in NICE dossier (efficacy)

Analysis set	Cut-off date	Cohorts	Description	Number of patients	Reporting
Cohort A all patients	1 February 2021	Cohort A	All subjects in Cohort A who received a dose of tepotinib. All were administered at least one dose of tepotinib by 1 November 2020.	152	Document A, B and Appendix E
ITT-2 Oct 2019	1 July 2020	Cohort A	All subjects in Cohort A received the first dose of tepotinib before 2 October 2019. This set of subjects had at least 9 months of follow-up.	146	Document B and Appendix E
SAF-1 Nov 2020	1 February 2021	Cohort A+C	All patients in Cohort A, and all patients in Cohort	275	Appendix E and

Analysis set	Cut-off date	Cohorts	Description	Number of patients	Reporting
			C who were administered at least one dose of tepotinib by 1 November 2020. Used for efficacy analysis for Cohort A+C.		Appendix R

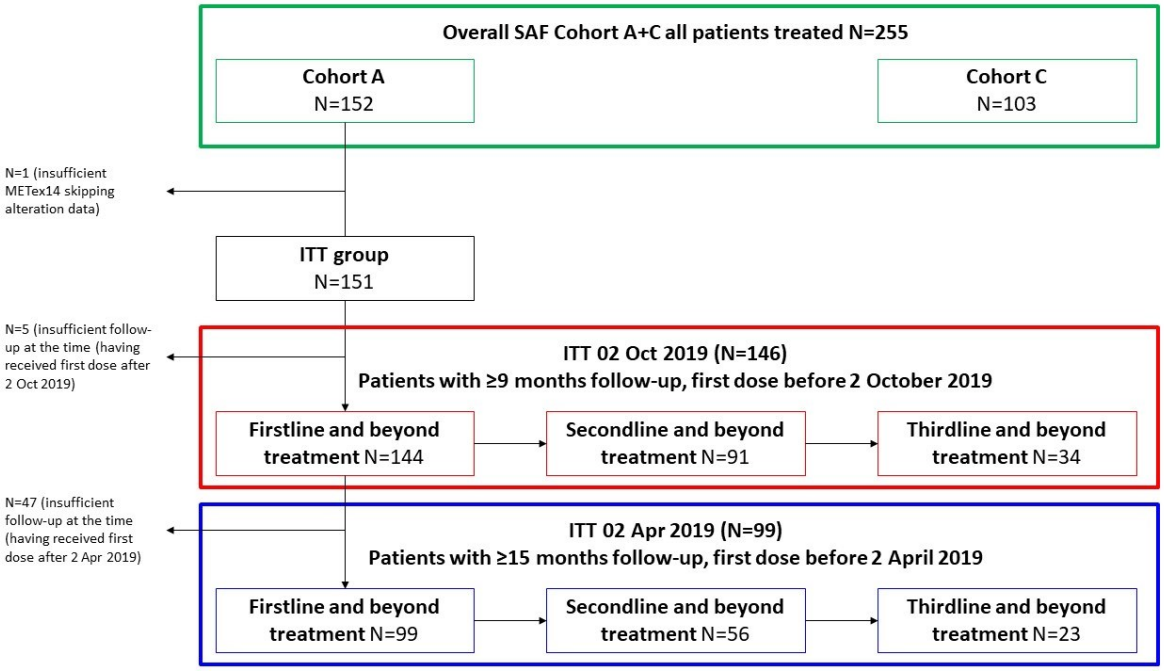
Abbreviations: ctDNA, circulating tumour deoxyribonucleic acid, ITT-02 Oct 2019, Intention-to-Treat analysis set restricted to subjects who received the first dose of tepotinib before 02 October 2019; SAF, safety analysis set

Table 9. VISION data synopsis presented in NICE dossier (safety)

Analysis set	Cut-off date	Cohorts	Description	Number of patients	Reporting
SAF-1 July 2020	1 July 2020	Cohort A+C	All subjects in Cohorts A + C were administered at least one dose of tepotinib by 1 July 2020.	255	Document A and B
SAF Cohort A+C all patients	1 February 2021	Cohort A+C	All subjects in Cohort A and Cohort C who received a dose of tepotinib for safety analysis.	291	Appendix R

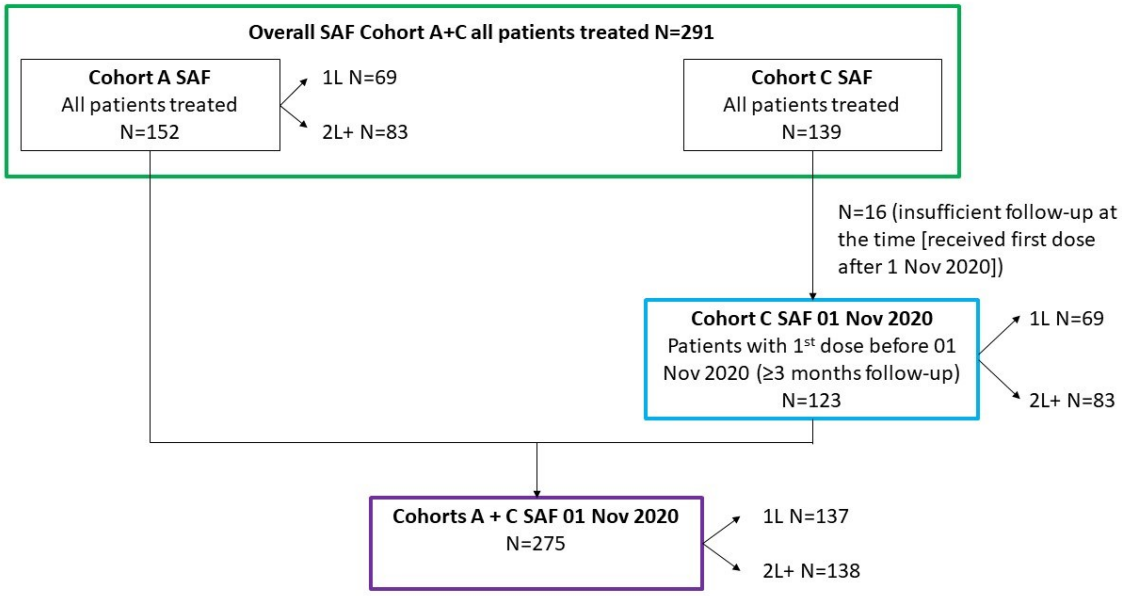
Abbreviations: SAF, safety analysis set

Figure 7: VISION analysis sets, at 1 July 2020 data cut-off



Abbreviations: ITT, intention to treat; ITT-02 Apr 2019, Intention-to-Treat analysis set restricted to subjects who received a first dose of tepotinib before 02 April 2019; ITT-02 Oct 2019, Intention-to-Treat analysis set restricted to subjects who received the first dose of tepotinib before 02 October 2019; SAF, safety set

Figure 8. VISION analysis sets, at 1 February 2021 data cut-off



Abbreviations: SAF=safety analysis set
Source: SAF-01 Nov 2020,
Notes: Safety Set analysis set restricted to subjects who received the first dose of tepotinib before 01 October 2020, so with at least 3 months follow; SAF, safety set; 1L, first-line treatment; 2L, second-line treatment

B.2.3.1.1. Study objectives

The primary endpoint of the VISION trial was objective response (ORR; confirmed CR or PR) determined according to RECIST Version 1.1, based on an IRC evaluation.

The key secondary objectives were as follows:

- ORR as per Investigator's assessment,
- Duration of response (DOR) per IRC and Investigator,
- Progression-free survival (PFS) per IRC and Investigator,
- Overall survival (OS).

Other endpoints included:

- Safety and tolerability,
- PROs as measured by:

- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30),
- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13),
- The EuroQol Five Dimension Five Level Scale (EQ-5D-5L) visual analog scale (VAS).

In addition to the endpoints mentioned above, this dossier also presents outcomes for tepotinib activity in patients with baseline brain metastasis. The presented outcomes for this specific subgroup included:

- ORR (INV and IRC)
- PFS (INV and IRC).

B.2.3.1.2. Eligibility criteria

Eligible subjects were required to have histologically or cytologically confirmed locally advanced or metastatic NSCLC with METex14 skipping alterations or MET amplification in either plasma samples or tissue samples of tumour biopsy. The inclusion and exclusion criteria for VISION are summarised in Table 10.

Table 10: VISION trial inclusion and exclusion criteria

Inclusion criteria
• Male or female, greater than or equal to (>=) 18 years of age (or having reached the age of majority according to local laws and regulations • Measurable disease in accordance with RECIST version 1.1 • ECOG PS of 0 or 1 • A female subject is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies: ▪ Not a woman of childbearing potential OR ▪ A woman of childbearing potential who agrees to use a highly effective contraception • A male subject must agree to use and to have their female partners of childbearing potential to use a highly effective contraception • Histologically confirmed advanced (Stage IIIB/IV) NSCLC (all histologies including squamous and sarcomatoid) • Untreated patients in first-line or previously-treated patients with no more than two lines of prior therapy

• Subjects with MET alterations, namely METex14 skipping alterations in plasma and/or tissue, or MET amplification only in plasma and/or tumour biopsy sample
Exclusion criteria
• Subjects with characterised EGFR activating mutations that predict sensitivity to anti-EGFR-therapy • Subjects with characterised ALK rearrangements that predict sensitivity to anti-ALK therapy • Active brain metastases • Any unresolved toxicity Grade 2 or more according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) from previous anticancer therapy • Need for transfusion within 14 days prior to the first dose of trial treatment • Prior chemotherapy, biological therapy, radiation therapy, hormonal therapy for anti-cancer purposes, targeted therapy, or other investigational anticancer therapy (not including palliative radiotherapy at focal sites) within 21 days prior to the first dose of trial treatment • Subjects who have brain metastasis as the only measurable lesion • Inadequate haematological, liver, renal, cardiac function • Prior treatment with other agents targeting the Hepatocyte Growth Factor c(HGF/c) -Met pathway • Hypertension uncontrolled by standard therapies (not stabilised to < 150/90 mmHg) • Past or current history of neoplasm other than NSCLC, except for curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix, or other cancer curatively treated and with no evidence of disease for at least five years • Medical history of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease, or conditions that may hamper compliance and/or absorption of the test product • Major surgery within 28 days prior to Day 1 of trial treatment • Known infection with human immunodeficiency virus, or an active infection with hepatitis B or hepatitis C virus • Substance abuse, active infection, or other acute or chronic medical or psychiatric condition or laboratory abnormalities that might increase the risk associated with trial participation at the discretion of Investigators • Known hypersensitivity to any of the trial treatment ingredients • Legal incapacity or limited legal capacity • Any other reason that, in the opinion of the principal investigator, precludes the subject from participating in the trial • Participation in another clinical trial within the past 30 days

Generalisability of the population treated

The study population in Cohort A (1 February 2021 cut-off) was representative of the METex14 skipping alterations NSCLC population, based on the reported disease history. Overall, [redacted] of patients had adenocarcinoma and the median and mean age were [redacted] and

[redacted] years respectively. The proportion of patients who were former smokers was [redacted]. These characteristics are aligned with estimates in the METex14 skipping alterations population identified within the literature (Section B.1.3.2.3). In the SLR conducted, a median of 79% of METEx14 skipping alterations patients were adenocarcinoma histology, the median age was 72 years and 56% were ever smokers.[47,121] At the conducted advisory board, the clinical experts (N=4) also agreed that VISION is generalisable to the wider METex14 skipping alterations population based on the literature.

B.2.3.1.3. Patient disposition

From the 1 February 2021 data cut-off, all 152 patients on Cohort A were included in the efficacy analysis. Of the 152 patients, 69 patients received tepotinib as 1L therapy, and 83 patients received tepotinib as 2L+ therapy (Table 11).

In Cohort A from the 1 July 2020 data cut-off, a total of 152 patients were treated up to 1 July 2020 and were part of the overall safety analysis set (SAF). The overall ITT analysis set comprised 151 patients; one patient was excluded from all efficacy analyses due to insufficient METex14 skipping alteration data. Of the 151 overall ITT patients, 69 patients received tepotinib as 1L therapy, and 82 patients received tepotinib as 2L+ therapy. All patients in the 1 July 2020 data cut-off had a follow-up of at least nine months from the start of treatment (expected to yield six months of follow-up after onset of response). Among responders, 84.8% had ≥12 months follow-up from onset of response or event (progressive disease or death) or discontinued treatment <12 months after onset of response (Table 14).

From the 1 July 2020 data cut-off, 124 (81.6%) patients permanently discontinued treatment due to progressive disease (77 patients), AE (26 patients), death (12 patients), consent withdrawal (five patients), protocol noncompliance (one patient), or other reason (three patients).

Table 11. Analysis Sets in VISION Study Cohort A

Number of patients in analysis set	Overall	1L	2L+
1 July 2020 data cut-off			
Overall SAF	152	69	83
Overall ITT	151	69	82
ITT-02 Oct 2019	146	65	81
ITT-02 Apr 2019	99	43	56

Number of patients in analysis set	Overall	1L	2L+
1 February 2021 data cut-off			
All patients	152	69	83

Source: VISION CSR 1 July 2020 cut-off, Table 15.1.1.2, 15.1.1.2o, 15.1.1.2s. Data on file for 1 February 2021 cut-off

Abbreviations: 1L=first line of therapy, 2L+=second or later line of therapy, CSR=Clinical Study Report, ITT=intention-to-treat, SAF=safety analysis set

METex14 Results at Pre-screening/Screening

Patients were screened for METex14 in tissue and blood samples and categorised into the liquid biopsy (L+) set, the tumour tissue biopsy (T+) set, or the combined set (one test was sufficient, but two tests were allowed). As of 1 July 2020, a total of 7,673 patients were prescreened to determine MET alteration status in tissue and blood samples. Pre-screening was not required for patients with a documented MET alteration status by an assay with appropriate regulatory status (i.e., Lung Cancer – Genomic Screening Project for Individualised Medicine); in these instances, MET alteration status did not need to be reconfirmed in tissue and/or blood for study recruitment. Results are not presented by liquid or tissue biopsy here, although are presented in Appendix E.

B.2.3.1.4. Demographic and Baseline Characteristics

In the 1 February 2021 cut-off, [redacted] of patients were male, [redacted] of patients were white, and [redacted] of patients were from Europe (see Table 12). Most patients ([redacted]) were ≥65 years of age and [redacted] of patients were ≥75 years of age.

Similar demographic and baseline characteristics were observed in 1L and 2L+ patients. Demographic and baseline characteristics in the 1 July 2020 cut-off were consistent to the 1 February 2021 cut-off across 1L and 2L+ patient populations (Appendix R).

Table 12. Demographics and Baseline Characteristics, VISION Cohort A – 1 February 2021 cut-off

	Overall	1L	2L+
	N=152 (100%)	**N=69 (100%)**	**N=83 (100%)**
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]

	Overall	1L	2L+
	N=152 (100%)	N=69 (100%)	N=83 (100%)
Asian	[redacted]	[redacted]	[redacted]
Not collected at site	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Age (years)			
Mean (StD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Age groups, n (%)			
<65 years	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]
65 to <75 years	[redacted]	[redacted]	[redacted]
75 to <85 years	[redacted]	[redacted]	[redacted]
≥85 years	[redacted]	[redacted]	[redacted]
Country, n (%)			
Belgium	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]
Italy	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
Poland	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
United States	[redacted]	[redacted]	[redacted]
South Korea	[redacted]	[redacted]	[redacted]
Taiwan	[redacted]	[redacted]	[redacted]
Netherlands	[redacted]	[redacted]	[redacted]
Israel	[redacted]	[redacted]	[redacted]
Geographic region, n (%)			
Europe	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]
Histology subtype, n (%)			
Adenocarcinoma	[redacted]	[redacted]	[redacted]
Adenosquamous	[redacted]	[redacted]	[redacted]
Squamous	[redacted]	[redacted]	[redacted]
Sarcomatoid	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

Source: VISION 1 February 2021 cut-off data on file.

Abbreviations: 1L=first line of therapy, 2L+=second or later line of therapy, CSR=Clinical Study Report, ITT=intention-to-treat analysis set, max=maximum, min=minimum, Q1=quartile 1, Q3=quartile 3, StD=standard deviation

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of statistical analysis methods is provided below. Please refer to Appendix D for a more detailed summary.

Study Design Overview	Single-arm, open-label, Phase II study was planned to assess the anti-tumour activity and tolerability of tepotinib, a highly selective small molecule inhibitor of MET in subjects with advanced (locally advanced or metastatic) NSCLC harbouring METex14 skipping alterations or MET amplification. Subjects were to be selected based on defined MET alterations or MET amplification identified in tumour tissue and/or in circulating tumour DNA (ctDNA) derived from plasma.
Treatment Assignment	All subjects received tepotinib in this single-arm study. Subject numbers were assigned in the appropriate format and reflected study number, study centre number, and subject number. Subject numbers were not reassigned to other subjects or reused in this study.
Analysis Populations	**Prescreened Analysis Set** The Prescreening analysis set comprised all subjects who provided informed consent for prescreening or screening. This included subjects enrolled in Japan who could be enrolled without prescreening. **Screened Analysis Set** The Screening analysis set comprised all subjects who provided informed consent for the main screening, regardless of the subject's treatment status in the study. **Safety Analysis Set** The Safety analysis set comprised all subjects who were administered at least one dose of tepotinib. **Intention-to-Treat Analysis Set** The ITT analysis sets comprised all subjects who were administered at least one dose of tepotinib and had METex14 skipping alterations or MET amplification confirmed by a validated central laboratory assay. The ITT analysis set for Cohort A was defined as follows (the ITT analysis for Cohort B and Cohort C is provided in the clinical study report [provided separately]): **Cohort A (METex14 Skipping Alterations)** For efficacy analyses, in the cohort of subjects who tested positive for METex14 skipping alterations, regardless of MET amplification status, the following primary ITT analysis sets were defined taking into account the assessment used to identify subjects with METex14 skipping alterations.

	• The ITT L+ and/or T+ analysis set (also referred to as the combined analysis set) was defined as all subjects who tested positive for METex14 skipping alterations in tumour tissue or plasma ctDNA (including those tested positive for METex14 skipping alterations in both tumour tissue and plasma ctDNA); • The ITT L+ analysis set (also referred to as the L+ analysis set) was defined as all subjects who tested positive for METex14 skipping alterations in plasma ctDNA; • The ITT T+ analysis set (also referred to as the T+ analysis set) was defined as all subjects who tested positive for METex14 skipping alterations in tumour tissue. Subjects who tested positive in tissue (TBx) and in plasma (LBx) were assigned to both the L+ and the T+ analysis sets. For those subjects with available samples for both TBx and LBx: • The ITT T+/L+ analysis set comprised all subjects tested positive for METex14 skipping alterations in both tumour tissue and plasma ctDNA; • The ITT T+/liquid biopsy negative (L−) analysis set comprised all subjects tested positive for METex14 skipping alterations in tumour tissue, but negative in plasma ctDNA; • The ITT tumour tissue biopsy negative (T−)/L+ analysis set comprised all subjects tested positive for METex14 skipping alterations in plasma ctDNA, but negative in tumour tissue.
Primary Endpoints	The primary endpoint of the VISION trial is objective response (ORR; confirmed CR or PR) determined according to Response Evaluation Criteria for Solid Tumours (RECIST) Version 1.1, based on an independent review committee (IRC) evaluation. Subjects are identified as having an objective response if they achieve either a confirmed CR or PR from first administration of trial treatment to first observation of PD. Confirmation needs to take place by a tumour assessment at least four weeks (28 days) after the tumour assessments initially indicating CR or PR.
Key Secondary Endpoints	The key secondary objectives were as follows: • ORR as per Investigator's assessment: Objective response as per Investigator is determined according to RECIST Version 1.1. Subjects are identified as having an objective response if they achieve either a confirmed CR or PR. Confirmation needs to take place by a tumour assessment at least four weeks (28 days) after the tumour assessments initially indicating CR or PR. • Duration of response (DOR) per IRC: For subjects with objective response based on independent review, DOR is the time from when the CR/PR (whichever is first) criteria are first met until PD or death due to any cause within 84 days of the last tumour assessment, whichever occurs first. Duration of response data will be censored on the date of the last adequate tumour

	assessment for subjects who do not have an event (PD or death) or for subjects with an event after 84 days of the last tumour assessment. Subjects who do not have a tumour assessment after objective response will be censored at the date CR/PR criteria are first met.
	• Duration of response as per Investigator: Duration of response will also be determined for subjects with objective response based on Investigator assessment.
	• Progression-free survival (PFS) per IRC: PFS is defined as the time (in months) from the first administration of trial treatment to the date of the first documentation of PD (based on independent review) or death due to any cause within 84 days of the last tumour assessment, whichever occurs first. The PFS data will be censored on the date of the last evaluable tumour assessment for subjects who do not have an event (PD or death) or for subjects with an event more than 84 days after the last tumour assessment. Subjects who do not have a baseline tumour assessment or who do not have any post baseline tumour assessments will be censored at the date of the start of trial treatment.
	• Progression-free survival (PFS) per Investigator: PFS will also be assessed based on Investigator assessment.
	• Overall survival (OS): Overall survival will be measured as the time (in months) from first trial treatment administration to the date of death. For subjects not known to be deceased at time of analysis, OS time will be censored at the last date the subject was known to be alive. If this date is after the data cut-off, subjects will be censored at the date of data cut-off.
	Other endpoints included:
	• Safety and tolerability
	  • Number of subjects with TEAEs based on the Medical Dictionary for Regulatory Activities (MedDRA) and Common Terminology Criteria for Adverse Events of the National Cancer Institute (NCI-CTCAE) version 4.03
	  • Number of deaths
	  • Number of subjects with markedly abnormal clinical laboratory tests (haematology and coagulation, biochemistry and urinalysis)
	  • Number of subjects with markedly abnormal vital signs, ECG, physical examination, including change in body weight and ECOG PS.
	• Patient reported outcomes (PROs) as measured by:
	  ○ The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30),

	○ The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13), ○ The EuroQol Five Dimension Five Level Scale (EQ-5D-5L) visual analogue scale (VAS).
Sample Size and Power	The trial enrolled subjects with MET alterations identified in tumour tissue and/or in ctDNA derived from plasma into three cohorts: • **Part 1: Cohort A** with subjects tested positive for METex14 skipping alterations, regardless of MET amplification status • **Part 1: Cohort B** with subjects tested positive for MET amplification and negative for METex14 skipping alterations • **Part 2: Cohort C** with subjects tested positive for METex14 skipping alterations, regardless of MET amplification status (confirmatory part for METex14 skipping alterations). **Part 1: Cohort A (METex14 skipping alterations)** For this cohort the primary analysis will be based on the three separate primary analysis sets: • TBx or LBx analysis set is defined as all subjects tested positive for METex14 skipping alterations irrespective of testing methodology i.e., tested positive in tumour tissue or plasma ctDNA (including those tested positive for METex14 skipping alterations in both, tumour tissue and plasma ctDNA) and • LBx analysis set of at least 60 subjects is defined as all subjects tested positive for METex14 skipping alterations in plasma ctDNA • TBx analysis set of at least 60 subjects is defined as all subjects tested positive for METex14 skipping alterations in tumour tissue. Subjects tested positive in tissue (TBx) and in plasma (LBx) will be assigned to the LBx as well as the TBx analysis set. Subjects who are enrolled in the trial based on a tissue-based assay only will be retrospectively tested for METex14 skipping alterations using LBx. These subjects, if tested positive for METex14 skipping alterations in plasma ctDNA, will be assigned to the LBx analysis set as well as the TBx analysis set. Enrolment into this cohort may continue until at least 60 subjects are included in the LBx as well as the TBx analysis set. Due to an anticipated overlap of subjects tested positive for METex14 skipping alterations in tumour tissue and in ctDNA derived from plasma, a total of approximately 100 subjects are currently estimated to be enrolled in Cohort A. At least 25 second or further line subjects will be enrolled in the overall population of Cohort A. **Part 1: Cohort B** and **Part 2: Cohort C** information is provided in the clinical study report (provided separately).

In each of the three primary analysis sets, the trial aims to show an ORR based on independent review (performed by an IRC) in the range of 40% to 50% and to demonstrate that the lower limit of the corresponding exact two-sided 95% confidence interval (CI; according to Clopper-Pearson) for ORR exceeds 20% across lines of therapy. With a sample size of 60 subjects per analysis set, a maximum width for the 95% CI of 26.4% was achieved in the range for ORR of 40% to 60%.

Confidence intervals for objective response rate:

Objective response rate	Corresponding exact 2-sided 95% CI
24/60 (40%)	(27.6%, 53.5%)
30/60 (50%)	(36.6%, 63.2%)
36/60 (60%)	(46.5%, 72.4%)

The 95% CI within line of therapy (with smaller sample sizes) and other subgroups, in the range of ORR from 40% to 60%.

Confidence intervals for objective response rate within line of therapy and other subgroups

Sample size	Objective response rate	Corresponding exact 2-sided 95% CI
10	4/10 (40%)	(12.2%, 73.8%)
	5/10 (50%)	(18.7%, 81.3%)
	6/10 (60%)	(26.2%, 87.9%)
20	8/20 (40%)	(19.1%, 63.9%)
	10/20 (50%)	(27.2%, 72.8%)
	12/20 (60%)	(36.1%, 80.9%)
30	12/30 (40%)	(22.7%, 59.4%)
	15/30 (50%)	(31.3%, 68.7%)
	18/30 (60%)	(40.6%, 77.3%)
40	16/40 (40%)	%24.9%, 56.7%)

		20/40 (50%)	(33.8%, 66.2%)
		24/40 (60%)	(43.3%, 75.2%)
	50	20/50 (40%)	(26.4%, 54.8%)
		25/50 (50%)	(35.5%, 64.5%)
		30/50 (60%)	(45.2%, 73.6%)

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

The quality assessment for the VISION clinical trial in Section B.2.2 is presented in Appendix D.

B.2.6. Clinical effectiveness results of the relevant trials

This section presents the efficacy results of Cohort A of the pivotal VISION study. Most results are presented for both 1 February 2021 and 1 July 2020 cut-off dates (with the exception of Safety data, Section B.2.10.). Analyses are also stratified by line of therapy (1L or 2L+). The data presented includes the combined set of Cohort A (which includes patients who are liquid biopsy positive, tumour tissue biopsy positive, or both). As mentioned earlier, the cost-effectiveness analysis is primarily based on the 1 February 2021 data cut-off and therefore this will be the main focus of the clinical effectiveness results section below. For a description of where all data cuts are reported, please see Table 68 in Appendix R.

B.2.6.1. Objective Response

The ORR based on independent evaluation in Cohort A was [redacted]% (95% CI: [redacted]) from the 1 February 2021 cut-off (Table 13).

Consistent results were observed between patients receiving tepotinib as 1L or 2L+ therapy, although in the most recent data cut-off, [redacted].

Table 13. Objective Response Rate by Line of Therapy, Based on Independent Evaluation, VISION Cohort A – 1 Feb 2021 cut-off

	Overall	1L	2L+
1 July 2020 cut-off, N	[redacted]	[redacted]	[redacted]
ORR [a] n (%)	[redacted]	[redacted]	[redacted]
[95% CI] [b]	[redacted]	[redacted]	[redacted]
1 Feb 2021 cut-off, N	[redacted]	[redacted]	[redacted]
ORR [a] n (%)	[redacted]	[redacted]	[redacted]
[95% CI] [b]	[redacted]	[redacted]	[redacted]

Source: VISION CSR 1 July 2020 cut-off, Tables 15.2.1.1bo, 15.2.1.1bs, 15.2.1.17bo, 15.2.1.17bs. Data on file for 1 February 2021 cut-off

Abbreviations: 1L=first line of therapy, 2L+=second or greater line of therapy, CI=confidence interval, CSR=Clinical Study Report, ITT=intention-to-treat, ORR=objective response rate.

Notes:

a Complete response/partial response were confirmed; b 95% exact CI using the Clopper-Pearson method.

B.2.6.2. Duration of Response

The mDOR based on independent evaluation in Cohort A was [redacted] months (95% CI: [redacted]) at 1 February 2021 cut-off (Table 14). For Kaplan-Meier curves, see Figure 9 for the 1 February 2021 cut-off and Appendix R for 1 July 2020 cut-off. Consistent results were observed between 1L and 2L+ patients.

Of note, among the 66 patients with a confirmed complete or partial response in 1 July 2020 cut-off, all patients (100%) had a duration of follow-up of at least six months after the onset of response and the majority (56 [84.8%] patients) had (at the time of cut-off) a duration of follow-up of ≥12 months or event (progressive disease or death) or treatment discontinuation due to any reason <12 months past onset of response.

Table 14. Duration of Response, Independent Evaluation, VISION Cohort A – 1 Feb 2021 cut-off

	Overall	1L	2L+
1 July 2020 cut-off			
Number of patients with confirmed CR or PR, N	[redacted]	[redacted]	[redacted]
Patients with an event (PD/death), n (%)	[redacted]	[redacted]	[redacted]
mDOR, months [95% CI] [a]	[redacted]	[redacted]	[redacted]
DOR [b], n (% of responders)			
≥6 months	[redacted]	[redacted]	[redacted]
≥9 months	[redacted]	[redacted]	[redacted]
≥12 months	[redacted]	[redacted]	[redacted]
Follow-up among responders[b], n (%)			
≥6 months follow-up from onset of response or event or discontinued treatment <6 months after onset of response	[redacted]	[redacted]	[redacted]
Ongoing response with <6 months duration	[redacted]	[redacted]	[redacted]
≥12 months follow-up from onset of response or event or discontinued treatment <12 months after onset of response	[redacted]	[redacted]	[redacted]
Ongoing response with <12 months duration	[redacted]	[redacted]	[redacted]
1 Feb 2021 cut-off			
Number of patients with confirmed CR or PR, N	[redacted]	[redacted]	[redacted]
mDOR, months [95% CI] [a]	[redacted]	[redacted]	[redacted]

Source: VISION CSR 1 July 2020 cut-off, Tables 15.2.2.1o, 15.2.2.1s, 15.2.2.3ao, 15.2.2.3as, 15.2.2.3co, 15.2.2.3do, 15.2.2.3cs, 15.2.2.4o, 15.2.2.4s. Data on file for 1 February 2021 cut-off.

Abbreviations: 1L=first line of therapy 2L+=second or later line of therapy, CI=confidence interval, CR=complete response, CSR=Clinical Study Report, DOR=duration of response, ITT=intention-to-treat, mDOR=median duration of response, ne=not estimable, PD=progressive disease, PR=partial response.

Notes:

a Based on Kaplan-Meier estimates, 95% CI using the Brookmeyer and Crowley method.

b Only patients that achieved confirmed CR or PR based on independent evaluation are considered in this table as the denominator for percentages.

Figure 9. Kaplan-Meier Curve Showing Duration of Response, Independent Evaluation, VISION Cohort A – 1 Feb 2021 cut-off

Source: VISION 1 Feb 2021 cut-off, data on file, Data on file for 1 February 2021 cut-off.
Abbreviations: CI=confidence interval

Figure 10, Figure 11 and Figure 12 provide swimmer plots by independent evaluation in 1 July 2020 cut-off (as these were not available for the 1 February 2021 data cut-off). In this assessment, a substantial percentage of patients achieved early tumour response, within the first three months; this observation was consistent regardless of line of therapy. Although most responses occurred early, few patients achieved late onset of response, showing that responses can still occur after three months.

Figure 10. Time on Treatment, Time to and Duration of Response Per Patient Receiving 1L Therapy, Independent Evaluation, VISION Cohort A – 1 July 2020 cut-off

Source: VISION CSR 1 July 2020 cut-off, Figure 15.2.2.20ao

Abbreviations: 1L=first line of therapy, BOR=best overall response, CR=complete response, CSR=Clinical Study Report, ITT=intention-to-treat, NE=not estimable, PD=progressive disease, PR=partial response, SD=stable disease.

Notes:

Patients with an arrow are still on treatment.

BOR: NE* = BOR of NE where ongoing patient has not had 2 post-baseline tumour assessments.

Only prior anti-cancer drug therapies administered for advanced (Stage IIIb/IIIc) or metastatic (IV) diseases are taken into account for the categorization of line of therapy.

Figure 11. Time on Treatment, Time to and Duration of Response Per Patient Receiving 2L Therapy, Independent Evaluation, VISION Cohort A – 1 July 2020 cut-off

Source: VISION CSR 1 July 2020 cut-off, Figure 15.2.2.20ao

Abbreviations: 2L=second line of therapy, BOR=best overall response, CR=complete response, CSR=Clinical Study Report, ITT=intention-to-treat, NE=not estimable, PD=progressive disease, PR=partial response, SD=stable disease.

Notes:

Patients with an arrow are still on treatment.

BOR: NE* = BOR of NE where ongoing patient has not had 2 post-baseline tumour assessments.

Only prior anti-cancer drug therapies administered for advanced (Stage IIIb/IIIc) or metastatic (IV) diseases are taken into account for the categorization of line of therapy.

Figure 12. Time on Treatment, Time to and Duration of Response Per Patient Receiving Third or Later Line Therapy, Independent Evaluation, VISION Cohort A – 1 July 2020 cut-off

Source: VISION CSR 1 July 2020 cut-off, Figure 15.2.2.20ao

Abbreviations: BOR=best overall response, CR=complete response, CSR=Clinical Study Report, ITT=intention-to-treat, NE=not estimable, PD=progressive disease, PR=partial response, SD=stable disease.

Notes:

Patients with an arrow are still on treatment.

BOR: NE* = BOR of NE where ongoing patient has not had 2 post-baseline tumour assessments.

Only prior anti-cancer drug therapies administered for advanced (Stage IIIb/IIIc) or metastatic (IV) diseases are taken into account for the categorisation of line of therapy.

B.2.6.3. Best Overall Response

By independent evaluation, best overall response (BOR) results by RECIST 1.1 are summarised in Table 15.

In the 1 February 2021 cut-off, [redacted]% of patients achieved partial response by the time of the data cut-off, whereas the proportion of patients with stable disease was [redacted]%. The proportion of patients with progressive disease was [redacted]%. Results were consistent with the earlier 1 July 2020 cut-off.

The proportion of patients achieving partial response in 1 February 2021 cut-off was higher for 1L over 2L ([redacted]% and [redacted]%, respectively).

Table 15. Best Overall Response, Independent Evaluation, VISION Cohort A – 1 Feb 2021 cut-off

	Overall	1L	2L+
1 July 2020, N	[redacted]	[redacted]	[redacted]
BOR, n (%) [a]			
Complete response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]
ORR, n (%) [95% CI] [b]	[redacted]	[redacted]	[redacted]
1 Feb 2021 cut-off, N	[redacted]	[redacted]	[redacted]
BOR, n (%) [a]			
Complete response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
Not evaluable	[redacted]	[redacted]	[redacted]
ORR, n (%) [95% CI] [b]	[redacted]	[redacted]	[redacted]

Source: VISION CSR 1 July 2020 cut-off, Table 15.2.1.1bo, 15.2.1.1bs, 15.2.1.17bo, 15.2.1.17bs. Data on file for 1 February 2021 cut-off.

Abbreviations: 1L=first line of therapy, 2L+=second or later line of therapy, BOR=best overall response, CI=confidence interval, CSR=Clinical Study Report, ITT=intention-to-treat, ORR=objective response rate.

OR evaluated by the independent evaluation was the primary endpoint.

Notes:

a Complete response and partial response must be confirmed, and stable disease must last at least 12 weeks.

b 95% exact CI using the Clopper-Pearson method.

B.2.6.4. Progression-free Survival

The mPFS based on independent evaluation in Cohort A was [redacted] months (95% CI: [redacted]) in 1 February 2021 cut-off (Table 16). Consistent results were observed between 1L and 2L+ patients.

For Kaplan-Meier curves on 1 February 2021 and by line of therapy, see Figure 13 and Figure 14, respectively. For the 1 July 2020 cut-off, Kaplan-Meier curves are reported in Appendix R.

Table 16. Progression-free Survival, Independent Evaluation, VISION Cohort A

	Overall	1L	2L+
ITT-02 Oct 2019, N	[redacted]	[redacted]	[redacted]
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]	[redacted]
mPFS [a], months [95% CI] [b]	[redacted]	[redacted]	[redacted]
1 Feb 2021 cut-off, N	[redacted]	[redacted]	[redacted]
mPFS [a], months [95% CI] [b]	[redacted]	[redacted]	[redacted]

Source: VISION CSR 1 July 2020 cut-off, Tables 15.2.3.1o, 15.2.3.1s, 15.2.3.9o, 15.2.3.9s. Data on file for 1 February 2021 cut-off.

Abbreviations: 1L=first line of therapy, 2L+=second or later line of therapy, CI=confidence interval, CSR=Clinical Study Report, ITT=intention-to-treat, mPFS=median progression-free survival.

Notes:

a Product-limit (Kaplan-Meier) estimates.

b 95% CI for the median calculated using the Brookmeyer and Crowley method.

Figure 13. Kaplan-Meier Curve Showing Progression-free Survival, Independent Evaluation, VISION Cohort A – 1 February 2021 cut-off

Source: Data on file for 1 February 2021 cut-off.
Abbreviations: CI=confidence interval

Figure 14. Kaplan-Meier Curve Showing Progression-free Survival by Line of Therapy, Independent Evaluation, VISION Cohort A – 1 February 2021 cut-off

Source: Data on file for 1 February 2021 cut-off.
Abbreviations: CI=confidence interval

B.2.6.5. Overall Survival

The mOS in Cohort A was [redacted] months (95% CI: [redacted]) in 1 February 2021 cut-off, with a total of [redacted] events (Table 17). Consistent results were observed between 1L and 2L+ patients.

For Kaplan-Meier curves on 1 February 2021 cut-off and by line of therapy, see Figure 15 and Figure 16, respectively. For the 1 July 2020 cut-off, Kaplan-Meier curves are reported in Appendix R.

Table 17. Overall Survival, VISION Cohort A

	Overall	1L	2L+
ITT-02 Oct 2019, N	[redacted]	[redacted]	[redacted]
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
mOS time [a], months [95% CI] [b]	[redacted]	[redacted]	[redacted]
1 Feb 2021, N	[redacted]	[redacted]	[redacted]
Patients with event, n (%)	[redacted]	[redacted]	[redacted]
mOS time [a], months [95% CI] [b]	[redacted]	[redacted]	[redacted]

Source: VISION CSR 1 July 2020 cut-off, Tables 15.2.4.1o, 15.2.4.1s, 15.2.4.4o, 15.2.4.4s. Data on file for 1 February 2021 cut-off.

Abbreviations: 1L=first line therapy, 2L+=second line therapy, CI=confidence interval, CSR=Clinical Study Report, ITT=intention-to-treat, mOS=median overall survival.

Notes:

a Product-limit (Kaplan-Meier) estimates.

b 95% CI for the median calculated using the Brookmeyer and Crowley method.

Figure 15. Kaplan-Meier Curve Showing Overall Survival, VISION Cohort A – 1 February 2021 cut-off

Source: Data on file for 1 February 2021 cut-off.
Abbreviations: CI=confidence interval

Figure 16. Kaplan-Meier Curve Showing Overall Survival by Line of Therapy, VISION Cohort A – 1 February 2021 cut-off

Source: Data on file for 1 February 2021 cut-off.
Abbreviations: CI=confidence interval

B.2.6.6. Patient-reported Outcomes: Health-related Quality of Life

All patients were asked to take part in all PRO assessments: EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13. The questionnaires were to be completed on Cycle 1, Day 1 (Baseline, before the first dose of study treatment), every six weeks thereafter for the first nine months, and then every 12 weeks thereafter until disease progression, death, or withdrawal of consent. For further details about the time points of these assessments, refer to VISION Study Protocol v8.0, Table 1. This section reports the 1 July 2020 data cut-off mostly, as the 1 February 2021 PRO outcomes reporting are not currently as comprehensive.

Overall, the completion rate for PROs in this study was approximately 90% per visit, and remained high up to Cycle 21.

For all PRO tools, a scale from 0 to 100 was used, with a mean change from baseline of 10 considered as a clinically meaningful improvement or worsening, as described in the literature (Heigener 2016).[122]

Results were consistent across the three PRO tools and suggested that HRQL remains stable over time. In EORTC QLQ-LC13, favourable effects with regards to stability of symptom intensities for dyspnoea and pain in chest, and a trend towards a clinically meaningful improvement in the coughing symptom scale was observed. The stability observed in the assessment of quality of life for patients treated with tepotinib indicates control of the symptoms in this population with advanced disease, as a worsening is to be expected in case of ineffective and/or toxic therapies.

No analyses of subgroups, including line of therapy, were performed for PROs.

B.2.6.6.1. EQ-5D-5L

The EQ-5D is a validated and widely used generic patient assessment tool, and this section presents the results from the EuroQol visual analogue scale (EQ VAS). At baseline, the majority of patients (89.0%) in completed the questionnaire and had a resulting EQ VAS score (refer to VISION CSR 1 July 2020 cut-off, Table 15.2.6.1o).

The mean (standard deviation [StD]) EQ VAS baseline score in 1 July 2020 data cut-off was 61 (20.3), in line with the literature in patients with advanced NSCLC (Novello 2015). Values were

stable over time in this generally elderly population with advanced disease, with the mean changes from baseline up to Cycle 21 in the combined set ranging from 0 to seven across cycles (Figure 17). For further details, refer to VISION CSR 1 July 2020 cut-off, Table 15.2.6.6o. Results were consistent with the 1 February 2021 data cut-off (Figure 18).

Figure 17. EQ-5D-5L Health Question Score – Boxplot of Change From Baseline Values by Time Point, VISION Cohort A – 1 July 2020 cut-off

Source: VISION CSR 1 July 2020 cut-off, Figure 15.2.6.11o.

Abbreviations: C=Cycle, CSR=Clinical Study Report, D=Day, EOT=end of trial, EQ-5D-5L=EuroQol Five-dimension Five-level Scale, EQ VAS=EuroQol visual analogue scale, FU=follow-up.

Notes:

Visits done with 10 or less patients are not summarized and presented, with the exception of end of treatment/30-day safety follow-up visits.

The duration of each cycle is 21 days.

Figure 18. EQ-5D-5L Health Question Score – Boxplot of Change From Baseline Values by Time Point, VISION Cohort A – 1 February 2021 cut-off

Source: VISION 1 February 2021 cut-off data on file.
Abbreviations: C=Cycle, D=Day, EOT=end of trial, EQ-5D-5L=EuroQol Five-dimension Five-level Scale, EQ VAS=EuroQol visual analogue scale, FU=follow-up.
Notes:
Visits done with 10 or less patients are not summarized and presented, with the exception of end of treatment/30-day safety follow-up visits.
The duration of each cycle is 21 days.

B.2.6.6.2. EORTC QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed to assess the QoL of cancer patients. The EORTC QLQ-C30 (Version 3.0) is available in 81 languages and has been used in clinical studies worldwide. It is cancer-specific and consists of five functional scales (physical, role, cognitive, emotional, social), 4 symptom scales (fatigue, pain, nausea, vomiting), a global health status (GHS) scale, and several single items (including dyspnoea, loss of appetite, and insomnia). The questionnaire consists of 30 multiple-choice questions.

At baseline, the majority of patients at 1 July 2020 cut-off (89.0%; combined set) completed the questionnaire and had QLQ-C30 data (refer to VISION CSR 1 July 2020 cut-off, Table 15.2.6.2o). The mean (SD) QLQ-C30 GHS score was 53.7 (24.27) at baseline, in line with what is known from literature in patients with advanced NSCLC (refer to Heigener, 2016).[122] Values were stable over time in this generally elderly population with advanced disease, with the mean changes from baseline up to Cycle 21 in the combined set ranging from -0.3 to 11.1 (Figure 19). For further details, refer to VISION CSR 1 July 2020 cut-off, Table 15.2.6.7o. Results were consistent in the 1 February 2021 data cut-off (Figure 20).

Figure 19. EORTC QLQ-C30 – Boxplot of Change From Baseline Values by Time Point, VISION Cohort A – 1 July 2020 cut-off

Source: VISION CSR 1 July 2020 cut-off, Figure 15.2.6.12o.

Abbreviations: C=Cycle, CSR=Clinical Study Report, D=Day, EOT=end of trial, EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, FU=follow-up.

Notes:

Visits done with 10 or less patients are not summarized and presented, with the exception of end of treatment/30-day safety follow-up visits.

The duration of each cycle is 21 days.

Figure 20. EORTC QLQ-C30 – Boxplot of Change From Baseline Values by Time Point, VISION Cohort A – 1 February 2021 cut-off

Source: VISION 1 February 2021 cut-off data on file.

Abbreviations: C=Cycle, CSR=Clinical Study Report, D=Day, EOT=end of trial, EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, FU=follow-up.

Notes:

Visits done with 10 or less patients are not summarized and presented, with the exception of end of treatment/30-day safety follow-up visits.

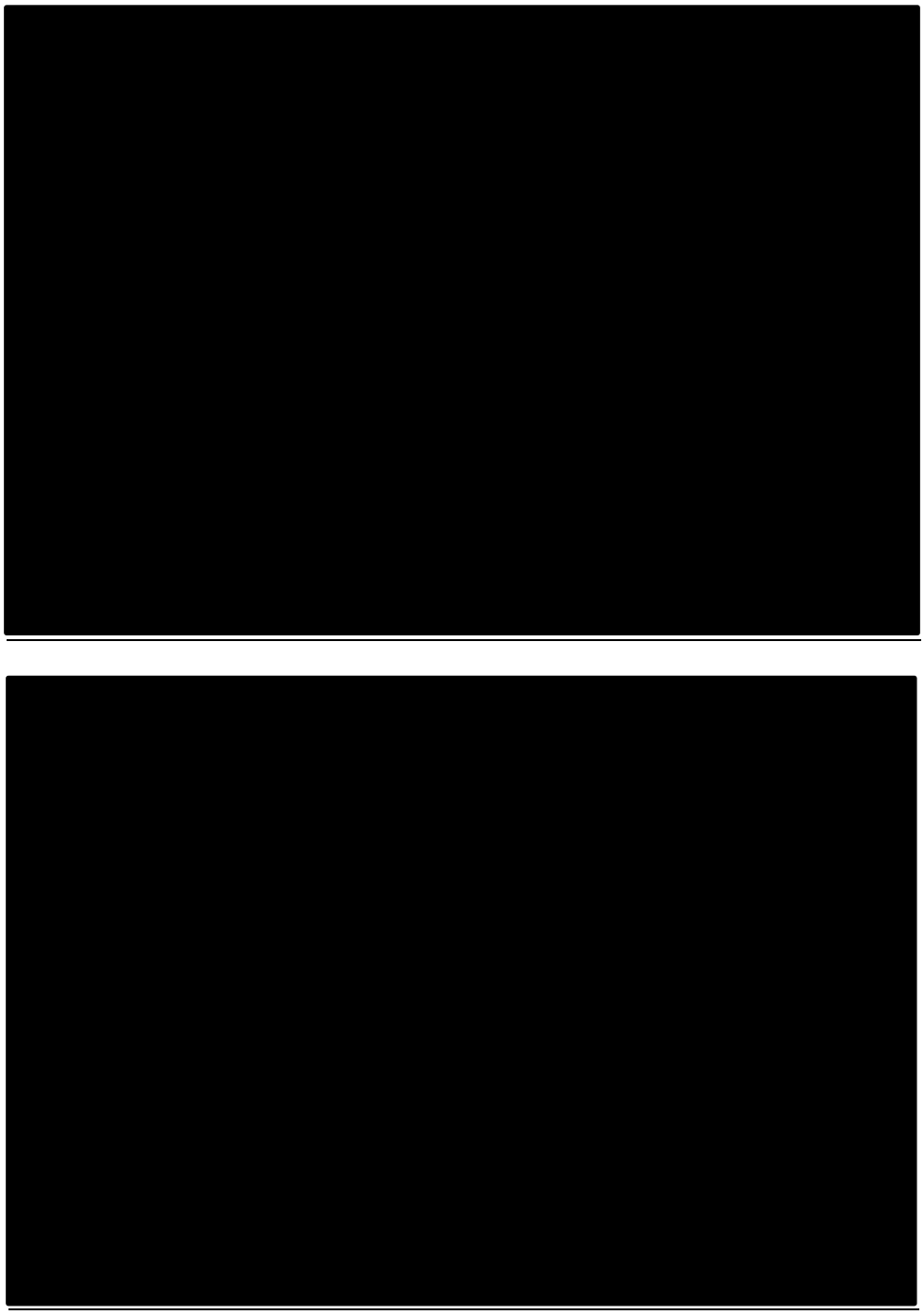
The duration of each cycle is 21 days.

B.2.6.6.3. EORTC QLQ-LC13

The EORTC QLQ-LC13 is a modular supplement to the QLQ-C30 for use in lung cancer studies. The QLQ-LC13 module comprises both multi-item and single-item measures of lung cancer-related symptoms (i.e. coughing, haemoptysis, dyspnoea, and pain in chest) and side effects from conventional chemo- and radiotherapy (i.e. hair loss, neuropathy, sore mouth, and dysphagia).

At baseline, the majority of patients in the 1 July 2020 data cut-off (89.0%) completed the questionnaire and had QLQ-LC13 data. Results for the mixed-effect model repeated measures approach are presented in Figure 21, Figure 22, and Figure 23. An improvement in the symptom scale of coughing was observed at Week 12; this scale levelled near the threshold for clinical meaningfulness (minimum important difference of 10) and remained approximately stable. For dyspnoea and pain in chest, symptom intensity remained stable over time. Due to low numbers at risk, data late in the study (after Week 75) should be interpreted with caution. Results at the 1 February 2021 data cut-off were consistent (Figure 21, Figure 22, Figure 23).

Figure 21. Line Plot of Scores Least Square Means of Change from Baseline by Visit for EORTC QLQ-LC13 Symptom Scale Coughing, VISION Cohort A – (A) 1 July 2020 cut-off; (B) 1 February 2021 cut-off



Source: VISION CSR 1 July 2020 cut-off, Figure 15.2.6.5o. 1 February data cut-off data on file.

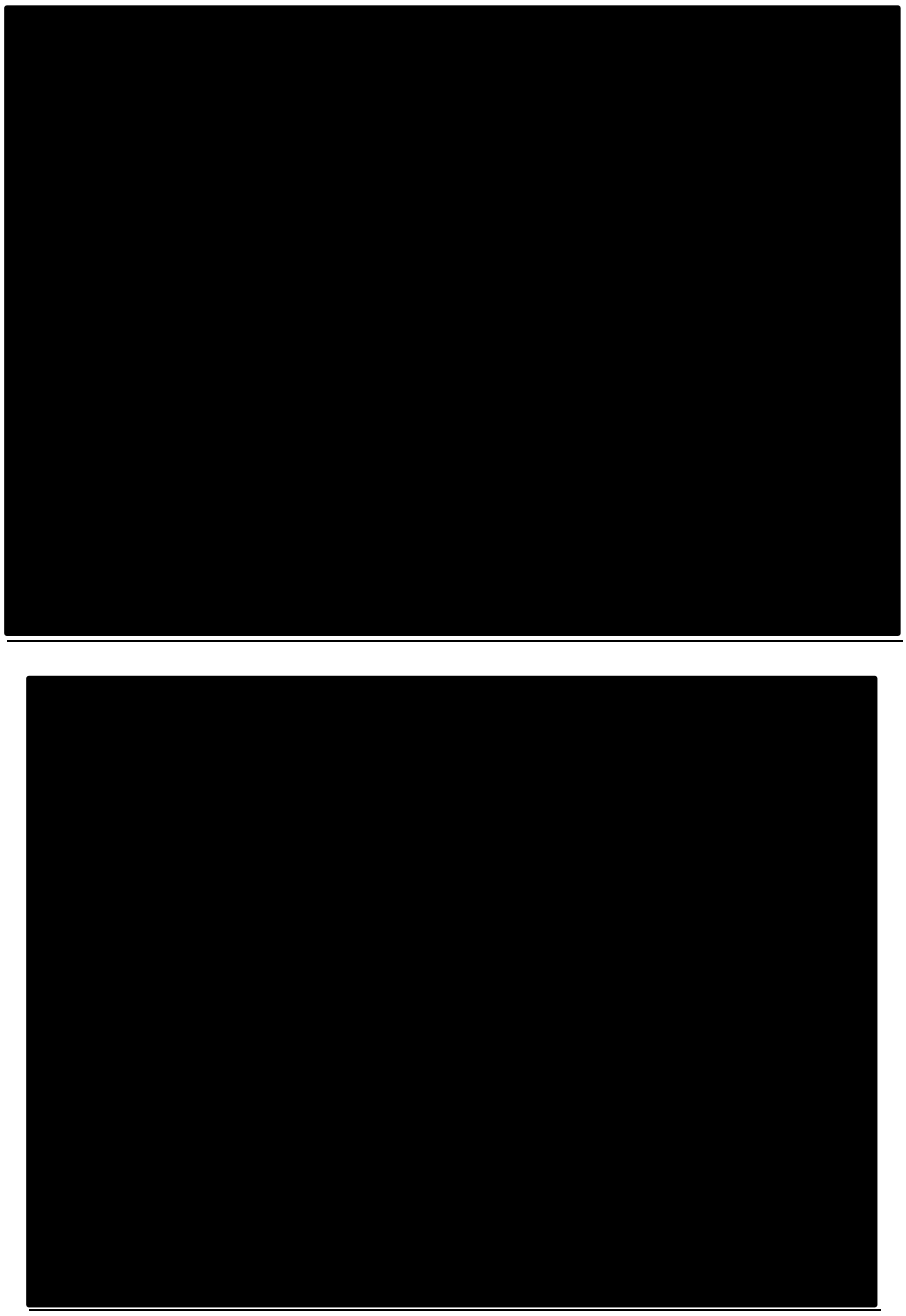
Abbreviations: BSL=Baseline, C=Cycle, CSR=Clinical Study Report, D=Day, EORTC QLQ-LC13=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13, LS=least square, SEM=standard error of mean.

Notes:

The QLQ-LC13 symptom scales range in score from 0 to 100, and a decrease in score represents an improvement in symptoms.

The duration of each cycle is 21 days

Figure 22. Line Plot of Scores Least Square Means of Change from Baseline by Visit for EORTC QLQ-LC13 Symptom Scale Dyspnoea, VISION Cohort A – (A) 1 July 2020 cut-off; (B) 1 February 2021 cut-off



Source: VISION CSR 1 July 2020, Figure 15.2.6.5o. 1 February data cut-off data on file.

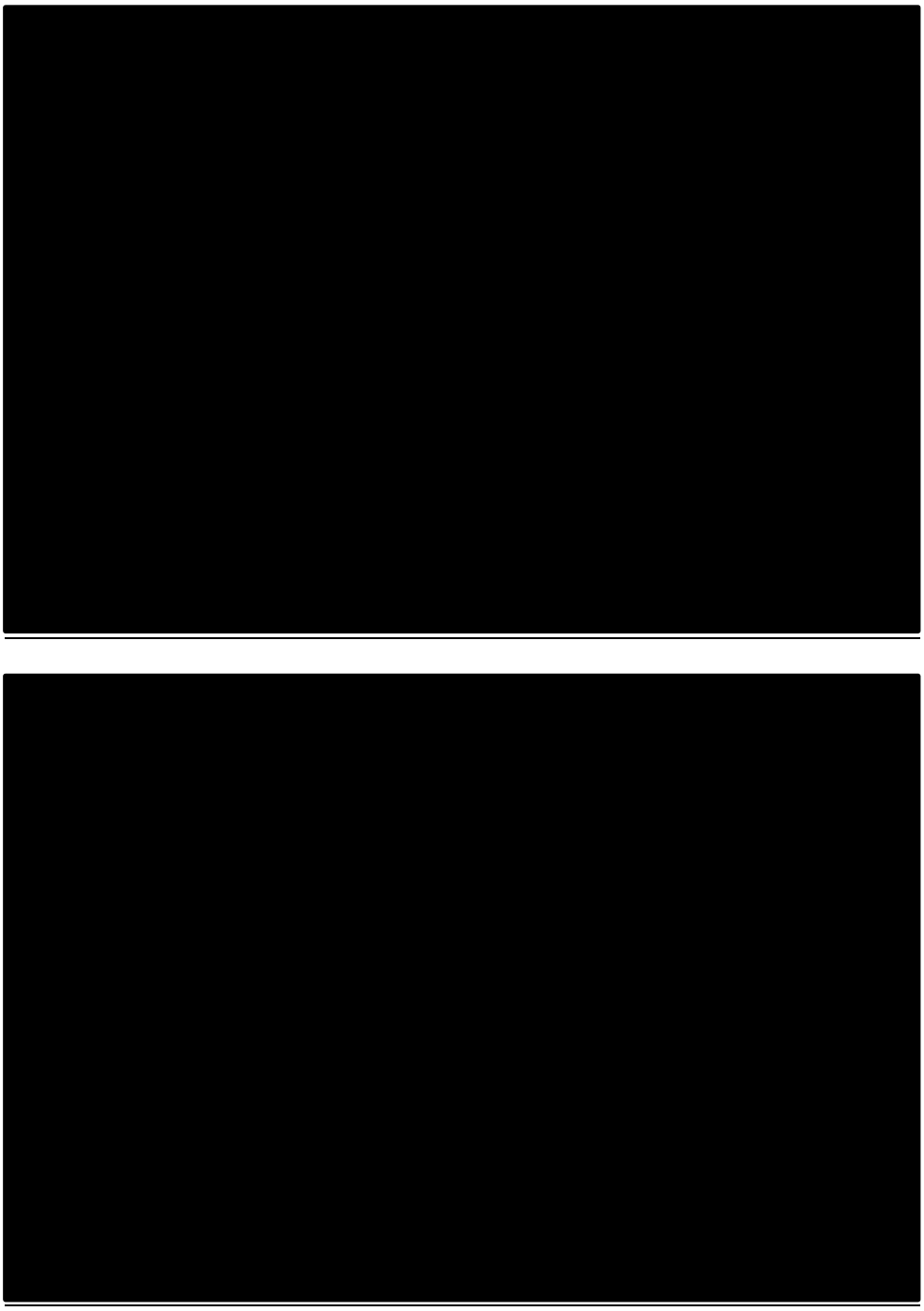
Abbreviations: BSL=Baseline, C=Cycle, CSR=Clinical Study Report, D=Day, EORTC QLQ-LC13=ITT=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13, LS=least square, SEM=standard error of mean.

Notes:

The QLQ-LC13 symptom scales range in score from 0 to 100, and a decrease in score represents an improvement in symptoms.

The duration of each cycle is 21 days

Figure 23. Line Plot of Scores Least Square Means of Change from Baseline by Visit for EORTC QLQ-LC13 Symptom Scale Pain in Chest, VISION Cohort A – (A) 1 July 2020 cut-off; (B) 1 February 2021 cut-off



Source: VISION CSR 1 July 2020, Figure 15.2.6.5o. 1 February data cut-off data on file.

Abbreviations: BSL=Baseline, C=cycle, CSR=Clinical Study Report, D=day, EORTC QLQ-LC13=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13, ITT=intention-to-treat, LS=least square, SEM=standard error of mean.

Notes:

The QLQ-LC13 symptom scales range in score from 0 to 100, and a decrease in score represents an improvement in symptoms.

The duration of each cycle is 21 days.

B.2.6.7. Efficacy Analyses by Investigator Assessment

Overall, the ORR, mDOR, and mPFS based on Investigator assessment strongly support the efficacy results based on independent evaluation, with a tendency for higher ORRs and a longer DOR (Table 18). Three patients were identified with complete responses by Investigator assessment (refer to VISION CSR 1 July 2020 cut-off, Table 15.2.1.9bo). The proportion of patients showing tumour shrinkage was consistent between the independent evaluation and Investigator assessment (see VISION CSR 1 July 2020 cut-off, Figure 15.2.1.14ao) and numerical differences in ORR may just reflect differences in the assessment of sum of longest diameters between both reads.

Table 18. Efficacy Results, Investigator Assessment, VISION Cohort A

	Overall	1L	2L+
1 July 2020, N			
ORR [a] n (%) [95% CI] [b]			
mDOR, months [c] [95% CI] [d]			
mPFS, months [c] [95% CI] [d] Patients with event (PD/Death), n (%)			
1 February 2021, N			
ORR [a] n (%) [95% CI] [b]			
mDOR, months [c] [95% CI] [d]			
mPFS, months [c] [95% CI] [d] Patients with event (PD/Death), n (%)			

Source: VISION CSR 1 July 2020 cut-off, Tables 15.2.1.9bo, 15.2.1.9bs, 15.2.2.11o, 15.2.2.11s, 15.2.3.12o, 15.2.3.12s, 15.2.2.15o, 15.2.2.15s, 15.2.3.16o, 15.2.3.16s, 15.2.1.18bo, 15.2.1.18bs. Data on file for 1 February 2021 data cut-off.

Abbreviations: 1L=first line therapy, 2L+ = second or later line of therapy, CI=confidence interval, CSR=Clinical Study Report, DOR=duration of response, mDOR=median duration of response, mPFS=median progression-free survival, mOS=median overall survival, ne=not estimable, ORR=objective response rate, PD=progressive disease.

Notes:

a Confirmed complete response/partial response.

b 95% exact CI using the Clopper-Pearson method.

c Product-limit (Kaplan-Meier) estimates.

d 95% CI for the median using the Brookmeyer and Crowley method.

B.2.7. Subgroup analysis

Tepotinib has shown consistent efficacy across lines of therapy (for first-line, second-line and third-line-and-beyond) for all outcomes assessed (ORR, DOR, OS, PFS and quality of life outcomes), as demonstrated in previous sections.

Results for additional subgroup analyses are provided in Appendix E. These subgroup analyses demonstrates that tepotinib has consistent efficacy across age groups (above or below 65 years), sex, race, geographic region, ECOG, metastatic disease (yes/no), baseline brain metastases (absent/present), time from diagnosis to first dose (above or below 6 months) and smoking status. Outcomes are also shown to be generally consistent regardless of biopsy method, although higher for certain outcomes in patients with tumour biopsy over liquid biopsy.

B.2.8. Meta-analysis

Pairwise meta-analysis was not conducted.

B.2.9. Indirect and mixed treatment comparisons

B.2.9.1. Available data

No head-to-head efficacy and safety data are available for tepotinib versus the comparators listed in the scope, and there are currently no comparator clinical trial data available in patients with advanced NSCLC harbouring METex14 skipping alterations (see Appendix D). Although clinical trial data are available for immunotherapy and/or chemotherapy in wildtype NSCLC, using this data to form an efficacy comparison to tepotinib would be inappropriately comparing different patient populations, therefore this comparison has not been performed. As already shown, NSCLC harbouring METex14 skipping alterations is typically associated with older age (typically 70 years and above), non-squamous histology and a higher occurrence in females[47], as well as poorer prognosis and poorer response to current treatments, particularly immunotherapies (Section B.1.3.2.2).[49,54-56] Clinical experts interviewed at the advisory board (see Section B.3.2) also confirmed that the presence of METex14 skipping alterations as an independent prognostic factor would make any comparisons to wildtype NSCLC clinical trial data highly uncertain. For this reason, data from retrospective real-world studies in patients with advanced NSCLC harbouring METex14 skipping alterations have been used to perform comparisons with tepotinib.

Patient level data from four retrospective real-world studies were available to conduct the comparisons.[123] In addition to the patient level data to which Merck were able to obtain access, three published studies in the METex14 skipping alterations population,[49,51,85] identified from the SLR, were also considered relevant for a comparison to VISION data; that is reporting patient characteristics and outcomes for patients treated with immunotherapy or

chemotherapy providing adequate detail to facilitate indirect treatment comparisons (ITC) – see Appendix D.

Details of the ITC using the four patient-level data sets (referred to as “real-world cohorts” from this point onwards) are presented below. This is the primary ITC which has been incorporated into the economic model and base case cost-effectiveness analysis. Match-adjusted indirect comparisons (MAIC) were also conducted to compare to published studies. Full details of the MAICs using published data are presented in the ITC report within Appendix L, as these are only used as supporting analyses and not included in the base case cost-effectiveness.

B.2.9.2. Patient population

The patient population considered in both primary and supplementary ITC is in line with the proposed license, final NICE scope and population of the Phase II VISION study, that is, adult patients with advanced NSCLC harbouring METex14 skipping alterations. As per the proposed licence, tepotinib covers all lines of treatment and histology subgroups, therefore the base case ITC analysis assumes a line agnostic population, regardless of histology.

Considering the line-agnostic population in the base case is beneficial for a number of reasons. Firstly, tepotinib has been shown to be clinically effective across all treatment lines (see Section B.2.7) and therefore there is no expected benefit for one treatment line group over the other. Secondly, using all patients across treatment lines allows for a larger data set for the indirect comparisons, in what is considered a small subset of the wider NSCLC population. This ensures the comparisons are more robust and allows for a simpler decision problem. Finally, the anticipated line agnostic label will allow clinicians the flexibility to choose the right treatment strategy for each individual patient, without the barrier of treatment history, and the base case for the NICE decision problem should reflect the label and the flexibility of treatment choice across lines of therapy and histology.

Subgroup analysis by treatment line for untreated and previously treated patients are presented separately (see ITC report within Appendix L) although are limited by low patient numbers. Patient numbers were too small to present subgroups by histology given the small proportion who have squamous NSCLC (approximately 9%). However, given the generalisability of disease characteristics and outcomes across the histology subgroups, clinicians at the advisory board were not concerned with this lack of analysis.

B.2.9.3. Treatments

As discussed in Section B.2.9.4, comparator data relied on studies using real-world retrospective studies in patients with METex14 skipping alterations. However, given the rarity of patients with METex14 skipping alterations (approximately 3% of patients with NSCLC),[40,124-132] patient numbers in these studies were too small to split out by each treatment regimen for the ITC (see Table 21 and Table 22). Therefore, treatments were grouped by treatment class, and so two comparisons were conducted using the real-world cohort data in the primary ITC:

1. VISION versus immunotherapy
2. VISION versus chemotherapy

The grouping of comparators has been used in previous NSCLC NICE submissions, such as TA531 where the comparator arm was comprised of a mix of chemotherapy and platinum-based chemotherapy regimens.[77] Additionally, this approach has been used in other NICE oncology submissions (TA517, TA502 and TA541)[133-135] where the comparators comprised a basket of chemotherapies. These were considered appropriate given the assumption of similar efficacy. As such, this approach was considered reasonable given the expected similar outcomes in efficacy within the treatment classes in NSCLC, supported by the literature. For immunotherapies, there have been several published studies concluding that there is no statistically significant difference in efficacy between anti-PD1/PD-L1 inhibitor monotherapy in advanced NSCLC.[136,137] There are also studies demonstrating similar efficacy between platinum-based chemotherapy regimens in advanced NSCLC, showing non-statistically significant differences in outcomes.[138-140] Clinical and health technology assessment (HTA) experts at an advisory board (see Section B.3.2) also considered the comparator grouping approach to be reasonable given the similar efficacy and safety profiles particularly within the relapsed setting and expectation of little difference in the first-line setting between the different immunotherapies and chemotherapies. However, it was noted that platinum-based chemotherapy regimens would not be considered similar to single-agent chemotherapy (mostly docetaxel) but given the low number of usage of single-agent chemotherapy within the data set (see Table 21), and the fact that clinicians use this treatment for later lines, this was not considered to have a substantial impact on results.

Patient numbers were too low to conduct an ITC of VISION versus immunotherapy in combination with chemotherapy, and given the differences in expected efficacy and costs, it did not seem appropriate to combine these within the immunotherapy group. As such,

alternative methods have been used to estimate an exploratory comparison between tepotinib and immunotherapy in combination with chemotherapy, for the untreated population subgroup only (see Appendix N).

B.2.9.4. Real-world cohort

Patient-level data[123] for NSCLC patients harbouring METex14 skipping alterations were available from the non-interventional study (NIS) 0027, comprising of three studies planned and conducted by Merck: NIS-0015, NIS-0035 and COTA. In addition to these data sets, patient-level data from British Columbia, Canada, was also made available by the authors of Wong et al. (2021).[141] Each study is discussed in turn below (further details in the ITC report within Appendix L).

B.2.9.4.1. NIS-0015

The NIS-0015 study consisted of data collected from the Concerto HealthAI US real-world database, taken from Electronic Medical Records (EMR), used in a non-interventional real-world retrospective cohort study. Prior to the application of inclusion and exclusion criteria (detailed in Section B.2.9.5.1), the dataset included complete data on 39 patients with MET alterations, with 76 treatment lines in total. The dates included in the study ran from 1 January 2004 to 30 March 2018.

A large number of patient characteristics were captured, including the treatment received by patients, treatment line, data on the MET alteration status of patients, and patient demographics. Outcomes captured included PFS, OS, and response rate. As the data were taken from clinical practice, all readings were investigator measured.

B.2.9.4.2. NIS-0035

The NIS-0035 study consisted of EMR data taken from a chart abstraction from oncology sites in multiple countries (including Israel, the Netherlands, Taiwan and the USA). Prior to the application of inclusion and exclusion criteria (see Section B.2.9.5.1), the dataset included data on 86 patients harbouring a MET alteration, with details of 165 treatment lines in total. Data was captured for the period between 1 January 2010 to 30 September 2018.

Although a large number of patient demographic information and disease characteristics were included in the dataset, the data captured did not include response rates or PFS. However, ‘Time to Next Treatment or Death’ (TTNTD) was recorded and used in this analysis as a proxy for PFS (where PFS was missing).

B.2.9.4.3. COTA

The COTA healthcare data service provides data on patients with MET gene mutations, treated in the US and Canada. The data were from COTA's Real - World Evidence (RWE) database, a de-identified data source drawn from EMRs of contributing mainly academic, for-profit, and community oncologist provider sites and hospital systems in the US and Canada.

In total 202 complete patient records were available with at least one data point, for a total of 680 lines of therapy.

This dataset is extensive in terms of the report of all tests and investigations given to patients (e.g., the outcomes of genetic tests over time). As a result, many of the treatment lines received by patients are not comparable to VISION (for instance, as a patient was at an earlier stage of disease). Treatment discontinuation for some patients was recorded, most of which were due to progression and as such used as the PFS data. OS was available for the majority (and patients were excluded without OS data). Where PFS/treatment duration was unavailable, TTNTD was able to be calculated from the information available in the dataset.

B.2.9.4.4. Wong et al. 2021

Patient level data was provided by the authors of Wong et al. (2021),[141] based on a retrospective review of treatments and outcomes for patients with metastatic NSCLC harbouring METex14 skipping alterations in British Colombia, Canada, from January 2016 to September 2019. Before the application of inclusion/exclusion criteria, data was available for 41 patients in total, although not all received treatment.

The dataset includes characteristics such as histology, treatment history, in addition to patient demographics. The main limitation of the data is that some of the specific treatments received by patients are not identified beyond class. Instead, some treatments are identified in classes, including 'platinum-doublet chemotherapy', and 'immunotherapy'. In addition, the information available was duration of treatment and overall survival time, and not the actual dates (for instance if there was an off-treatment period between interventions). For this reason, it has been assumed patients begin their next treatment on the day after discontinuation of the previous treatment. PFS was therefore estimated based on duration of treatment from this data set.

B.2.9.5. Construction of a comparable data set

Data from the four retrospective real-world studies, detailed in Section B.2.9.4 (NIS-0015, NIS-0035, COTA and Wong et al.), were imported into a Common Data Model (CDM) with variables categorised consistently in order to perform the primary ITC. Multiple lines of therapy were available for patients in the real-world cohort data, which were categorised in line with the VISION study (i.e., the first line of therapy being the first treatment received post diagnosis of advanced or metastatic disease).

As mentioned previously, in many patients PFS was not available within the real-world cohort data (65% in the chemotherapy arm and 59% in the immunotherapy arm). Therefore, TTNTD or duration of treatment was used as a proxy for PFS as this was preferred to a substantial reduction in patient numbers from exclusion. TTNTD was considered a conservative estimate by clinical experts given that some patients will generally have a delay in between progression and starting their next treatment, and so may over estimate 'actual' PFS. Conversely, using duration of treatment may under-estimate PFS as some patients may discontinue treatment for other reasons than confirmed progression. For completeness, a sensitivity analysis using only patients with a PFS date was also conducted and presented in the ITC report within Appendix L.

Due to the nature of the real-world data, there were inconsistencies with the data collected for some patients. For example, some patients had a censored OS event earlier than their last known treatment discontinuation event, or in Wong et al, the total duration of treatment for each line was greater than the overall survival time. As such, a number of rules were put in place to ensure censoring was consistent across endpoints:

- Where patients continue on treatment, but without an overall survival event, they are assumed to be censored for overall survival at their last contact point for treatment
- Where a patient has a confirmed death event, any data after this point is discarded as it likely represents either estimated or predicted data (for example when a patient would be due for retreatment)
- Should a patient's treatment times add up to more than their survival time, the final line of treatment will be shortened such that the overall survival matches that recorded in the data

These rules ensure that the assumed known event was taken forward for the analysis, however the impact of amending the OS censoring times meant that the OS data looked better (and were longer) than if the actual dates reported in the real-world data were used.

B.2.9.5.1. Inclusion/exclusion criteria

To align with the patient population in VISION, inclusion/exclusion criteria as per the VISION trial were applied to the real-world patient data in the following order to form a comparable dataset:

- Age ≥ 18 years
- Exclude stages I-IIIA
- Exclude if missing both disease stage and advanced/metastatic disease status
- Exclude ECOG ≥ 2
- Exclude if missing both PFS/TTNTD and OS
- Include only the METex14 skipping alterations population
- Exclude anaplastic lymphoma kinase positive (ALK+)
- Exclude epidermal growth factor receptor positive (EGFR+)

Table 19 provides the number of patients and lines available at each stage of applying the inclusion/exclusion criteria to the CDM, resulting in a total of 140 patients with data for 273 lines of therapy from all four datasets. Over half of the patients had a missing ECOG status. However clinical expert opinion suggested that missing ECOG status was not likely to impact results given that most patients that are given chemotherapy or immunotherapy are likely to be ECOG 1 at most. Therefore, retaining patients with a missing ECOG was considered preferable over removing those patients and reducing the sample size. A sensitivity analysis using only patients with an ECOG status was also conducted and presented in the ITC report within Appendix L.

Table 19: Application of inclusion/exclusion criteria to real world data

Criteria	Total		Excluded	
	n	Lines	n	Lines
All patients	[redacted]	[redacted]	[redacted]	[redacted]
Age 18+	[redacted]	[redacted]	[redacted]	[redacted]
Exclude stages I-IIIA	[redacted]	[redacted]	[redacted]	[redacted]
Missing stage and advanced/metastatic status	[redacted]	[redacted]	[redacted]	[redacted]

Criteria	Total		Excluded	
	n	Lines	n	Lines
Exclude ECOG 2+	[redacted]	[redacted]	[redacted]	[redacted]
Missing PFS/TTNTD and OS	[redacted]	[redacted]	[redacted]	[redacted]
MET Skipping population	[redacted]	[redacted]	[redacted]	[redacted]
Exclude ALK+	[redacted]	[redacted]	[redacted]	[redacted]
Exclude EGFR+	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviation: ALK, anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition; OS, overall survival; PFS, progression-free survival; TTNTD, time to next treatment or death.

B.2.9.5.2. Resulting patient characteristics

A maximum of 1 treatment line per patient was included within each analysis (VISION vs. immunotherapy, and VISION vs. chemotherapy) by selecting a random line as suggested in the publication by Hernán & Robins et al. (2016).[142] This is to avoid one patient being included multiple times within the data set. For example, a patient with first-line immunotherapy followed by two lines of chemotherapy would have their data included in the immunotherapy comparison and one of the two chemotherapy lines selected at random for the chemotherapy comparison.

Following this sampling process, a total of 66 chemotherapy-treated patients and 51 immunotherapy-treated patients were available in order to conduct the primary ITC with the tepotinib VISION data. The resulting patient characteristics are presented in Table 20.

Table 20: Comparator baseline patient characteristics prior to weighting

Characteristic	VISION	Chemotherapy	Immunotherapy
n	[redacted]	[redacted]	[redacted]
Study (%)			
0015	[redacted]	[redacted]	[redacted]
0035	[redacted]	[redacted]	[redacted]
COTA	[redacted]	[redacted]	[redacted]
Wong et al.	[redacted]	[redacted]	[redacted]
VISION	[redacted]		
Age (mean, (SD))	[redacted]	[redacted]	[redacted]
Age over 75 (%)	[redacted]	[redacted]	[redacted]
Treatment Experienced (%)	[redacted]	[redacted]	[redacted]
Male (%)	[redacted]	[redacted]	[redacted]
Race			
Asian	[redacted]	[redacted]	[redacted]

Characteristic	VISION	Chemotherapy	Immunotherapy
Black or African American	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
History of smoking (%)	[redacted]	[redacted]	[redacted]
ECOG			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Stage (%)			
IIIB	[redacted]	[redacted]	[redacted]
IIIB/C	[redacted]	[redacted]	[redacted]
IIIC	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]
IVB	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Metastatic disease; (%)	[redacted]	[redacted]	[redacted]
Histology			
Adenocarcinoma	[redacted]	[redacted]	[redacted]
Squamous	[redacted]	[redacted]	[redacted]
Sarcomatoid	[redacted]	[redacted]	[redacted]
Others	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation

B.2.9.5.3. Treatment groups

Table 21 presents the different treatments received by patients within the chemotherapy group. Of the patients who received chemotherapy, the majority were pemetrexed ([redacted]) or platinum containing regimens ([redacted]).

Table 21: Treatment regimens received in the chemotherapy treatment group

Line	Chemotherapy (n=66)	
	Frequency	Percent
Carboplatin & pemetrexed	[redacted]	[redacted]
Platinum doublet[a]	[redacted]	[redacted]
Bevacizumab, carboplatin & pemetrexed	[redacted]	[redacted]
Carboplatin & paclitaxel	[redacted]	[redacted]

Line	Chemotherapy (n=66)	
	Frequency	Percent
Docetaxel	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]
Cisplatin & pemetrexed	[redacted]	[redacted]
Pemetrexed & bevacizumab	[redacted]	[redacted]
Bevacizumab, cisplatin & pemetrexed	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Carboplatin & gemcitabine	[redacted]	[redacted]
Cisplatin & etoposide	[redacted]	[redacted]
Cisplatin & gemcitabine	[redacted]	[redacted]
Cisplatin & vinorelbine	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]
Gemcitabine & vinorelbine	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]

Notes:
a The Wong et al data set only labelled treatments as per the treatment class.

Table 22 presents the immunotherapies patients received within the immunotherapy group. Pembrolizumab was the most common immunotherapy followed by nivolumab.

Table 22: Treatment regimens received in the immunotherapy treatment group

Line	Immunotherapy (n=51)	
	Frequency	Percent
Pembrolizumab	[redacted]	[redacted]
Immunotherapy [a]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Ipilimumab & nivolumab	[redacted]	[redacted]
Durvalumab	[redacted]	[redacted]
Spartalizumab	[redacted]	[redacted]

Notes:
a The Wong et al data set only labelled treatments as per the treatment class.

B.2.9.6. Indirect treatment comparison method

Propensity scoring was implemented in the primary ITC in order to achieve an improved balance in patient characteristics between tepotinib and the comparators. This was done to create a fairer comparison, accounting for prognostic patient characteristics, versus a naïve comparison between groups.

The propensity score is a logistic regression to predict treatment assignment, which captures the probability of being treated with tepotinib, given the observed patient characteristics. The propensity score uses a selected set of baseline patient characteristic variables in order to

balance between groups. Assuming there is no imbalance in unobserved characteristics, balancing on the propensity score can result in a statistically unbiased sample and is in line with the NICE DSU 17 guidance.[143]

Several approaches to balancing groups based on the propensity score are available, such as matching and weighting. Matching searches for patients with similar characteristics between groups. While a tight match can be achieved, the maximum number of patients is limited to the number of patients available in the smallest group, resulting in a loss of patient data. As inclusion/exclusion criteria were applied to the comparator datasets to obtain a group similar to VISION, propensity score weighting (rebalancing characteristics to match between datasets, resulting in no loss of data) was preferred over matching in order to avoid discarding patient records.

Standardised Mortality Ratio (SMR) Weights were chosen to weight the samples. An SMR weighting approach reweights the observational data to match the tepotinib data.[144] This means that the tepotinib data remains constant between comparisons (when comparing to the immunotherapy group, and the chemotherapy group) for VISION, and is also consistent with the trial publication and clinical study report.

Interviews with two separate clinical experts with extensive experience in treating NSCLC were conducted to obtain input on the characteristics considered to be prognostic and/or predictive in the disease area in order to inform the variables included in the calculation of the propensity score. All characteristics available for inclusion were presented to the clinical experts, with input taken on the most important factors to be included in addition to the order of importance. The resulting covariates in order of relevance were:

- Prior treatment experience
- Age (as a mean)
- Metastatic/stage 4 disease (vs non-metastatic)
- Sex
- Histology
- Presence of smoking history

Clinical experts explained smoking history was expected to be a negative prognostic factor in the chemotherapy group and a positive prognostic factor in the immunotherapy dataset, therefore, it was included in both models. Clinical input also indicated that ECOG

performance status was an important variable to match on, however this was not possible to include due to the amount of missing data ([redacted]% unknown within the chemotherapy group and [redacted]% unknown within the immunotherapy group). In addition, patient numbers were only sufficiently large enough to match on the percentage of patients with adenocarcinoma histology, as there are relatively small proportions of patients with alternative histology groups in both the VISION and real-world studies.

B.2.9.7. Indirect treatment comparison results

B.2.9.7.1. Patient characteristics

Baseline characteristics of the reweighted data for the immunotherapy and chemotherapy groups were presented to the clinicians involved, with the match deemed acceptable based on their input. Table 23 and Table 24 present the baseline patient characteristics for the tepotinib group, with the unweighted and weighted characteristics for the immunotherapy and chemotherapy treatment groups, respectively. P-values and standardised mean differences (SMDs) are also presented where values of >0.1 and <0.1, respectively, are considered measures of acceptable similarity in data.[145]

For the chemotherapy data (Table 23), all weighted p-values and SMDs were within their respective acceptable thresholds, indicating a good match to the tepotinib data. All characteristics with the exception of one looked balanced between tepotinib and the immunotherapy data (Table 24). An imbalance remained for the metastatic disease category likely due to small patient numbers, resulting in weighted SMDs greater than 0.1. Clinical input indicated that the resulting match was acceptable and that it was preferrable for all key characteristics to be matched upon, rather than any removed from the propensity score model. The differences seen were also felt to be acceptable, and would not be remarked on in a randomised comparison.

Table 23: Baseline patient characteristics for the chemotherapy data, before and after weighting, compared to the VISION data

Characteristic	Chemotherapy		Tepotinib	p-value		SMD	
	Unweighted	Weighted		Unweighted	Weighted	Unweighted	Weighted
n	[redacted]	[redacted]	[redacted]				
Age (mean, (SD))	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age over 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment				[redacted]	[redacted]	[redacted]	[redacted]
Untreated	[redacted]	[redacted]	[redacted]				
Treatment Experienced	[redacted]	[redacted]	[redacted]				
Sex				[redacted]	[redacted]	[redacted]	[redacted]
Female (%)	[redacted]	[redacted]	[redacted]				
Male (%)	[redacted]	[redacted]	[redacted]				
Race							
Asian	[redacted]	[redacted]	[redacted]				
Black or African American	[redacted]	[redacted]	[redacted]				
Other	[redacted]	[redacted]	[redacted]				
White	[redacted]	[redacted]	[redacted]				
Unknown	[redacted]	[redacted]	[redacted]				
History of smoking (%)				[redacted]	[redacted]	[redacted]	[redacted]
No (%)	[redacted]	[redacted]	[redacted]				
Yes (%)	[redacted]	[redacted]	[redacted]				
ECOG							
0	[redacted]	[redacted]	[redacted]				
1	[redacted]	[redacted]	[redacted]				
Unknown	[redacted]	[redacted]	[redacted]				
Stage (%)							
IIIB/C	[redacted]	[redacted]	[redacted]				
IIIB	[redacted]	[redacted]	[redacted]				
IV	[redacted]	[redacted]	[redacted]				

Characteristic	Chemotherapy		Tepotinib	p-value		SMD	
	Unweighted	Weighted		Unweighted	Weighted	Unweighted	Weighted
IVB	[redacted]	[redacted]	[redacted]				
NA	[redacted]	[redacted]	[redacted]				
Metastatic disease (%)				[redacted]	[redacted]	[redacted]	[redacted]
No (%)	[redacted]	[redacted]	[redacted]				
Yes (%)	[redacted]	[redacted]	[redacted]				
Histology							
Adenocarcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous	[redacted]	[redacted]	[redacted]				
Others	[redacted]	[redacted]	[redacted]				

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; SMD, standardised mean difference

Table 24: Baseline patient characteristics for the immunotherapy data, before and after weighting, compared to the VISION data

Characteristic	Immunotherapy		Tepotinib	p-value		SMD	
	Unweighted	Weighted		Unweighted	Weighted	Unweighted	Weighted
n	[redacted]	[redacted]	[redacted]				
Age (mean, (SD))	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age over 75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment				[redacted]	[redacted]	[redacted]	[redacted]
Untreated	[redacted]	[redacted]	[redacted]				
Treatment Experienced	[redacted]	[redacted]	[redacted]				
Sex				[redacted]	[redacted]	[redacted]	[redacted]
Female (%)	[redacted]	[redacted]	[redacted]				
Male (%)	[redacted]	[redacted]	[redacted]				
Race							
Asian	[redacted]	[redacted]	[redacted]				
Black or African American	[redacted]	[redacted]	[redacted]				
Other	[redacted]	[redacted]	[redacted]				

Characteristic	Immunotherapy		Tepotinib	p-value		SMD	
	Unweighted	Weighted		Unweighted	Weighted	Unweighted	Weighted
White	[redacted]	[redacted]	[redacted]				
Unknown	[redacted]	[redacted]	[redacted]				
History of smoking (%)				[redacted]	[redacted]	[redacted]	[redacted]
No (%)	[redacted]	[redacted]	[redacted]				
Yes (%)	[redacted]	[redacted]	[redacted]				
ECOG							
0	[redacted]	[redacted]	[redacted]				
1	[redacted]	[redacted]	[redacted]				
Unknown	[redacted]	[redacted]	[redacted]				
Stage (%)							
IIIB/C	[redacted]	[redacted]	[redacted]				
IIIB	[redacted]	[redacted]	[redacted]				
IV	[redacted]	[redacted]	[redacted]				
IVB	[redacted]	[redacted]	[redacted]				
NA	[redacted]	[redacted]	[redacted]				
Metastatic disease (%)				[redacted]	[redacted]	[redacted]	[redacted]
No (%)	[redacted]	[redacted]	[redacted]				
Yes (%)	[redacted]	[redacted]	[redacted]				
Histology							
Adenocarcinoma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Squamous	[redacted]	[redacted]	[redacted]				
Others	[redacted]	[redacted]	[redacted]				

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; SMD, standardised mean difference.

B.2.9.7.2. Overall survival

The weighted patient level data from the real-world cohorts were used to provide OS estimates for each comparator, presented in turn below.

Chemotherapy

Median OS was [redacted] months (95% CI: [redacted]) for the chemotherapy treatment group, with a restricted mean survival time (RMST) of [redacted] months (capped at 35.1 months), compared to a median of [redacted] months (95% CI: [redacted]) for tepotinib and RMST of [redacted] months (Table 25). A summary of the unweighted and weighted OS data for the chemotherapy treatment arm is provided in Figure 24, which shows a consistent benefit of overall survival for tepotinib versus chemotherapy until around 24 months after which the KM's overlap, however at this point the numbers at risk are small.

Figure 24: Overall survival – Chemotherapy

[redacted]

Abbreviations: Chemo, chemotherapy; OS, overall survival; RWD, real-world data

Immunotherapy

Median OS was [redacted] months (95% CI: [redacted]) for the immunotherapy treatment group, with a RMST of [redacted] months (capped at 35.1 months) compared to a median of [redacted] months (95% CI:

[redacted]) for tepotinib and RMST of [redacted] months (Table 25). A summary of the unweighted and weighted OS data for the immunotherapy treatment arm is provided in Figure 25. As per the chemotherapy comparison, the results show a consistent benefit of OS for tepotinib versus immunotherapy until around 12 months, after which the KM's overlap.

Figure 25: Overall survival – Immunotherapy

Abbreviations: IO, immunotherapy; NIS, non-interventional study; OS, overall survival; RWD, real-world data

B.2.9.7.3. Progression-free survival

The weighted patient level data from the real-world cohort data were used to provide PFS estimates for each comparator, presented in turn below. Where PFS was not available from the real-world data, TTNTD was used as a proxy in order to form a comparison to tepotinib. A sensitivity analysis using only patients with a PFS outcome was also conducted and presented in the ITC report within Appendix L, and these results were supportive of the findings of the base case ITC, suggesting the use of TTNTD as proxy did not majorly change the expected PFS results.

Chemotherapy

Median PFS was [redacted] months (95% CI: [redacted]) for the chemotherapy treatment group, with a RMST of [redacted] months (capped at 32.9 months), compared to a median of [redacted] months (95% CI:

[redacted]) for tepotinib and RMST of [redacted] months (Table 25). A summary of the weighted PFS data for the chemotherapy treatment arm is provided in Figure 26 showing a consistent and sustained benefit of PFS for tepotinib.

Figure 26: Progression-free survival – Chemotherapy

Abbreviations: Chemo, chemotherapy; PFS, progression-free survival; RWD, real-world data

Immunotherapy

For immunotherapy, median PFS was [redacted] months (95% CI: [redacted]) with a RMST of [redacted] months (capped at 32.9 months), compared to a median of [redacted] months (95% CI: [redacted]) for tepotinib and RMST of [redacted] months (Table 25). A summary of the weighted PFS data for the immunotherapy treatment arm is provided in Figure 27 showing a consistent and sustained benefit of PFS for tepotinib.

Figure 27: Progression-free survival – Immunotherapy

Abbreviations: IO, immunotherapy; PFS, progression-free survival; RWD, real-world data

B.2.9.7.4. Summary

Table 25 presents the summary of the primary ITC results. Tepotinib showed a substantial clinical benefit of PFS in comparison to chemotherapy and immunotherapy and marginal benefit for OS. As shown in Section B.3.5.4, the real-world cohort patients had a higher number of subsequent treatments, and more aggressive sets of subsequent therapies compared to VISION and UK practice, as such, the OS estimates could be underestimating the OS benefit for tepotinib compared to chemotherapy and immunotherapy in the METex14 skipping alterations population and could explain the reasons why the main benefit for tepotinib is seen in PFS.

The Cox proportional hazard ratios demonstrated a statistically significant PFS benefit for tepotinib versus chemotherapy and immunotherapy, and non-statistically significant OS benefit. However, Cox proportional hazard ratios should be taken with caution as they are based on the assumption of proportional hazards, which we have demonstrated does not hold for the comparison of tepotinib and chemotherapy or immunotherapy (see Appendix M). To this end, the RMST provides a better outcome to measure the treatment effect without the need for assumptions[146] and shows that tepotinib has a greater PFS and OS than

chemotherapy and immunotherapy when capped at the same time point (i.e., using the minimum maximum time point between the three treatment arms).

Table 25: Summary of ITC efficacy results

	Tepotinib (n=151)	Chemotherapy (n=66, WSS=152)	Immunotherapy (n=51, WSS=150)
Overall survival			
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
RMST, months [a]	[redacted]	[redacted]	[redacted]
HR versus tepotinib (95% CI)	-	[redacted]	[redacted]
p-value	-	[redacted]	[redacted]
Progression-free survival			
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
RMST, months [a]	[redacted]	[redacted]	[redacted]
HR versus tepotinib (95% CI)	-	[redacted]	[redacted]
p-value	-	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; RMST, restricted mean survival time; WSS, weighted sample size

Note:

a RMST capped by maximum immunotherapy time (35.1 months for OS and 32.9 months for PFS)

B.2.9.8. Uncertainties in the indirect and mixed treatment comparisons

Several uncertainties were identified with the ITC approach for forming a comparison to tepotinib in NSCLC harbouring METex14 skipping alterations, discussed in turn below:

- PFS data was not available for all patients included in the real-world cohort data, with TTNTD or duration of treatment included as a proxy where data was missing to inform this outcome.
    - While TTNTD is generally highly correlated with PFS, it does not provide an exact match. For instance, some patients may spend time off-treatment post progression, prior to receiving their next treatment, while others may discontinue due to toxicity rather than progression and start another treatment shortly afterward. Therefore, using TTNTD as a proxy for PFS is likely to overestimate the 'real' PFS as this could be expected to be shorter.
    - As above, duration of treatment is generally highly correlated with PFS but does not provide an exact match. Some patients may stop treatment for other

reason's other than progression such as toxicity. Therefore, using duration of treatment as a proxy for PFS could likely bias the comparators as the 'real' PFS could be expected to be longer. In the COTA data set, for those discontinuing treatment for reasons other than PFS, TTNTD was used instead of treatment duration. Wong et al did not include time between treatment line, as such only duration of treatment was able to be used as PFS. This limitation is tempered by the fact Wong et al provided relatively few patients (Table 20).

  - Although using TTNTD or duration of treatment is a limitation of the real-world data, including all patients increases the number available for the comparison to tepotinib, and provides a more robust statistical comparison for OS.

  - The sensitivity analysis using only patients with a PFS time resulted in similar outcomes, though patient numbers were reduced hence uncertainty increased (see the ITC report within Appendix L).

- Following the application of the inclusion/exclusion criteria, the remaining patients from the real-world studies cannot be confirmed as being eligible for VISION as other reasons may have prevented them being included should they have been screened.

  - Although this is an uncertainty, patients enrolled in VISION would have definitely been excluded due to the criteria shown in Table 19. Thus by removing these patients prior to performing the weighting analysis, the remaining patients are as aligned with VISION as was possible with the available information.

  - A large number of patients had missing ECOG status, however this was not expected to have much impact on the results given that most patients treated with chemotherapy and immunotherapy would likely be ECOG 1 at most. The sensitivity analysis using only patients with an ECOG status resulted in similar outcomes, though patient numbers were reduced so the uncertainty increased (see the ITC report within Appendix L).

- The SMR weighting approach is technically less statistically efficient than a standard weighting approach, as the distribution of patients from one group are entirely reweighted to match another, rather than the distributions of both groups adjusted to the overlap area.

- Despite this, the overlap in patient characteristics, and thus propensity scores, between studies was high. Therefore, this was considered acceptable.

- In addition, the method provides the ability to include all VISION patients within the analysis and allow for easier interpretation compared to other available methods.

- An imbalance remained in the immunotherapy data with the weighted SMD for metastatic disease remaining greater than 0.1 (0.14), suggesting a meaningful difference between the proportion of patients with metastatic disease compared to the data from VISION.

    - Though this remains a source of uncertainty, the significant difference seen is likely due to small patient numbers. Clinical input indicated that the resulting match for the immunotherapy group was acceptable. Furthermore, clinical experts consulted stated that it was preferrable for all key characteristics to be matched upon, rather than to remove any from the propensity score model in an attempt to achieve a closer match.

- The comparability of data for these analyses is uncertain due to limitations when comparing trial data to real-world evidence.

    - In VISION, monitoring of patients is frequent and includes regularly scheduled imaging investigation as per the study protocol. The patients in the real-world data sets were likely to be monitored less frequently and without routine imaging. Mandated imaging in VISION will identify progression-events, including those who are asymptomatic and do not require treatment. In the real-world setting, it is likely that progression-events are determined only after symptomatic presentation. It is therefore possible that progression-events are recorded later in the real-world setting than in VISION and could overestimate PFS for the real-world data cohort.

    - Another limitation of using real-world data is the variations in treatment sequencing based on the different clinical practices. A large majority of the patients in the real-world cohort (particularly for chemotherapy) had more aggressive subsequent treatment pathways, particularly with higher rates of subsequent immunotherapy or another MET inhibitor such as crizotinib. This

would be expected to give the real-world cohort data patients additional OS benefit, and as such, the estimated OS gain is likely to be underestimated for tepotinib compared to chemotherapy and immunotherapy in the METex14 skipping alterations population.

- There are general limitations associated with comparing trial data to real-world data, however the access to patient-level data had several benefits and alleviates some of these limitations. Firstly, the data enabled application of inclusion/exclusion criterion to the real-world data set to match the patients who would be included within the VISION study. Secondly, this allowed for adjusting of the patients to be matched to the VISION cohort using robust statistical techniques. Finally, this approach meant that the VISION cohort could remain unadjusted and consistent between the two comparisons (with a resulting impact on being able to use the same curve fits, for example). This is an unusual situation, given many prior appraisals with non-comparative data have to rely on published data.[147]

- There are currently very little data in the METex14 skipping alterations population for patients treated with immunotherapy in combination with chemotherapy. These are newer treatment options, so there has been little time to collect data. In all the real-world cohorts identified, very few patients treated with immunotherapy in combination with chemotherapy were included (n=5), with very few in published studies from the systematic literature review either. This is a limitation, as it is unclear how efficacious immunotherapy in combination with chemotherapy will be in this specific population, given the associated poor response these patients have to immunotherapy when used as monotherapy (see Section B.3.2.3).

B.2.10. Adverse reactions

B.2.10.1. Safety set

The safety set (SAF) for VISION is for the larger Cohort A+C. The presented data is from the 1 July 2020 data cut-off. The summary safety data for Cohort A+C at the 1 February 2021 is presented in Appendix R.

Data for the pooled METex14 skipping alteration Cohorts A+C SAF is presented in Table 26.

For the combined group, the median duration of tepotinib therapy ranged between 0.03 and 43.33 months, with a median duration of 5.125 months. The majority of patients in the SAF analysis set did not have any dose reduction for tepotinib (70.2%). The tepotinib dose was reduced from 500 mg once daily (equivalent to 450 mg free form tepotinib) to 300 mg 17.3% of patients, to 250 mg for 4.7% of patients, and to 200 mg for 7.8% of patients.

Table 26: Overview of safety set (SAF)

	Cohort A+C (N=255)
Duration of tepotinib therapy*, months (95% CI)	5.125 (0.03–43.33)
Dose reduction of tepotinib, n (%) **	
Number of subjects without any dose reduction for tepotinib	179 (70.2)
Number of subjects with at least 1 tepotinib dose reduction	76 (29.8)
Number of subjects with minimum tepotinib dose level, n (%)	
200 mg (40%)	20 (7.8)
250 mg (50%)	12 (4.7)
300 mg (60%)	44 (17.3)
500 mg (100%)	179 (70.2)
Treatment delay, n (%)	
Number of subjects with delays	128 (50.2)
Number of subjects with maximum consecutive delays of, n (%)	
1-2 days	39 (15.3)
3-7 days	23 (9.0)
8-14 days	24 (9.4)
15-21 days	32 (12.5)
> 21 days	10 (3.9)

Source: VISION CSR 1 July 2020 cut-off

Abbreviations: AE, adverse events, IMP=investigational medicinal product

Notes:

* Duration of therapy (months) was calculated as: (date of last dosing day – date of first dosing day + 1)/30.4375.

** Dose reduction was defined as any dose less than 500 mg. Dose omission was not considered as dose reduction

B.2.10.2. Safety set baseline characteristics

Table 27: Safety set demographic and baseline characteristics

Characteristic	**Cohort A+C (N=255)**
Age (years)	
Median	**72.0**
Range	**41; 94**
Gender, n (%)	

Characteristic	Cohort A+C (N=255)
Male	123 (48.2)
Female	131 (51.8)
Race, n (%)	
White	171 (67.1)
Black or African American	3 (1.2)
Asian	72 (28.2)
Not collected at this site	7 (2.7)
Other	1 (0.4)
Missing	1 (0.4)
Geographic region, n (%)	
Europe	128 (50.2)
North America	54 (21.2)
Asia	73 (28.6)
ECOG PS, n (%)	
0	71 (27.8)
1	184 (72.2)
Smoking history, n (%)	
Yes	121
No	124 (48.6)
Prior therapy for advanced / metastatic disease, n (%)	
Untreated	125 (49.0)
Previously treated	130 (51.0)
Histology subtype, n (%)	
Adenocarcinoma	207 (81.2)
Squamous	25 (9.8)
Other	23 (9.0)
Stage at study entry, n (%)	
IIIb	8 (3.1)
IIIc	3 (1.2)
IV	243 (95.3)
Missing	1 (0.4)
Brain metastases as identified by IRC, n (%)	
Non-target lesion	INV: 31 (12.2) IRC: 31 (12.2)
Target lesion	INV: 1 (0.4) IRC: -

Source: VISION CSR 1 July 2020 cut-off

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance scale; INV, investigator assessment; IRC, independent review committee

B.2.10.3. Adverse Events

Tepotinib was well tolerated at the proposed dose administered once daily in VISION Cohorts A+C. The majority of AEs were nonserious and mild or moderate in severity (Grade 1 or 2), with low discontinuation rates due to treatment-related adverse events (TRAE).

B.2.10.4. Overview of TEAEs and TRAEs

In VISION Cohorts A + C, 96.5% of patients had ≥1 TEAE, 52.9% had Grade ≥3 TEAEs, and 45.1% had serious TEAEs (see Table 28). Although most patients (86.3%) had TRAEs, Grade ≥3 TRAEs and serious TRAEs were reported with lower incidences of 25.1% and 12.2%, respectively.

Most of the AEs leading to tepotinib dose reduction or temporary treatment discontinuation were considered treatment-related. The incidence of TRAEs leading to permanent treatment discontinuation was 10.6%. Thirty patients died from any causality, including two patients that were considered treatment-related by the Investigator (Section B.2.10.5).

Table 28. Overview of TEAEs and TRAEs

	Tepotinib 500 mg
	VISION Cohorts A + C (N=255) n (%)
Any TEAE	246 (96.5)
TEAE, NCI CTCAE Grade ≥ 3	135 (52.9)
Any TRAE	220 (86.3)
TRAE, NCI CTCAE Grade ≥ 3	64 (25.1)
TEAE leading to treatment dose reduction	76 (29.8)
TRAE leading to treatment dose reduction	71 (27.8)
TEAE leading to temporary treatment discontinuation	112 (43.9)
TRAE leading to temporary treatment discontinuation	90 (35.3)
TEAE leading to permanent treatment discontinuation [a]	52 (20.4)
TRAE leading to permanent treatment discontinuation	27 (10.6)
Serious TEAE	115 (45.1)
Serious TRAE	31 (12.2)
TEAE with an outcome of death [b]	30 (11.8)
TRAE with an outcome of death [b]	2 (0.8)

Source: Section 2.7.4, Table 11.

Abbreviations: NCI CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events, TEAE=treatment- emergent adverse event, TRAE=treatment-related adverse event

Notes:

a The number reflects information from the adverse event eCRF page, resulting in a difference to the number of patients with an AE as primary reason for treatment discontinuation, which is based on the disposition eCRF page.
b There was an additional TRAE leading to death by the cut-off date, which was not recorded in the clinical database.

B.2.10.5. Common adverse events

The most common TRAEs in VISION Cohorts A + C irrespective of the severity were peripheral oedema (54.1%), nausea (20.0%), diarrhoea (19.6%), blood creatinine increased (17.6%), and hypoalbuminemia (14.5%). Most of these TRAEs were mainly Grade 1 or 2 in severity.

The most frequently affected System Organ Classes (SOCs) or Preferred Terms (PTs) in VISION Cohorts A + C are consistent with the AEs reported with other MET inhibitors or with the underlying disease. Patients had TRAEs belonging most often to the following SOCs:

- General disorders and administration site conditions, with the most frequent PTs being peripheral oedema (54.1%), fatigue (7.1%), and asthenia (5.5%).
- Gastrointestinal disorders, with the most frequent PTs being nausea (20.0%), diarrhoea (19.6%), and constipation (5.9%).
- Investigations, with the most frequent PTs being blood creatinine increased (17.6%) and alanine aminotransferase increased (ALT) increased (8.6%).
- Respiratory, thoracic and mediastinal disorders, with the most frequent PTs being dyspnoea (3.9%) and pleural effusion (6.3%).

Peripheral oedema was the most frequently reported TEAE and TRAE in VISION Cohorts A+C. Peripheral oedema has been consistently reported for other MET inhibitors (e.g. capmatinib,[148] and crizotinib,[149]), suggesting a potential class effect. The development of peripheral oedema might be associated with the role of MET/HGF in vascular and lymphatic endothelial tissue.[150] Most adverse events were managed with temporary dose interruptions or dose reductions.[1]

B.2.10.6. Severity and Relatedness of Adverse Events

B.2.10.6.1. Grade ≥3 Adverse Events

A summary of Grade ≥ 3 TEAE/TRAEs is presented in Table 29. Overall, Grade ≥ 3 TRAE occurred in 25.1% of patients.

The most common grade ≥ 3 TRAE was peripheral oedema (7.5%), followed by pleural effusion (3.1%) and hypoalbuminemia (2.4%).

Table 29: Overview of Grade ≥ 3 TEAE and TRAEs

Patients with at least one, n (%)	Grade ≥ 3 TEAE	Grade ≥ 3 TRAE
Any AE	135 (52.9)	64 (25.1)
Peripheral oedema	20 (7.8)	19 (7.5)
Hypoalbuminemia	14 (5.5)	6 (2.4)
Pleural effusion	13 (5.1)	8 (3.1)
Pneumonia	11 (4.3)	0 (0.0)
ALT increased	8 (3.1)	5 (2.0)
Dyspnoea	7 (2.7)	4 (1.6)
Decreased appetite	3 (1.2)	1 (0.4)
Vomiting	3 (1.2)	1 (0.4)
Asthenia	3 (1.2)	1 (0.4)
Nausea	2 (0.8)	1 (0.4)
Back pain	2 (0.8)	0 (0.0)
Diarrhoea	1 (0.4)	1 (0.4)
Blood creatine increased	1 (0.4)	1 (0.4)
Fatigue	1 (0.4)	1 (0.4)
Cough	1 (0.4)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)

Source: VISION CSR 1 July 2020 cut-off
Abbreviations: AE, adverse events; ALT, alanine aminotransferase

B.2.10.7. Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events

B.2.10.7.1. Deaths

In VISION Cohorts A + C, 85 (33.3%) patients died due to any reason. Disease progression was the most common primary cause of death, occurring in 66 (25.9%) patients. During the on-treatment period (within 30 days after the last dose of study drug), the primary cause of death was disease progression in 16 (6.3%) patients.

Three TRAEs were fatal: acute respiratory failure secondary to interstitial lung disease (ILD), respiratory failure secondary to anasarca after severe worsening of dyspnoea and acute hepatic failure after the patient withdrew consent.

In VISION Cohorts A + C, 30 (11.8%) patients had TEAEs leading to death. The most frequent fatal TEAEs were disease progression (nine patients, 3.5%) and general physical health deterioration (four patients, 1.6%).

B.2.10.7.2. Serious Adverse Events

In VISION Cohorts A + C, 115 (45.1%) patients had at least one serious TEAE and 31 (12.2%) patients had at least one serious TRAE. The most common TRAEs were pleural effusion in 3.5% of patients, followed by peripheral oedema (2.4%), generalized oedema (1.6%), and dyspnoea (1.6%).

The most common serious TEAEs were pleural effusion (6.7%), pneumonia and disease progression (each in 4.7%), dyspnoea (3.9%) and general physical health deterioration (3.5%), which are typical of the underlying disease.

B.2.10.7.3. Adverse Events Leading to Permanent/Temporary Treatment Discontinuation or Dose Reduction

In VISION Cohorts A + C, most of the events leading to permanent discontinuation of tepotinib were consistent with the tepotinib safety profile and the underlying disease.

A summary of TRAEs leading to dose reduction and treatment discontinuation in ≥2% of patients is presented in Table 30.

Permanent discontinuations of treatment due to TRAEs occurred in 10.6% of patients; 35.3% of patients temporarily discontinued treatment, and 27.8% required a dose reduction. Peripheral oedema was the most common TRAE that resulted in temporary treatment discontinuation (16.1%) and dose reduction (14.1%); permanent treatment discontinuation, as a result, was rare (3.5%).

Table 30. Overview of TRAEs leading to dose reduction/treatment discontinuation ≥2% of patients

TRAE leading to dose reduction / treatment discontinuation ≥2% of patients, n (%)	Temporary treatment discontinuation	Permanent treatment discontinuation	Dose reduction
Any AE	90 (35.3)	27 (10.6)	71 (27.8)
Peripheral oedema	41 (16.1)	9 (3.5)	36 (14.1)
Blood creatine increased	16 (6.3)	2 (0.8)	7 (2.7)
Pleural effusion	9 (3.5)	3 (1.2)	5 (2.0)
ALT increased	7 (2.7)	0 (0.0)	2 (0.8)
Generalized oedema	8 (3.1)	0 (0.0)	6 (2.4)
Oedema	6 (2.4)	1 (0.4)	5 (2.0)
Diarrhoea	5 (2.0)	1 (0.4)	0 (0.0)

Source: VISION CSR 1 July 2020 cut-off

Abbreviations: AE, adverse events; ALT, alanine aminotransferase

B.2.11. Ongoing studies

The following clinical trials are ongoing:

- The VISION study is ongoing and is expected to be completed by [redacted] (final data cut). Subsequent data cuts are expected to provide additional PFS and OS data, with ongoing follow-up expected post study completion to allow more mature OS data to be captured.

B.2.12. Innovation

As shown in Section B.1.3.2, METex14 skipping alterations can cause aggressive tumours with a poor prognosis. Currently, there are no available treatment options that specifically target advanced NSCLC harbouring METex14 skipping alterations. Current standard of care with non-targeted therapies do not address the medical need of this severely diseased and predominantly elderly population. In addition, chemotherapies and immunotherapies require lengthy infusions where patients need to come into hospital.[151-154]

MET TKIs, including tepotinib, appear to result in better response rates and PFS than immunotherapies, as well as numerically greater survival compared to immunotherapies and chemotherapies in patients with METex14 skipping alterations.[49,155] Real-world clinical outcomes show that highly-selective MET inhibitors, such as tepotinib, have a reduced risk of off-target toxicity compared to other types that are not highly selective for MET.[2]

In the UK, tepotinib is the first precision medicine targeting MET for patients with NSCLC assessed by the MHRA and to be appraised by NICE. [redacted].

Tepotinib, administered orally at 500 mg once daily (equivalent to 450 mg tepotinib free form), has shown a substantial and clinically meaningful benefit for patients with NSCLC harbouring METex14 skipping alterations. Along with a tolerable and manageable safety profile, tepotinib provides a convenient and therapeutic option for the targeted population.[1,156,157] Tepotinib will be taken as an oral administration, allowing for patient-friendly once-daily dosing that is known to promote patient adherence and reduce administration and monitoring costs, as well as allowing patients to manage their treatment at home (vs. immunotherapies and chemotherapies which require lengthy infusions in a hospital setting).[158]

Tepotinib is an innovative therapy with the potential to make a substantial impact on health-related benefits and treatment tolerability in patients with advanced NSCLC with METex14 skipping alterations. As such, tepotinib will address the critical unmet need for a therapy that sustains and improves therapeutic responses, thereby improving survival outcomes and maintaining HRQL in this patient population.

B.2.13. Interpretation of clinical effectiveness and safety evidence

Retrospective studies have shown that patients with NSCLC harbouring METex14 skipping alterations have a poorer prognosis compared to those without METex14 skipping alterations, and often a poor response to current treatments, particularly response rates and PFS with immunotherapies. This makes treatment of this population clinically challenging, exacerbated by the comorbidities and overall frailty of the elderly patient population, which limit the use of currently available non-targeted treatment options, ultimately impacting on the prognosis of this subset of patients. Predictive biomarkers are used to inform treatment decisions in advanced NSCLC. Oncogenic driver mutations that are currently tested for, including EGFR, ALK and ROS1, can be treated with NICE-recommended targeted therapies. However, there are currently no EMA or MHRA approved treatments in the UK specifically targeting NSCLC with METex14 skipping alterations. In the absence of specific MET-targeted therapies, treatments currently used for patients without any identifiable

biomarkers in advanced NSCLC make up the current NHS standard of care (SoC), including immunotherapies and/or chemotherapy.

Principal findings from the available clinical evidence to support tepotinib

Tepotinib will be the first MET inhibitor available in the UK. Tepotinib demonstrated durable antitumour activity in patients with advanced NSCLC with METex14 skipping alterations with consistent activity across treatment lines and promising activity in patients with brain metastases, with an ORR of [redacted]%, a median DOR of [redacted] months, median PFS of [redacted] months and median OS of [redacted] months (N=152) at the latest VISION data cut-off (1 February 2021).

Tepotinib penetrates the blood-brain barrier at therapeutic levels. The response to tepotinib was consistent in patients with stable brain metastases at baseline. IRC-assessed ORR was [redacted]% (95% CI: [redacted]), and median DOR was [redacted] months (95% CI: [redacted]). IRC-assessed median PFS was [redacted] months (95% CI: [redacted]).

Patients' quality of life was maintained during treatment with tepotinib; dyspnoea symptoms were stable, whereas cough symptoms were reduced. The stability observed in the assessment of quality of life for patients treated with tepotinib indicates control of the symptoms in this population with advanced disease, as worsening of symptoms is to be expected in case of ineffective and/or toxic therapies.

In general, tepotinib was well tolerated with a manageable safety profile. Tepotinib is also administered orally, once daily which allows patients to manage their disease at home.

ITCs were conducted comparing tepotinib to immunotherapy or chemotherapy in the METex14 skipping alterations NSCLC population. Data for immunotherapy and chemotherapy were sourced from a real-world cohort of patients with NSCLC and METex14 skipping alterations. This is one of the largest efficacy datasets in this population used for an ITC, where published data are limited. Therefore, the dataset and ITC represent the best available evidence in the METex14 skipping alterations population, with PLD available, and allows for robust statistical comparisons. When comparing to published data in the MEtex14 skipping alterations population, the real-world cohort data is largely aligned in terms of patient characteristics and outcomes (Section B.3.2). Outcomes are also similar when comparing to clinical trial data for immunotherapy and chemotherapy (Section B.3.2), further supporting the external validity of the data set. Clinical experts interviewed were also

supportive of the outcomes and said they were aligned to their expectations of the METex14 skipping alterations population.

Results showed a large clinical benefit of PFS for tepotinib in comparison to chemotherapy ($p<0.0001$) or immunotherapy ($p=0.0131$), and a median benefit for OS of [redacted] months in comparison to chemotherapy, with a marginal OS benefit to immunotherapy. This is despite the higher number and aggressive set of subsequent treatments in the real-world cohort compared to VISION. These results are supported by the MAICs conducted to published studies in the METex14 skipping alterations population (Appendix L).

Strengths and limitations of the data package

There are no Phase 3 randomised controlled trials (RCTs) for tepotinib. RCTs are considered the gold-standard in facilitating the comparability of treatment arms. However, in certain circumstances exist where randomisation can be considered ethically questionable or unfeasible due to a disease's rarity impacting only a small population.[159] With a prevalence of roughly 3% in NSCLC patients, METex14 skipping alterations in NSCLC is such a disease, as it would require considerable time and resources to accrue a sufficient amount of subjects to conduct an RCT.[159] In this instance a Phase 2 study provides sufficient information on efficacy in this very rare cancer with high unmet medical need were no approved treatments are available yet in the UK. When building on a strong biological rationale in a biomarker-selected population of patients, there is a precedent for single-arm trials to provide a strong alternative to RCTs provided the patient population is well-defined and the drug produces a substantial ORR that exceeds that of existing treatments.[159] METex14 skipping alterations is a novel mutation, and until recently, there were no approved therapies specifically targeting this mutation. Tepotinib, however, has a durable ORR and manageable safety profile, allowing for an adequate assessment of the risk/benefit ratio. The VISION trial builds on strong scientific evidence and pre-clinical data. Taking this into consideration, the single-arm study design was the most feasible and appropriate method for VISION.

No head-to-head data are available for tepotinib versus the comparators listed in the scope, and there are currently no comparator clinical trial data available in patients with advanced NSCLC harbouring METex14 skipping alterations. Although clinical trial data is available for immunotherapy and/or chemotherapy in wildtype NSCLC, using these data to form an efficacy comparison to tepotinib would involve comparing two different patient populations. As such, data from four real-world studies in patients with advanced NSCLC harbouring

METex14 skipping alterations were used to perform comparisons with tepotinib, which included high quality comparative data to supplement the tepotinib data package. These studies enabled an ITC to be performed by treatment class and were well-matched in patient characteristics across all studies, and allowed comparisons in the specific patient population. In addition, subgroup analysis was conducted by line of therapy in the population with locally advanced or metastatic NSCLC with METex14 skipping alterations for which limited data are available. However, there were no data in the METex14 skipping population for patients treated with immunotherapy in combination with chemotherapy which remains a limitation of the available data.

In conclusion, the data provided for tepotinib (VISION) and the primary ITC results informed by the real-world cohorts in the METex14 skipping alterations population demonstrates the clinical benefits associated with tepotinib compared to the current SOC, in this elderly population which have no any targeted treatments currently available. Clinical experts interviewed highlighted the high unmet need for a targeted treatment option in this patient population, as is already available for other oncogenic mutation driver NSCLC (EGFR, ALK, ROS1), with the freedom to prescribe at first-line or subsequent lines of therapy depending on individual patient need.

B.2.13.1. End-of-life considerations

As discussed in Section B.1.3.2.3, patients with NSCLC harbouring METex14 skipping alterations have a poorer prognosis compared to wildtype NSCLC.[49,54-56] METex14 skipping alterations were found to be independent poor prognostic factors for NSCLC patients.[57] In addition, studies reporting outcomes of patients harbouring METex14 skipping alterations show a poorer response to treatment, particularly with immunotherapies:

- Median OS for patients with NSCLC harbouring METex14 skipping alterations since the diagnosis of Stage IV disease was only 8.1 months for patients treated with therapies that did not target MET - mostly chemotherapies (Awad 2019).[49]

- Median OS for METex14 skipping alterations patients treated with immunotherapy was found to be 13.4 months (Guisier et al)[85] and 18.2 months (Sabari et al).[51]

Patients with NSCLC harbouring METex14 skipping alterations tend to be older than other oncogenic driven NSCLC subpopulations, making treatment for this population clinically challenging (due to comorbidities and overall frailty), impacting on the prognosis of this subset of patients.[57] Older patients typically have a poorer response to treatments.[160] One

study investigating the efficacy of first-line chemotherapy in older patients found that the median survival reduced from 9.9 months in patients < 70 years to 7.7 months in patients ≥ 70 years.[161] In a study of the efficacy of nivolumab in older patients with pre-treated NSCLC, median survival was 14.85 months.[162]

The results of the primary ITC using the real-world data cohort could be considered more optimistic than what is reported in the literature for METex14 skipping alterations. However the ITC results still show a relatively low median OS ([redacted] months for the immunotherapy arm and [redacted] months for the chemotherapy arm – see Section B.2.9.7.4).

The above evidence demonstrates that patients with NSCLC harbouring METex14 skipping alterations are expected to have a short life expectancy, less than 24 months, regardless of treatment. Mean life-years projected by the model also demonstrate that even using optimistic survival curves for the comparators (see Section B.3.3.1), mean life expectancy is estimated to be less than 24 months for patients treated with chemotherapy ([redacted] months).

The results of the primary ITC using the real-world data cohort shows an increase of [redacted] months in median survival between tepotinib and chemotherapy and the mean survival difference from the cost-effectiveness model (using a 30-year time horizon) is estimated to be [redacted] months (see Section B.3.7.1). Therefore, we believe that tepotinib meets the end-of-life criteria for the chemotherapy comparison – in a group of patients who treated with chemotherapy (some of whom are contraindicated or unsuitable for immunotherapy), in either first-line or second-line.

The evidence from the literature suggests that survival for METex14 skipping alterations patients treated with immunotherapy is less than 24 months, regardless of treatment (Table 31). However, given the uncertainty in the additional survival benefit, it is unlikely tepotinib will meet the end-of-life criteria versus immunotherapy.

Table 31: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Evidence in the literature suggests that life expectancy for patients with NSCLC harbouring METex14 alterations is less than 24 months, regardless of treatment. This is supported by the results from the ITC for patients treated with chemotherapy and immunotherapy (median OS of [redacted] and [redacted] months, respectively) and mean modelled outcomes for chemotherapy (mean [redacted] months) regardless of treatment	Section B.2.13.1 page 115,116 Section B.2.9.7.2, page 97
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Median survival between tepotinib and chemotherapy demonstrated a difference of [redacted] months in favour of tepotinib. Mean overall survival from the model projects a difference of [redacted] months between tepotinib and chemotherapy.	Section B.2.9.7.2, page 97 Section B.3.7, page 191

Abbreviations: ITC, indirect treatment comparison; MAIC, mixed adjusted indirect comparison; NHS, National Health Service; NSCLC, non-small cell lung cancer

B.3. Cost effectiveness

Executive summary

- The base case patient population considers advanced NSCLC patients harbouring METex14 skipping alterations, regardless of treatment history and histology, in line with the proposed marketing authorisation and VISION study population.
- The economic analysis encompasses evidence from the Phase II VISION study and real-world data cohort for NSCLC patients harbouring METex14 skipping alterations.
  - The real-world data cohorts are adjusted using propensity scoring such that the population is matched to the tepotinib cohort in the VISION study.
- Due to the low incidence of NSCLC patients harbouring METex14 skipping alterations, patient numbers from the real-world data were too small to allow for comparisons against individual treatments. As such, treatments were combined by treatment class (chemotherapy and immunotherapy).
- The model used a partitioned survival structure with three health states; progression-free, progressed and death which is consistent with previous NSCLC submissions.
- Parametric models were fitted to the VISION study and the adjusted real-world cohort data to estimate long-term projections of OS, PFS and ToT. In some cases, flexible models such as splines and piece-wise were used if parametric models provided poor fits. Base case curves were chosen in line with NICE DSU guidance and clinical opinion.
- Utility data based on progression status was analysed based on EQ-5D-5L data collected in the VISION study and used for all treatment arms.
  - Disutilities associated with adverse events were considered separately for each treatment.
- Results demonstrated that tepotinib was cost-effective versus both chemotherapy and immunotherapy at both the £30,000 and £50,000 willingness-to-pay thresholds.
  - Tepotinib is dominant over immunotherapy showing a marginal increase in survival and quality-adjusted life-year (QALY) gain whilst saving [redacted] per person.
  - Tepotinib increases survival by 10.3 months compared to chemotherapy resulting in a [redacted] QALY gain at an additional cost of [redacted] per person resulting in an ICER of £19,512.
- Tepotinib remains cost-effective regardless of whether a patient is untreated or previously treated, including for compared to immunotherapy in combination with chemotherapy in the untreated population.
- Sensitivity analysis demonstrated that tepotinib is cost-effective when varying parameters within their associated distributions and testing different assumptions, the majority of scenarios being less than the £50,000/QALY threshold compared to chemotherapy and all scenarios under the threshold versus immunotherapy.
- Key strengths of the analysis include the availability of patient-level data for all treatment arms allowing more robust statistical techniques to be used for the comparative efficacy.
  - The analysis uses the most relevant evidence available for the specific METex14 skipping populations despite the limitations of evidence within the literature for a rare mutation.
- Tepotinib represents a novel treatment offering a cost-effective targeted alternative to chemotherapy-based and immunotherapy-based treatment options.
  - Tepotinib will also offer patients an oral drug option, where currently only infusions, which require frequent hospital visits, are available.

B.3.1. Published cost-effectiveness studies

A comprehensive SLR search was conducted to identify cost-effectiveness evidence in the METex14 skipping alteration NSCLC population. The systematic reviews were performed following the National Institute for Health and Care Excellence (NICE) preferred methodological principles of conducting systematic reviews as detailed in the University of York Centre for Reviews and Dissemination guidance for undertaking systematic reviews in health care. A systematic database and grey literature (conference proceedings) search was performed on 13 June 2021 which identified 45 hits. A total of six records were deduplicated and 39 unique title/abstracts were screened for inclusion. No cost-effectiveness analyses were identified for inclusion therefore no records were taken forward to full text screening. Full details of the SLR search strategy, inclusion/exclusion criteria and results are presented in Appendix G.

B.3.2. Economic analysis

As discussed in Section B.3.1, no previously published economic evaluations in METex14 NSCLC patients were identified from the SLR. Therefore, a *de novo* economic model was built to assess the cost-effectiveness of tepotinib versus relevant comparators for patients with NSCLC harbouring METex14 skipping alterations.

Table 32 provides an overview of the key features of the economic analysis for tepotinib in the treatment of NSCLC harbouring METex14 skipping alterations. This is the NICE first submission in the METex14 skipping alterations NSCLC population, therefore no comparison to previous appraisals have been included. However, the key features of the analysis are consistent with previous submissions in the wider NSCLC populations.[72-77,79,163,164] The model's population covers the anticipated marketing authorisation and is consistent with the population in the VISION study. Comparators are aligned with the comparators listed in the scope grouped by category due to the lack of individual data to allow for a comparison (see Section B.2.9).

Table 32: Key features of the economic analysis

Factor	Assumption	Justification
Patient population	Adult patients with advanced NSCLC harbouring METex14 skipping alterations	As per the expected marketing authorisation for tepotinib and patient population in the VISION study
Model health states	Progression-Free Progressed Death	This structure is consistent with the majority of previous NICE submissions in advanced NSCLC and accepted as appropriate for decision making by NICE

Factor	Assumption	Justification
Intervention	Tepotinib	Intervention being assessed in this appraisal
Comparators	Immunotherapy Chemotherapy Immunotherapy in combination with chemotherapy (untreated population)	Aligned with comparators included in NICE scope; Individual treatment regimens combined into treatment groups due to lack of individual treatment data for the METex14 skipping alterations NSCLC population (see Section B.2.9).
Time horizon	30 years	Lifetime horizon for the defined population. Given the starting mean age of 73 years, all patients have died by the end of the time horizon in all treatment arms.
Cycle length	7 days	Considered short enough to capture the various dosing regimens included in the model
Perspective	NHS and Personal Social Services	As per NICE reference case
Discount	3.5% for costs and benefits	As per NICE reference case
Source of utilities	Utilities derived from the VISION EQ-5D-5L data (mapped to 3L). Values from the published literature and from previous NSCLC submissions used in scenario analysis.	EQ-5D utilities collected from a relevant METex14 skipping alterations patient population and used to inform health specific states to the model.
Source of costs	From the published literature, from resource utilisation and costs used in previous NSCLC submissions.	These reflect resource utilisation and costs accepted in previous NSCLC NICE submissions.
Treatment waning effect	Not considered for tepotinib.	Tepotinib is given until progression therefore no treatment waning effects are included in the model for tepotinib. Treatment waning effects are not included for immunotherapies given the lack of clinical evidence and uncertainty within the METex14 skipping alterations population.
Subsequent therapy	Subsequent therapy following tepotinib and comparator treatments included in analysis	Subsequent treatments are costed as one-off costs when patients enter the 'progressed' health state based on distributions observed in VISION and the real-world cohort data.

Abbreviations: NSCLC, non-small-cell lung cancer

B.3.2.1. Patient population

The patient population considered in the model is in line with the proposed license, final NICE scope and population of the Phase II VISION study, that is, adult patients with advanced NSCLC harbouring METex14 skipping alterations. As per the proposed marketing authorisation, tepotinib covers all lines of treatment and histology groups, therefore the base case model analysis assumes a line agnostic population regardless of histology. Subgroup analysis results for untreated and previously treated patients are presented separately in

Section B.3.1. Inputs for these subgroups are presented in Appendix N. Subgroup by histology was not possible due to small patient numbers in histology groups other than adenocarcinoma in VISION (86.8% versus 13.3% for others). However, clinical experts confirmed that although squamous patients tend to not do as well on treatments as adenocarcinoma, the overall costs and outcomes are generalisable between histology groups. In addition, immunotherapies and chemotherapies are used within both squamous and non-squamous groups, therefore, the overall approach to modelling is unaffected (see Section B.3.2.3 for details of modelling comparators).

Baseline patient characteristics applied in the economic model are based on the VISION trial cohort for the base case (as shown in Table 33). For body surface area (BSA) and weight data there is an option to select just the European patients from the VISION, however the results are very similar to the full patient cohort (1.73m^2 and 65.9 kg for all patients versus 1.72 m^2 and 65.0 kg for European patients), therefore the full cohort has been used in the base case analysis.

Table 33: Baseline characteristics

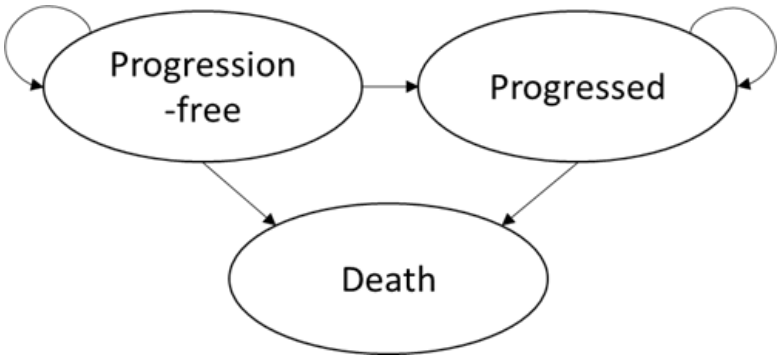
Characteristic	Mean	SD	Source
Age	73	8.97	VISION[121]
% female	47.7%	-	
BSA (m^2)	1.7	0.23	
Weight (kg)	65.9	14.09	

Abbreviations: BSA, body surface area; SD, standard deviation

B.3.2.2. Model structure

A *de novo* partitioned survival analysis was developed with a three-health state structure; progression-free, progressed and death. This structure revolves around the key secondary endpoints from VISION of OS and PFS and is consistent with the majority of previous NICE submissions in advanced NSCLC and accepted as appropriate for decision making by NICE.[72-77,79,163,164] In the model, patients start in the 'progression-free' health state and in each cycle can transition to 'progressed' or 'death' or remain 'progression-free'. Once a patient progresses, they can either remain progressed or transition to death per model cycle (Figure 28).

Figure 28: Model structure



The proportion of patients within each health state are based on OS and PFS curves and calculated as follows:

- Progression-free = PFS
- Progressed = OS - PFS
- Death = 1 - OS

The progression-free state was designed to capture the relatively higher health-related quality of life (HRQL) while disease is stable prior to progression. The model therefore captures the changes in HRQL between the progression-free and progressed states.

B.3.2.2.1. Time horizon and cycle length

A time horizon of 30 years was applied to cover a patient's lifetime. A cycle length of 7 days is used in the model as this is considered short enough to capture the various dosing regimens included within the model. Given the short cycle length, a half cycle correction is not included the economic model.

B.3.2.2.2. Discount and perspective

As per the NICE reference case, all health effects were measured in quality-adjusted life years (QALYs), a 3.5% discount rate was used for QALYs and costs, and the perspective is that of the NHS and Personal Social Services (PSS).

B.3.2.2.3. Sources of costs and utilities

Utilities for each health state are based on the observed EQ-5D data from VISION, with published literature and previous NSCLC submissions used in scenario analysis. All treatments are modelled in line with the current summary of product characteristics (SmPC),

and using ToT data or literature data to inform the proportion of patients on treatment per model cycle. Resource use costs are defined according to a patient's progression status and were based on frequencies used in previous NSCLC appraisals. Terminal care costs were applied as a one-off cost once a patient enters the 'death' heath state. Adverse event costs were calculated as one-off costs applied at the first cycle of the model using data from VISION for tepotinib and literature for the comparators.

B.3.2.2.4. Subsequent therapy

Subsequent treatments are costed as one-off costs when patients enter the 'progressed' health state based on distributions observed in VISION and the real-world cohort data. Scenarios exploring UK based distributions are also presented (Section B.3.8.3).

B.3.2.3. Intervention technology and comparators

In the model, tepotinib is dosed at 450 mg daily (equivalent to 500 mg of tepotinib hydrochloride hydrate) until disease progression or toxicity, in line with the proposed license and dose received in the VISION trial.[121,165]

The comparators included within the model are consistent with those listed within the NICE final scope.[166] However, given the lack of individual treatment data within a METex14 skipping alterations NSCLC population, comparator data is categorised into three treatment groups; immunotherapy, chemotherapy, and immunotherapy in combination with chemotherapy. As discussed in Section B.2.9, the immunotherapy and chemotherapy categories use the efficacy based on real-world cohort data. There were limited patient numbers within the real-world cohort data for the immunotherapy in combination with chemotherapy category. As such, hazard ratios reported in studies of immunotherapy in combination with chemotherapy are applied to the METex14 population chemotherapy data, and so used to create an estimation of what outcomes might be achieved in the METex14 skipping alterations population. As immunotherapy in combination with chemotherapy is only given as a first-line treatment in current practice, this comparator group is only considered within the untreated population presented in Appendix N, and not in the base case population.

Cost inputs are calculated by weighting each specific comparator included within each category. Pemetrexed maintenance is included as an option in the model after the chemotherapy plus platinum regimens and considered in scenario analysis. It was unclear if any patients from the real-world cohort data set were on pemetrexed maintenance, therefore

the proportion of patients who receive this treatment after the initial treatment is based on clinical opinion, and costs are only included in a scenario. The treatment mixes are informed by the efficacy data in the base case, with variations explored in scenario analysis informed by clinical opinion based on UK clinical practice. Table 34 presents the treatments within each category and the mixes used within the model in the base case and scenario. Treatments which were not considered part of UK clinical practice in the real-world cohort data were re-weighted to the other treatments (e.g., everolimus was redistributed between the included chemotherapy regimens and spartalizumab was redistributed between the included immunotherapy regimens).

Table 34: Comparator groups and treatment mixes

Category	Treatment	Real-world data (base case)	Clinical expert opinion (scenario)
Immunotherapy	Pembrolizumab	[redacted]	66.3%
	Atezolizumab	[redacted]	21.7%
	Nivolumab	[redacted]	12.0%
	Nivolumab + ipilimumab	[redacted]	0.0%
Chemotherapy	Docetaxel + platinum	[redacted]	1.0%
	Gemcitabine + platinum	[redacted]	23.1%
	Paclitaxel + platinum	[redacted]	10.2%
	Vinorelbine + platinum	[redacted]	18.2%
	Pemetrexed + platinum	[redacted]	9.8%
	Docetaxel monotherapy	[redacted]	11.7%
	Docetaxel + nintedanib	[redacted]	24.8%
	Docetaxel + gemcitabine [a]	[redacted]	0.0%
	Gemcitabine monotherapy [a]	[redacted]	0.6%
	Vinorelbine monotherapy [a]	[redacted]	0.6%

Notes: [a] These treatments were not listed within the NICE final scope however are included as they are incorporated within the efficacy and therefore costed for.

The approach to combine the individual treatment regimens within categories was driven by the availability of data for the METex14 skipping alterations NSCLC population. As discussed in Section B.2.9, comparing to clinical trials in wildtype NSCLC would be comparing different populations which would be difficult to interpret given the underlying heterogeneity and disease characteristics. Consequently, comparator data relied on studies using real-world retrospective studies in patients with METex14 skipping alterations. The grouping of treatments approach has been used in previous NICE submissions where the comparators are a mix of different treatments,[77,133-135] and was considered reasonable by clinical experts given the expectation of similar efficacy between treatment groups which is supported by the literature.[136-140]

Literature suggests there could be some efficacy difference between different immunotherapy in combination with chemotherapy treatments;[167] however, of the two combinations considered for the untreated population (pembrolizumab/pemetrexed/platinum and atezolizumab/bevacizumab/carboplatin/paclitaxel - see Appendix N), clinicians confirmed that the atezolizumab combination was used very little in clinical practice. As such, the potential efficacy differences between these treatments is negligible.

B.3.3. Clinical parameters and variables

Efficacy data from the VISION trial were used to inform OS, PFS and time on treatment (ToT) within the economic model for tepotinib using the Cohort A ITT population (N=151) from the latest VISION data cut (1 February 2021). As discussed in Section B.2.9, comparator data is categorised by treatment group; immunotherapy, and chemotherapy, with efficacy data taken from the real-world cohort data, which was weighted to align with VISION.

Survival modelling was required to inform the economic model, due to the specification of a lifetime horizon over which modelled costs and QALYs are required to be estimated. Parametric survival models (PSMs) were fitted to OS, PFS and ToT data using the exponential, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions to extrapolate outcomes over a lifetime horizon. If these were deemed to provide poor fits to the observed data, then flexible models i.e., splines or piece-wise models were considered.

The proportional hazards assumption between tepotinib and the comparators (immunotherapy of chemotherapy) was assessed, resulting in no clear evidence to support the assumption (see Appendix M). In addition, the fitting of dependent curves to the tepotinib data would mean the survival for tepotinib would differ between the comparison to chemotherapy and the comparison to immunotherapy, which was considered unrealistic. Therefore, independent models were fitted to all treatment groups in the economic model.

The selection of the most appropriate distribution has been made in accordance with NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[168] The approach taken is described below:

- Firstly, log cumulative hazard plots were produced to evaluate how the hazards change over time.

- Secondly, visual inspection and comparison of the Akaike information criterion (AIC) and Bayesian information criterion (BIC) were then used to compare which distributions provides the best fit to the KM data.

- Thirdly, expert validation was used to ensure the final extrapolated curve was clinically plausible at an advisory board with four clinical experts and two UK HTA experts (see Section B.3.2).

B.3.3.1. Overall survival

B.3.3.1.1. Tepotinib

Diagnostic plots were produced to assess the suitability of PSMs to model the tepotinib OS data. The plots are presented in Figure 29 and discussed in turn below.

Figure 29: Diagnostic plots - VISION OS (ITT)

Abbreviations: ITT, intention to treat; OS, overall survival; S(t), survivor function; t, time; Tep, tepotinib

Notes:

Plot A: An approximately straight line indicates that the survivor function is Weibull. If the gradient is approximately equal to 1, the survivor function is exponential.

Plot B: An approximately straight line indicates the survivor function is log-logistic.

Plot C: An approximately straight line indicates the survivor function is log-normal.

Plot D: Turning points indicate the need for parametric survival models that are able to reflect non-monotonic hazard functions. A maximum time point of 42 months was selected to calculate the smoothed hazard estimation within the R muhaz package.

A log-cumulative hazard plot (LCHP) was produced to assess the appropriateness of fitting exponential and Weibull PSMs that assume proportional hazards (Figure 29: A). The gradient of the curve in the LCHP appears to be both relatively constant over time and greater than 1, indicating that the gradient is steeper than that of an exponential PSM. The plot indicates a Weibull PSM may provide a good fit to the data with the approximately constant gradient; however, the interpretation of the LCHP is subjective and so no models were discounted from consideration.

To assess the suitability of a log-logistic PSM, the logit function of survival (the log-odds of the survivor function) can be plotted against the log of time. If approximately straight lines are observed, then a log-logistic PSM may provide a good fit to the data. Figure 29: B presents the logit survival plot with an approximately straight line observed for the OS VISION data, indicating that the log-logistic PSM may provide a good fit to the data.

To assess the suitability of a log-normal PSM, the inverse normal cumulative function applied to the probability of death over time may be plotted against the log of time. If approximately straight lines are observed, a log-normal PSM may provide a good fit to the data. Figure 29: C presents the inverse normal survival plot with an approximately straight line observed for the OS VISION data, indicating that the log-normal PSM may provide a good fit to the data.

The final assessment of the survivor data undertaken was the inspection of the smoothed hazard plot. A maximum time of 42 months was set when producing the smoothed hazard plot as hazard estimates are subject to substantial uncertainty and become unstable when the number of patients at risk is small. The smoothed hazard plot (Figure 29: D) demonstrated that the hazard of death does not appear to be constant overtime, suggesting an exponential model may not provide a good fit to the data. In addition, a clear turning point is visible on the plot, suggesting the Weibull or Gompertz models, which assume monotonic hazards (increasing or decreasing), may not provide a good fit to the data.

Based on the diagnostic plots, no specific parameterisations were ruled out. Consequently, a total of 6 OS extrapolations were available for use in the OS tepotinib treatment arm within the economic model.

To determine the most appropriate PSM for use in the base-case analysis, guidance from NICE TSD 14 was followed.[168] Following an inspection of the Kaplan-Meier curve for OS, and the assessment of the underlying hazard function, the following features of the fitted models were considered:

- Visual assessment: *does the parametric model provide a reasonable fit versus the Kaplan-Meier curve (within the time period over which data are available)?*

- Statistical goodness-of-fit: *does the parametric model yield an improved fit to the data relative to another model when considering its complexity (within the time period over which data are available)?*

- Long-term plausibility: *does the extrapolated portion of the model yield clinically realistic estimates of survival (beyond the time period over which data are available)?*

The statistical goodness-of-fit of all fitted PSMs is provided in Table 35. Based on the AIC and BIC scores, log-logistic and exponential models provided the best fit, however all models provided a reasonably similar fit to the data (within five points) and so were visually compared in order to select the base-case extrapolation (shown in Figure 30).

Table 35: Statistical goodness-of-fit scores - VISION OS (ITT)

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Exponential	745.8	748.8	5	1
Weibull	744.8	750.9	2	3
Gompertz	747.2	753.2	6	5
Log-logistic	743.5	749.6	1	2
Log-normal	744.9	750.9	3	4
Generalised-gamma	745.0	754.1	4	6

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; ITT, intention to treat; OS, overall survival.

Figure 30: Parametric curve fits – VISION OS (ITT)

Time (years)	0	1	2	3	4	5	6	7	8	9	10
Numbers at risk	151	91	22	6	1	0	0	0	0	0	0

Abbreviations: ITT, intention to treat; KM, Kaplan-Meier; OS, overall survival.

All curves appeared to fit the data reasonably well until around two years where some curves appear to overestimate the observed date. This is possibly due to overfitting to the tail of the Kaplan-Meier (caused by censoring) where very few patients remain at risk. Clinical experts consulted at an advisory board suggested that all curves could be plausible and noted that OS is hard to estimate due to interactions with subsequent therapy. However, they considered that the higher estimates (log-logistic and log-normal) seemed more plausible as they wouldn't expect tepotinib to perform any worse than immunotherapies and the other curves appeared too pessimistic in comparison. Therefore, based on clinical feedback and given log-logistic had the lowest AIC score, this was selected as the base case curve.

B.3.3.1.2. Comparators

Patient-level data from the real-world cohort data were weighted in an ITC to form a comparison between tepotinib and immunotherapy, and tepotinib and chemotherapy (see Section B.2.9).

As with the tepotinib data, a range of PSMs; exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma, were fitted to the weighted OS data from the real-world cohorts for immunotherapy and chemotherapy. Candidate PSMs were selected based on guidance from the NICE TSD 14,[168] with a series of hazard-based plots produced and described in turn below (Figure 31).

Figure 31: Diagnostic plots - Comparators OS (weighted)

Abbreviations: Chemo, chemotherapy; IO, immunotherapy; OS, overall survival; S(t), survivor function; t, time

Notes:

Plot A: An approximately straight line indicates that the survivor function is Weibull. If the gradient is approximately equal to 1, the survivor function is exponential.

Plot B: An approximately straight line indicates the survivor function is log-logistic.

Plot C: An approximately straight line indicates the survivor function is log-normal.

Plot D: Turning points indicate the need for parametric survival models that are able to reflect non-monotonic hazard functions. A maximum time point of 30 months was selected to calculate the smoothed hazard estimation within the R muhaz package.

A LCHP was produced to assess the appropriateness of fitting exponential and Weibull PSMs that assume proportional hazards (Figure 31:A). The gradient of the chemotherapy curve in the LCHP appears to be relatively constant over time and seems to be greater than one, indicating that the gradient is steeper than that of an exponential PSM. The plot indicates a Weibull PSM may provide a good fit to the chemotherapy data with the approximately constant gradient. The gradient of the immunotherapy curve appears relatively constant for the initial 3.5 years, with a slightly steeper gradient observed from that point until the end of follow up. This indicates non-linearity, therefore PSMs that assume PH may be inappropriate for consideration of the immunotherapy arm. The non-constant gradient of the curve indicates that both the Weibull and exponential PSMs are unlikely to provide a good fit to the immunotherapy data. However, for completeness, these PSMs were not discounted from consideration, as the interpretation of LCHP is subjective.

To assess the suitability of a log-logistic PSM, Figure 31:B presents the logit survival plot for the comparator OS data. An almost straight line is seen for the chemotherapy comparator indicating that the log-logistic PSM may provide a reasonable fit to the data. Conversely, the immunotherapy curve does not appear to be approximately straight over time, indicating that the log-logistic PSM is unlikely to provide a good fit to the data.

To assess the suitability of a log-normal PSM, Figure 31: C presents the inverse normal survival plot showing an approximately a straight line observed for the OS chemotherapy data, indicating that the log-normal PSM may provide a good fit to the data. As seen with the logit survival plot, the immunotherapy curve does not appear straight, therefore it is unlikely that the log-normal PSM will provide a reasonable fit to the immunotherapy OS data.

The final assessment of the comparator survivor data undertaken was the inspection of the smoothed hazard plot. A maximum time period of 30 months was set when producing the smoothed hazard plot as hazard estimates are subject to substantial uncertainty and become unstable when the number of patients at risk is small. The smoothed hazard plot (Figure 31:D) demonstrated that the hazard of death does not appear to be constant overtime for either comparator, suggesting an exponential model is unlikely to provide a good fit to the data. Both curves show turning points indicating that the underlying hazard function is not monotonic (either consistently increasing or decreasing), providing evidence to suggest that the Weibull and Gompertz models may provide a poor fit to the data. The immunotherapy arm in particular shows clear turning points indicating a more flexible model may be required to capture the OS for this comparator.

Based on the diagnostic plots, it is unlikely that the exponential, Weibull and Gompertz models will provide a good fit to either comparator, however, for completeness, no specific parameterisations were ruled out of the economic model. Consequently, a total of 6 OS extrapolations were available for use in the OS comparator treatment arms within the economic model.

The diagnostic plots indicated that the immunotherapy data is likely to require a more flexible model to capture overall survival, with two clear turning points observed in the smoothed hazard plot. Consequently, odds, hazard and normal restricted cubic spline models, varying from one to three knots, were fit to the immunotherapy data, in line with NICE TSD 21.[169] All spline models, in addition to the six parametric extrapolations, were available for use in the OS immunotherapy treatment arm within the economic model.

To determine the most appropriate PSMs for use in the base-case analysis, guidance from NICE TSD 14 was followed, as described for the tepotinib OS data.[168] The statistical goodness-of-fit of all fitted PSMs to the chemotherapy and immunotherapy OS data is provided in Table 36. Based on the AIC and BIC scores, the log-normal and generalised gamma models provided the best statistical fit to the chemotherapy data, with the log-logistic providing a reasonably similar fit (within five points). All PSMs were visually compared in order to select the base-case extrapolation (shown in Figure 32).

From the parametric models, the generalised gamma PSM provided the best statistical fit to the immunotherapy arm closely followed by the Weibull distribution with all other models providing a poor fit to the data. Figure 33 presents the visual fit of all PSMs, demonstrating the some of the curves provided unsuitable fit to the data. The spline model fits to the immunotherapy curve provided an improved statistical (Table 36) and visual fit, shown in Figure 34.

Table 36: Statistical goodness-of-fit scores - Comparators OS (weighted)

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Chemotherapy				
Exponential	840.8	843.0	4	4
Weibull	842.0	846.5	6	6
Gompertz	842.0	846.3	5	5
Log-logistic	832.6	837.0	3	3
Log-normal	828.2	832.6	2	1

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Generalised-gamma	827.9	834.5	1	2
Immunotherapy – parametric curves				
Exponential	754.9	756.8	3	3
Weibull	752.6	756.5	2	2
Gompertz	756.9	760.7	4	4
Log-logistic	761.1	765.0	5	5
Log-normal	765.5	769.4	6	6
Generalised-gamma	748.6	754.4	1	1
Immunotherapy – splines				
Odds 1 knot	757.7	763.5	9	9
Odds 2 knot	749.7	757.5	3	3
Odds 3 knot	751.8	761.5	6	7
Hazard 1 knot	752.9	758.7	7	4
Hazard 2 knot	749.2	757.0	2	2
Hazard 3 knot	751.4	761.0	5	6
Normal 1 knot	756.5	762.3	8	8
Normal 2 knot	748.6	756.3	1	1
Normal 3 knot	750.7	760.3	4	5

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

Figure 32: Parametric curve fits – Chemotherapy OS (weighted)

Time (years)	0	1	2	3	4	5	6	7	8	9	10
Numbers at risk	152	76	34	16	0	0	0	0	0	0	0

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

Figure 33: Parametric curve fits – Immunotherapy OS (weighted)

Time (years)	0	1	2	3	4	5	6	7	8	9	10
Numbers at risk	150	78	31	0	0	0	0	0	0	0	0

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

Figure 34: Spline curve fits – Immunotherapy OS (weighted)

Time (years)	0	1	2	3	4	5	6	7	8	9	10
Numbers at risk	150	78	31	0	0	0	0	0	0	0	0

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

The range of plausible curves were presented to clinical and HTA experts at the advisory board (see Section B.3.2), who considered the long-term estimates projected by the survival curves. For chemotherapy, it was agreed by the clinical experts at the advisory board that the expected survival at five years to be around 5%, although they expected some survival in the longer term. In TA683, the survival of the chemotherapy group for the untreated non-squamous NSCLC population was considered clinically plausible between 5% and 11% at five years.[164] At five years, only the Weibull and exponential projected within this range ([redacted]% and [redacted]%, respectively). Given that these METex14 skipping alteration patients are generally older and comprise of both untreated and previously treated, the expectation of survival at 5-years would be lower than the estimate provided in TA683 suggesting Weibull may be more plausible. Therefore, to better represent the longer-term outcomes, the Weibull curve was selected as the base case. The Weibull distribution gave the most clinically plausible estimate at five-years in comparison to the others which projected greater than 12% survival, however the survival is still considered to be over-estimated compared to clinical opinion and external validation (see Section B.3.8.7). It is important to remember the

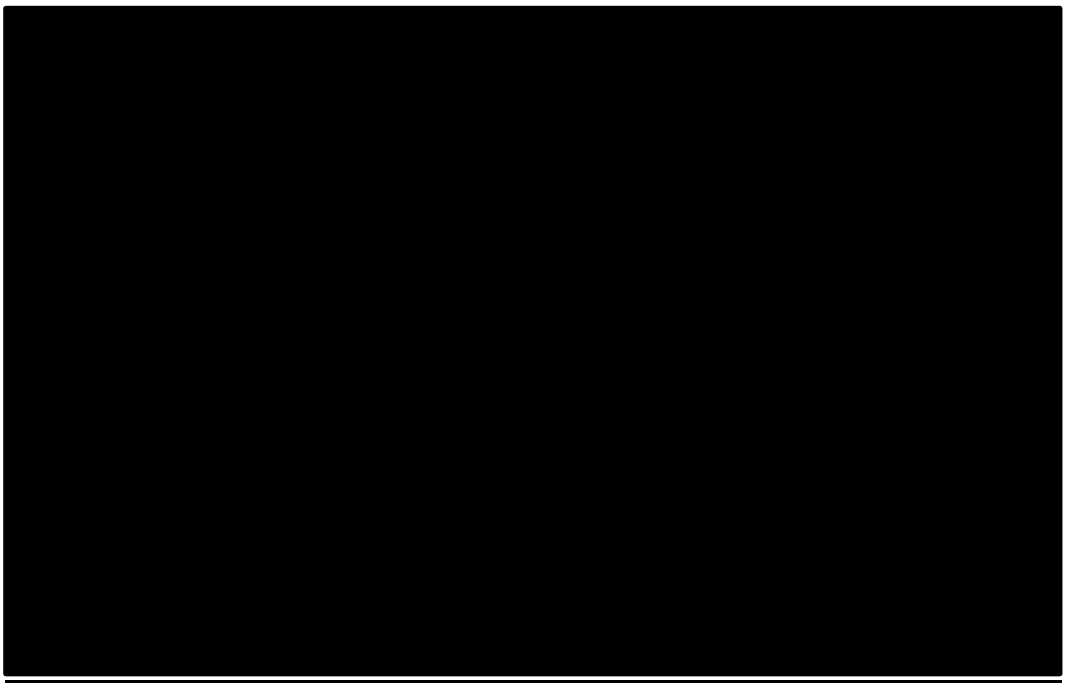
subsequent immunotherapy a large proportion of these patients received in the chemotherapy group.

For immunotherapy, the clinical experts believed the curves to underrepresent the plateau they would expect between five and eight years where fewer patients are expected to die if they have survived up to that time point when considering the wildtype NSCLC population. Spline one knot odds was considered to most realistically represent the long-term immunotherapy benefit but represents the most optimistic choice. Therefore, based on expert opinion and considering the poorer outcomes associated with METex14 skipping alteration patients, the one knot normal spline model was selected as the base case which is still considered one of the more optimistic options available to inform the immunotherapy survival but less so than the Spline one knot odds, to reflect the poorer outcomes in the MEtex14 skipping alterations population.

B.3.3.1.3. Base-case OS settings

The log-logistic, Weibull and one knot normal spline models were selected to inform the base-case OS extrapolations for tepotinib, chemotherapy and immunotherapy, respectively. These curves were validated against external sources for their appropriateness indicating that the choices for the comparators are quite optimistic compared to external sources and expected differences (see Section B.3.2). Alternative plausible survival extrapolations for tepotinib, immunotherapy and chemotherapy were explored within scenario analysis (detailed in Section B.3.8.3). The base case-curve fits are provided in Figure 35 and Figure 36.

Figure 35: Base-case OS extrapolations (VISION ITT, Chemotherapy)



Abbreviations: KM, Kaplan-Meier; ITT, intention to treat; OS, overall survival

Figure 36: Base-case OS extrapolations (VISION ITT, Immunotherapy)

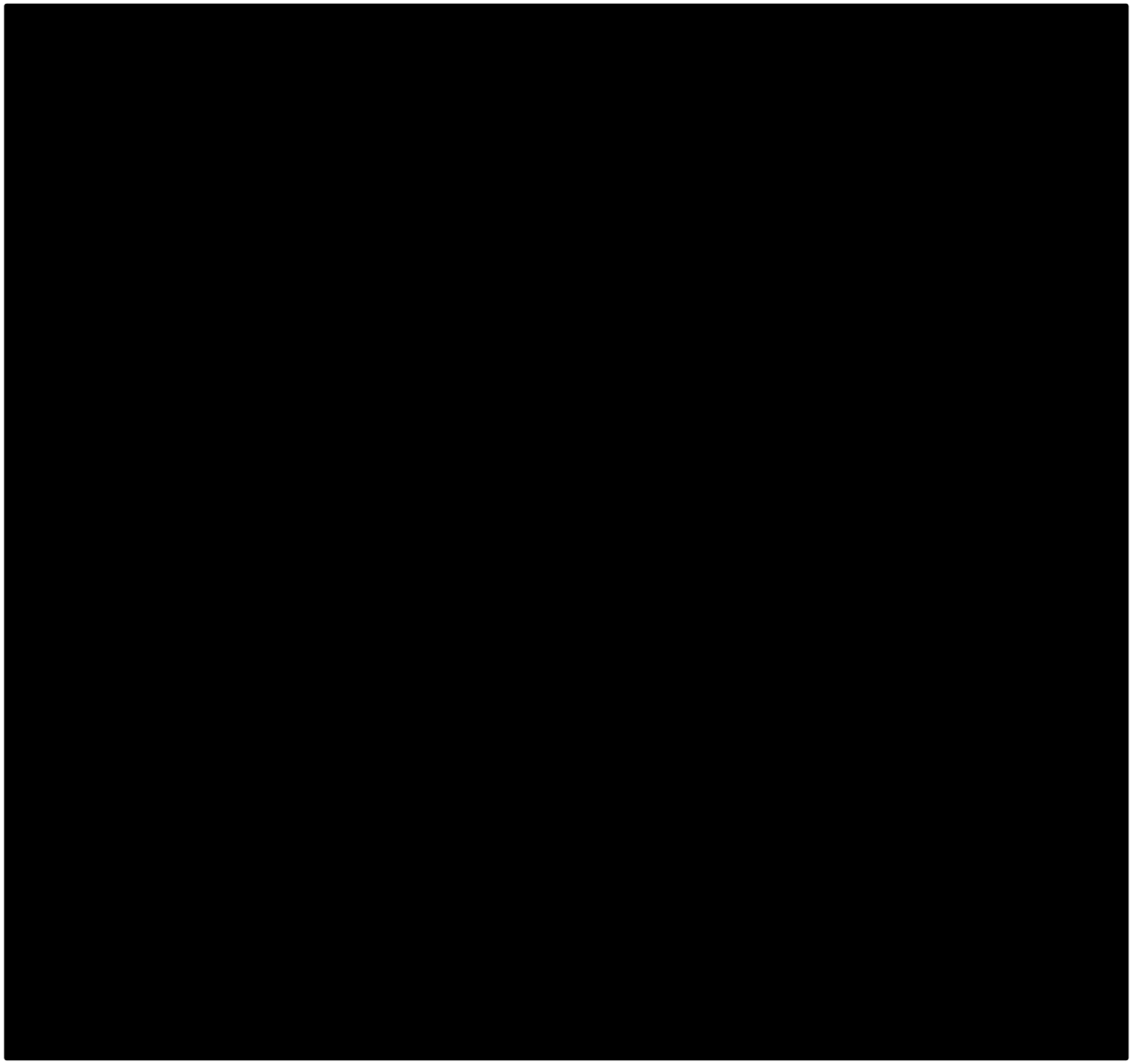
Abbreviations: KM, Kaplan-Meier; ITT, intention to treat; OS, overall survival

B.3.3.2. Progression-free survival

B.3.3.2.1. Tepotinib

PFS was a secondary endpoint of the VISION trial (defined as the time from first study treatment administration until the earlier of progressed disease or death).[121] Two definitions of progression are available within the VISION trial; independent review committee (IRC) or investigator assessment. As the PFS data collected for the comparators (from the real-world cohort data) was in the real-world setting, the investigator definition of progression in VISION is more likely to reflect the definition of PFS used for patients in the chemotherapy and immunotherapy arms. Therefore, the investigator definition of PFS from the VISION study is used in the cost-effectiveness analysis. Diagnostic plots were produced to assess the suitability of the PSMs to model the tepotinib PFS data. The plots are presented in Figure 37 and discussed in turn below.

Figure 37: Diagnostic plots – VISION PFS (ITT)



Abbreviations: ITT, intention to treat; PFS, progression free survival; S(t), survivor function; t, time; Tep, tepotinib

Notes:

Plot A: An approximately straight line indicates that the survivor function is Weibull. If the gradient is approximately equal to 1, the survivor function is exponential.

Plot B: An approximately straight line indicates the survivor function is log-logistic.

Plot C: An approximately straight line indicates the survivor function is log-normal.

Plot D: Turning points indicate the need for parametric survival models that are able to reflect non-monotonic hazard functions. A maximum time point of 42 months was selected to calculate the smoothed hazard estimation within the R muhaz package.

A LCHP was produced to assess the appropriateness of fitting exponential and Weibull PSMs that assume proportional hazards (Figure 37: A). The gradient of the curve in the

LCHP appears to be relatively constant over time, indicating that an exponential or Weibull PSM may provide a reasonable fit to the data.

To assess the suitability of a log-logistic PSM, Figure 37: B presents the logit survival plot for the VISION PFS data. A relatively straight line is seen for the PFS data indicating that the log-logistic PSM may provide a reasonable fit to the data, however, deviations are seen in the initial portion of the curve.

To assess the suitability of a log-normal PSM, Figure 37: C presents the inverse normal survival plot. An approximately straight line is observed for the VISION PFS data for the latter portion of the curve; however deviations are observed in the initial section. This indicates that the log-normal PSM may not provide a good fit to the data.

The final assessment of the PFS data undertaken was the inspection of the smoothed hazard plot. A maximum time of 42 months was set when producing the smoothed hazard plot as hazard estimates are subject to substantial uncertainty and become unstable when the number of patients at risk is small. The smoothed hazard plot (Figure 37: D) demonstrated that the hazard of death does not appear to be constant overtime for tepotinib PFS, suggesting an exponential model is unlikely to provide a good fit to the data. The curve appears to be monotonically decreasing (with the exception of a small turning point at approximately three to six months), providing evidence to suggest that the Weibull and Gompertz models may provide a reasonable fit to the data.

Based on the diagnostic plots, it is unlikely that the exponential model will provide a good fit to the tepotinib PFS data, however, for completeness, no specific parameterisations were ruled out of the economic model. Consequently, a total of six PFS extrapolations were available for use in the PFS tepotinib arm within the economic model.

To determine the most appropriate PSMs for use in the base-case analysis, guidance from NICE TSD 14 was followed, as detailed for the tepotinib OS data.[168] The statistical goodness-of-fit of all fitted PSMs to the tepotinib PFS data is provided in Table 37. Based on the AIC and BIC scores, the log-normal model provided the best statistical fit to the tepotinib PFS data, with the log-logistic and generalised gamma providing reasonably similar fits (within five points), and so were visually compared in order to select the base-case extrapolation (shown in Figure 38).

Table 37: Statistical goodness-of-fit scores - VISION PFS (ITT)

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Exponential	787.3	790.3	4	4
Weibull	788.9	794.9	6	6
Gompertz	787.3	793.3	5	5
Log-logistic	777.5	783.5	2	2
Log-normal	776.5	782.5	1	1
Generalised-gamma	778.4	787.4	3	3

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

Figure 38: Parametric curve fits – VISION PFS (ITT)

Time (years)	0	1	2	3	4	5	6	7	8	9	10
Numbers at risk	151	48	13	2	1	0	0	0	0	0	0

Abbreviations: KM, Kaplan-Meier; ITT, intention to treat; PFS, progression-free survival

The four clinical experts agreed that the curves predicting the higher estimates (log-logistic, log-normal, Gompertz and generalised gamma) provide the most plausible long-term estimates based on experience with other first-generation targeted treatments for EGFR, ALK or ROS1 driven NSCLC. Therefore, based on the assessment of visual fit, statistical goodness-of-fit and long-term plausibility, the log-normal model was chosen to inform the estimation of PFS for tepotinib.

B.3.3.2.2. Comparators

Patient-level data from the real-world cohort data were weighted in an ITC to form a comparison between tepotinib and immunotherapy, and tepotinib and chemotherapy (Section B.3.3.1.2). The weighted data were used to provide PFS estimates for each comparator.

Diagnostic plots were produced to assess the suitability of the PSMs to model the tepotinib OS data. The plots are presented in Figure 39 and discussed in turn below.

Figure 39: Diagnostic plots - Comparators PFS (weighted)

Abbreviations: Chemo, chemotherapy; IO, immunotherapy; PFS, progression free survival; S(t), survivor function; t, time

Notes:

Plot A: An approximately straight line indicates that the survivor function is Weibull. If the gradient is approximately equal to 1, the survivor function is exponential.

Plot B: An approximately straight line indicates the survivor function is log-logistic.
Plot C: An approximately straight line indicates the survivor function is log-normal.
Plot D: Turning points indicate the need for parametric survival models that are able to reflect non-monotonic hazard functions. A maximum time point of 12 months was selected to calculate the smoothed hazard estimation within the R muhaz package.

A LCHP was produced to assess the appropriateness of fitting exponential and Weibull PSMs that assume proportional hazards (Figure 39: A). The gradient of the chemotherapy curve in the LCHP appears to be relatively constant for the initial two years, with a deviation from the diagonal seen from here onwards. In addition, the immunotherapy curve does not appear to be constant over time. This indicates non-linearity for both treatment arms, therefore PSMs that assume PH may be inappropriate for in modelling the comparator PFS. The non-constant gradients of the curves indicate that both the Weibull and exponential PSMs are unlikely to provide a good fit to the data. However, for completeness, these PSMs were not discounted from consideration and included in the model, as the interpretation of LCHP is subjective.

To assess the suitability of a log-logistic PSM, Figure 39: B presents the logit survival plot for the comparator PFS data. Neither curve appears to be approximately straight over time, particularly the immunotherapy curve, indicating that a log-logistic PSM is unlikely to provide a good fit to the PFS data for the comparators.

To assess the suitability of a log-normal PSM, Figure 39: C presents the inverse normal survival plot. Similar to the logit survival plot, neither curve appears approximately straight, therefore it is unlikely that a log-normal PSM will provide a reasonable fit to the PFS data.

The final assessment of the comparator survivor data was the inspection of the smoothed hazard plot. A maximum time period of 12 months was set when producing the smoothed hazard plot as hazard estimates are subject to substantial uncertainty and become unstable when the number of patients at risk is small. The smoothed hazard plot (Figure 39: D) demonstrated that the hazard of death does not appear to be constant overtime for either comparator, suggesting an exponential model is unlikely to provide a good fit to the data. The chemotherapy curve appears to be monotonically decreasing over time after 3 months, suggesting a Weibull or Gompertz PSM may provide a reasonable fit to the data. The immunotherapy curve show turning points indicating that the underlying hazard function is not monotonic (either consistently increasing or decreasing), providing evidence to suggest that the Weibull and Gompertz models may provide a poor fit to the data.

Based on the diagnostic plots, it is unlikely a PSM will provide a good fit to either comparator; however, for completeness, no specific parameterisations were ruled out of the

economic model. Consequently, a total of six PFS extrapolations were available for use in the comparator treatment arms within the economic model.

The diagnostic plots indicated that the comparator data is likely to require a more flexible model to capture PFS. Consequently, odds, hazard and normal restricted cubic spline models, varying from one to three knots, were fitted to the data, in line with NICE TSD 21.[169] Not all spline models converged to the data, with the two- and three-knot models unable to converge for the immunotherapy data and the two-knot and three-knot hazard models unable to converge for the chemotherapy arm. While splines provided reasonable visual fits to the immunotherapy PFS data, given the extremely poor fits of the single parametric curves, piecewise models were fitted to the data, using the Kaplan-Meier until 3.2 months and parametric extrapolations from there onwards. The cut-off time of 3.2 months was selected based on two factors; a) median PFS was 3.2 months allowing enough information in the remining data set to fit parametric curves, and b) the shape of the smoothed hazard plot becomes more constant over time following the turning point around 3.2 months (Figure 39: D). The piecewise models provided a much-improved visual fit to the data and were included as options in the economic model.

To determine the most appropriate models for use in the base-case analysis, guidance from NICE TSD14 was followed, as described for the tepotinib OS data.[168] The statistical goodness-of-fit of all fitted PSMs and splines to the chemotherapy PFS data and piecewise models and splines fitted to the immunotherapy PFS data, are provided in Table 38. Based on the AIC and BIC scores, the three-knot odds spline model provided the best statistical fit to the chemotherapy data, with all other models providing a worse fit (>5 points). All PSMs and converging spline models were visually compared in order to select the base-case extrapolation (shown in Figure 40 and Figure 41). The log-logistic, and log-normal and models show a poor visual fit to the chemotherapy PFS curve, with neither model capable of fully capturing the shape of the Kaplan-Meier. The splines presented in Figure 40 display an improved visual fit, providing a range of reasonable extrapolations to choose from.

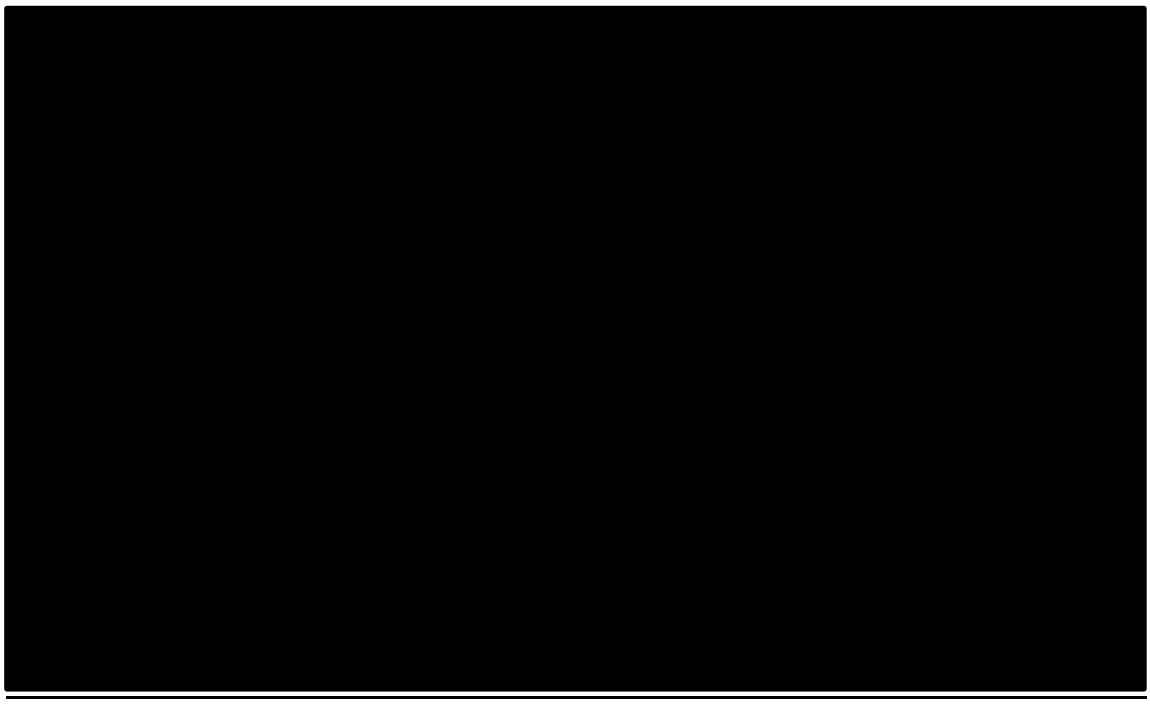
For the immunotherapy PFS data, the log-logistic piecewise model provided the best statistical fit to the data, with all other piecewise models excluding the Weibull and Gompertz, producing reasonably good fits (within five points). None of the spline models appeared to provide good visual fit, therefore just the piecewise parametric models were visually compared in order to select the base-case extrapolation (Figure 42).

Table 38: Statistical goodness-of-fit scores - Comparators PFS (weighted)

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Chemotherapy – parametric curves				
Exponential	831.1	833.3	5	5
Weibull	793.6	798.0	3	2
Gompertz	792.3	796.7	1	1
Log-logistic	811.2	815.5	4	4
Log-normal	920.7	925.0	6	6
Generalised-gamma	792.7	799.3	2	3
Chemotherapy – splines				
Odds 1 knot	739.2	745.7	2	2
Odds 2 knot	762.0	770.8	4	5
Odds 3 knot	726.2	737.2	1	1
Hazard 1 knot	764.2	770.8	5	4
Normal 1 knot	771.1	777.7	6	6
Normal 2 knot	780.1	788.9	7	7
Normal 3 knot	741.2	752.2	3	3
Immunotherapy – piece-wise parametric curves				
Exponential	380.8	381.9	5	4
Weibull	382.3	384.6	6	6
Gompertz	379.1	381.4	3	3
Log-logistic	376.3	378.6	1	1
Log-normal	377.3	379.6	2	2
Generalised-gamma	379.3	382.7	4	5
Immunotherapy – splines				
Odds 1 knot	265.5	271.2	2	2
Hazard 1 knot	241.3	247.0	1	1
Normal 1 knot	267.1	272.8	3	3

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

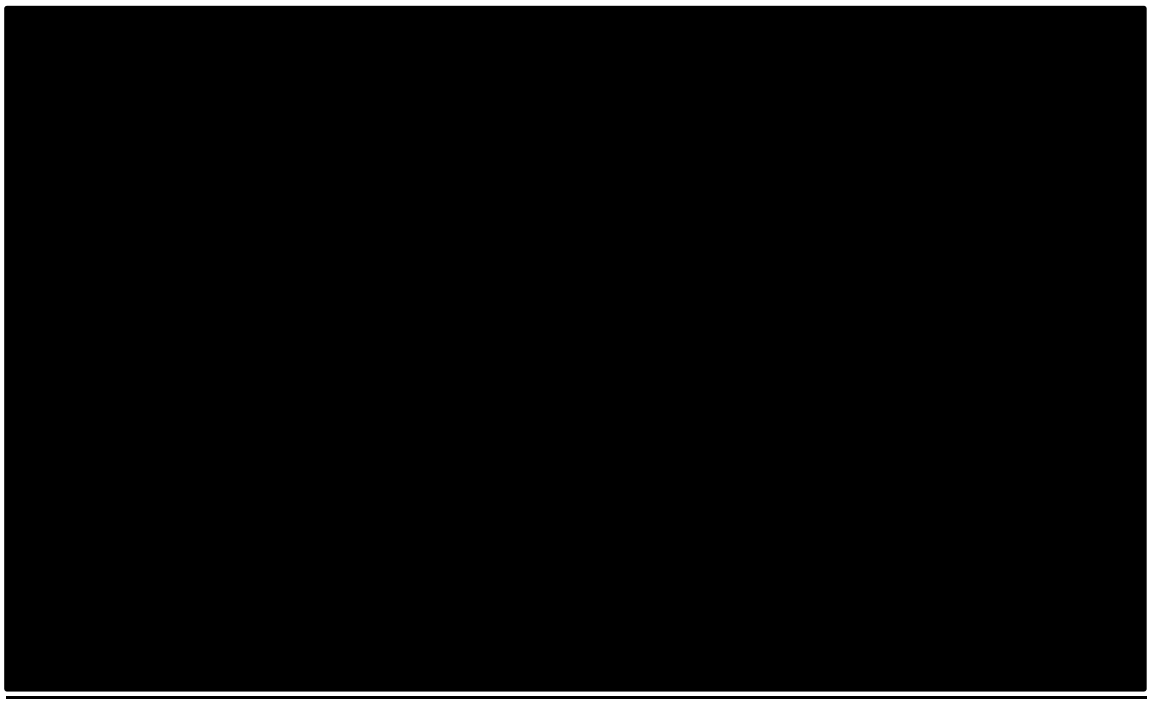
Figure 40: Parametric curve fits – Chemotherapy PFS (weighted)



Time (years)	0	1	2	3	4	5	6	7	8	9	10
Numbers at risk	152	24	8	6	0	0	0	0	0	0	0

Abbreviations KM, Kaplan-Meier; PFS, progression free survival.

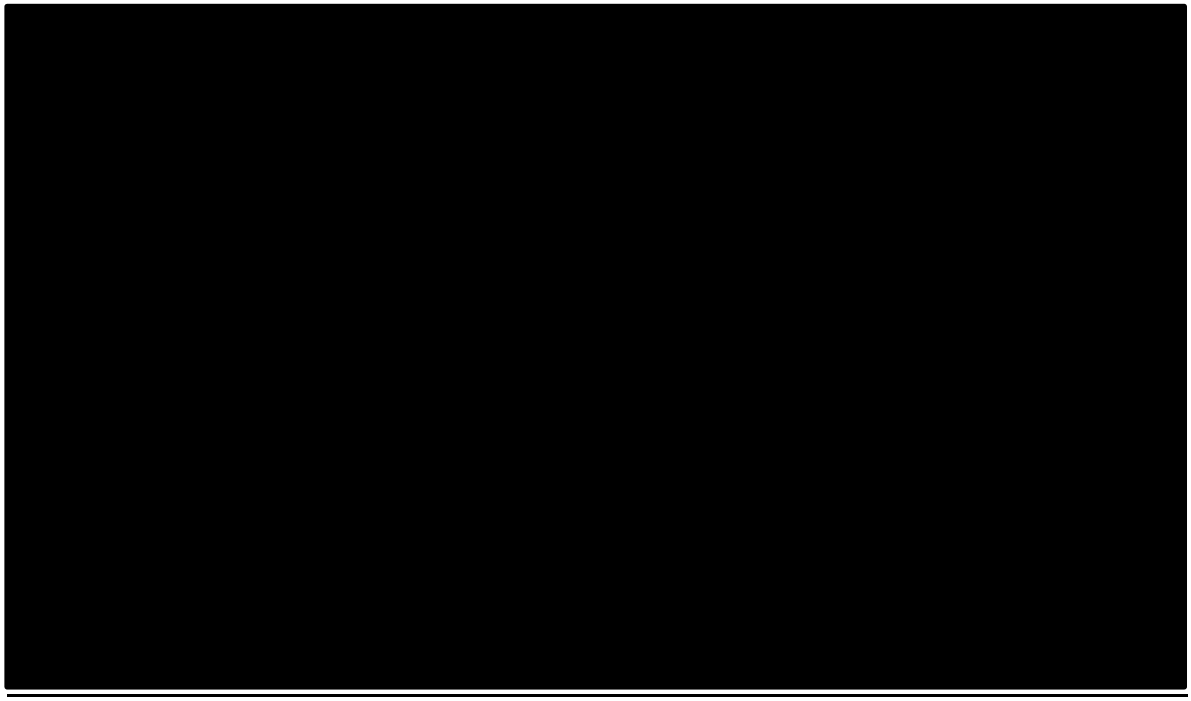
Figure 41: Spline curve fits – Chemotherapy PFS (weighted)



Time (years)	0	1	2	3	4	5	6	7	8	9	10
Numbers at risk	152	24	8	6	0	0	0	0	0	0	0

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

Figure 42: Parametric curve fits (piece-wise) – Immunotherapy OS (weighted)



Time (years)	0	1	2	3	4	5	6	7	8	9	10
Numbers at risk	146	32	15	0	0	0	0	0	0	0	0

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

For the chemotherapy arm, clinical experts stated that it was reasonable to assume a very small proportion of patients would be progression-free in the long-term, as one or two patients will always be longer-term survivors. They agreed that 1% seemed a reasonable estimate at five-years, which left the Weibull, one knot odds, two knot odds and two knot normal as plausible options. Based on visual fit and AIC/BIC, the one knot odds spline model was selected as the base case for the chemotherapy arm.

For immunotherapies, clinical experts expected between 1-4% to be progression-free at around five-years, leaving the piece-wise exponential, generalised gamma, log-logistic and Weibull as options. Therefore, based on the clinical feedback and AIC/BIC, the piece-wise log-logistic was taken forward as the base case for the immunotherapy arm.

B.3.3.2.3. Base-case PFS settings

The log-normal, one knot odds spline and piece-wise log-logistic models were selected to inform the base-case PFS extrapolations for tepotinib, chemotherapy and immunotherapy, respectively. These curves were validated against external sources for their appropriateness

(see Section B.3.2). Alternative plausible PFS extrapolations for tepotinib, immunotherapy and chemotherapy were explored within scenario analysis (detailed in Section B.3.8.3). The base case-curve fits are provided in Figure 43.

Figure 43: Base-case PFS extrapolations (VISION ITT, Chemotherapy)

Abbreviations: KM, Kaplan-Meier; ITT, intention to treat; PFS, progression-free survival

Figure 44: Base-case PFS extrapolations (VISION ITT, Immunotherapy)

Abbreviations: KM, Kaplan-Meier; ITT, intention to treat; PFS, progression-free survival

B.3.3.3. Time on treatment

B.3.3.3.1. Tepotinib

To estimate the proportion of patients on tepotinib per cycle, time-on-treatment (ToT) data from VISION was utilised. Kaplan-Meier data was estimated and extrapolated using parametric survival curves.

Table 39 presents the AIC and BIC goodness-of-fit statistics for the ToT extrapolations. The exponential model appears to provide the best fit to the data with the second smallest AIC and smallest BIC values. The log-logistic model also arguably provides a reasonable fit to the data based on the criteria though the values are fairly close suggesting that all curves provide a statistically reasonable fit. The parametric model fits to the ToT data is presented in Figure 45. All models show a reasonable fit to the data, particularly in the initial 16 months. Between 16 and 24 months the extrapolations overestimate the time on treatment observed in the KM estimates however, this is likely due to the models attempting to compensate for the long plateau observed in the latter portion of the KM (due to heavy censoring).

Table 39: AIC and BIC – ToT – tepotinib (VISION)

Model	Goodness-of-fit		Rank	
	AIC	BIC	AIC	BIC
Exponential	932.5	935.5	3	1
Weibull	934.3	940.4	5	4
Gompertz	933.0	939.1	4	3
Log-logistic	929.8	935.8	1	2
Log-normal	937.5	943.5	6	6
Generalised gamma	932.2	941.3	2	5

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ToT, time on treatment

Figure 45: ToT parametric curves for tepotinib

Time (years)	0	1	2	3	4	5	6	7	8	9	10
N at risk (censored)	151	52	11	4	1	0	0	0	0	0	0

Abbreviations: KM, Kaplan-Meier; ToT, time on treatment

The models provide fairly different predictions of ToT with the exponential providing a more conservative estimate than the log-logistic and log-normal models. Clinical expert opinion suggests that most patients would be expected to be off treatment at around five years. The clinical input indicates that the log-logistic and log-normal models may provide a greater estimate of ToT than would be expected, and that the other four models provide a more

realistic projection of ToT. Clinical input also indicated that in practice there are usually one or two patients who would remain responsive to treatment and remain on treatment for a long period of time however, most will have stopped treatment by five years. Therefore, based on clinical opinion, the generalised gamma PSM has been selected as the base case. Other plausible parametric curves are explored in scenario analysis (see Section B.3.8.3).

B.3.3.3.2. Comparators

ToT data was limited from the real-world data cohort therefore the model includes several options to estimate the proportion of patients on treatment per cycle for the comparators.

- Option 1: ToT estimated using literature data and extrapolated assuming an exponential distribution
- Option 2: Assume ToT = PFS
- Option 3: Estimate a ToT curve using the estimated difference between ToT and PFS from VISION ($HR_{PFS\ vs\ ToT}$: 0.82, 95% CI: 0.63 – 1.07).

All options described are limited as they are not representative of the actual duration of treatment matching the efficacy used for PFS and OS. However, given that different treatments have different durations, option 1 allows for these differences to be captured and therefore used in the base case. The other options are tested in scenario analysis (see Section B.3.8.3). For all ToT options, maximum treatment durations are accounted for to ensure the ToT are capped at these timepoints (presented in Table 52).

Median or mean duration of treatment was sourced from the literature and extrapolated assuming an exponential distribution, this may not be appropriate for some treatments however does allow for some estimation of treatment duration to be included in the model. In some cases, this resulted in the proportion of patients on treatment to be greater than those who are progression-free. Most treatments will be treated until progression or maximum treatment duration, but in some cases patients may be taken off treatment due other reasons such as toxicity. As such, ToT would be expected to be similar but slightly lower than the estimated PFS. Therefore, ToT is capped at PFS to ensure no one is on treatment after they progress. Table 40 presents the mean or median duration of treatment used to model the comparator ToT. The resulting curves after assuming exponential and capping at PFS are presented in Appendix O.

Table 40: Mean or median duration of treatment

Treatment	Drug	Value - months	Type	Source
IO monotherapy	Pembrolizumab - 1L	7.9	Median	TA531[77]
	Pembrolizumab - 2L+	5.4	Mean	TA428[74]
	Atezolizumab	3.4	Median	TA520[76]
	Nivolumab - non squamous	5.8	Mean	TA484[75]
	Nivolumab - squamous	6.1	Mean	TA483[170]
Nivolumab/ ipilimumab	Nivolumab	6.2	Median	Hellmann et al, 2020[171]
	Ipilimumab	4.1	Median	
Docetaxel/ platinum	Docetaxel	4.1	Median	Fossella et al 2003[172]
	Cisplatin	4.1	Median	
	Carboplatin	4.1	Median	
Gemcitabine/ platinum	Gemcitabine	3.4	Median	Scagliotti et al, 2008[173]
	Cisplatin	3.4	Median	
	Carboplatin	3.4	Median	
Paclitaxel/ platinum	Paclitaxel	3.4	Median	Sandler et al, 2006[174]
	Cisplatin	3.4	Median	
	Carboplatin	3.4	Median	
Vinorelbine/ platinum	Vinorelbine	2.8	Median	Fossella et al 2003[172]
	Cisplatin	2.8	Median	
	Carboplatin	2.8	Median	
Pemetrexed/ platinum	Pemetrexed	8.1	Median	Gadgeel et al, 2020[175]
	Cisplatin	3.4	Median	
	Carboplatin	3.4	Median	
Docetaxel monotherapy	Docetaxel	3.2	Mean	TA428[74]
Docetaxel/ nintedanib	Docetaxel	5.0	Median	TA347[72]
	Nintedanib	4.2	Median	
Docetaxel/ gemcitabine	Docetaxel	4.1	Median	Casal et al, 2007[176]
	Gemcitabine	4.1	Median	
Vinorelbine monotherapy	Vinorelbine	1.6	Median	Kang et al, 2019[177]
Pemetrexed maintenance	Pemetrexed	7.9	Mean	TA402[73]
Pembrolizumab/ pemetrexed/ platinum [a]	Pembrolizumab	13.40	Mean	Gadgeel et al, 2021[175]
	Pemetrexed	11.20	Mean	
	Cisplatin	3.60	Mean	
	Carboplatin	3.60	Mean	
Atezolizumab/ bevacizumab/	Atezolizumab	9.70	Mean	TA584[79]
	Bevacizumab	8.40	Mean	

Treatment	Drug	Value - months	Type	Source
carboplatin/ paclitaxel [a]	Carboplatin	2.20	Median	Socinski et al, 2018[178]
	Paclitaxel	2.20	Median	

Abbreviations: 1L, first-line; 2L+, second-line plus; IO, immunotherapy
Notes: [a] Immunotherapies in combination with chemotherapies are included as a comparator for the untreated population, presented in Appendix N.

B.3.3.4. Summary

Table 41 summarises the base case setting for each of the clinical parameters.

Table 41: Clinical parameter summary

Outcome	Tepotinib	Chemotherapy	Immunotherapy
OS	Log-logistic	Weibull	1 knot normal spline
PFS	Log-normal	1 knot odds spline	Piece-wise log-logistic
ToT	Generalised gamma	Mean/median duration from the literature	

Abbreviations: OS, overall survival; PFS, progression-free survival; ToT, time on treatment

B.3.3.5. Safety

Adverse events of treatments were included to account for the additional costs incurred due to treatment toxicities. Grade ≥3 adverse events with incidence of greater than 5% in either VISION or any of the comparators was included within the economic model. Five percent was selected as this cut-off ensured that all the important adverse events were costed whilst enabling the list of adverse events to be consolidated to a reasonable amount.

Adverse events for tepotinib were taken from the VISION study. Due to the lack of safety data within the data sets used to inform the comparator efficacy, adverse events for the individual treatment regimens were included from either previous NSCLC appraisals or published literature. The overall adverse event incidences were calculated using the treatment weightings presented in Table 34. For pembrolizumab, adverse events are available for both the untreated and previously treated populations, therefore for the population considering all patients, these adverse events are weighted based on the untreated and previously treated split in the VISION trial (45.7% versus 54.3%, respectively). Similarly, for nivolumab, adverse events are available for both the non-squamous and squamous populations, therefore the overall adverse events for nivolumab were split using the non-squamous versus squamous split in the VISION trial (9.3% versus 90.7%, respectively).

The incidence of the adverse events used in the base case is summarised in Table 42 and Table 43. A constraint of relying on adverse events from the literature is the limited reporting on certain adverse events, compared to tepotinib where all adverse events reported from VISION can be included. As such, this approach is conservative given the expectation of an improved safety profile of tepotinib compared to chemotherapies and immunotherapies. Another limitation is the reliance of the comparator adverse events being based on the wider NSCLC population as it is unclear how adverse events would differ for the METex14 skipping alteration patient group.

Table 42: Grade ≥3 adverse event incidence – immunotherapies ± chemotherapy

Adverse event	Tepotinib	Pembrolizumab		Atezolizumab	Nivolumab		Pembrolizumab/ pemetrexed/ platinum	Atezolizumab/ bevacizumab/ carboplatin/ paclitaxel	Nivolumab/ ipilimumab
		Untreated	Previously treated		Non-squamous	Squamous			
Alanine aminotransferase) increase	[redacted]				0.3%				
Alopecia									
Amylase increase	[redacted]								
Anaemia	[redacted]	4.5%	0.9%	0.5%			18.3%	6.8%	1.4%
Asthenia	[redacted]	0.6%	0.3%		3.5%		6.7%		1.4%
Bilirubin increased								4.3%	
Cardiac failure	[redacted]								
Cough	[redacted]						0.0%		
Diarrhoea	[redacted]	6.5% [a]	3.5% [a]		1.0%		5.2%	3.0%	1.7%
Dyspnoea	[redacted]	1.9%			4.9%		4.2%		
Fatigue	[redacted]	1.3%	1.2%	1.7%	3.1%	0.8%	6.9%	3.3%	1.7%
Febrile neutropenia								10.3%	
Hyperglycaemia	[redacted]	2.6%			2.4%				
Hypertension	[redacted]							7.5%	
Hypoalbuminemia	[redacted]								
Hypomagnesemia	[redacted]								
Infection	[redacted]	0.6%							
Leukopenia	[redacted]					0.8%		2.0%	
Lipase increase	[redacted]								
Lymphocyte count decrease	[redacted]								
Nausea	[redacted]		0.3%				3.5%	4.0%	0.5%
Neuromotor									

Adverse event	Tepotinib	Pembrolizumab		Atezolizumab	Nivolumab		Pembrolizumab/ pemetrexed/ platinum	Atezolizumab/ bevacizumab/ carboplatin/ paclitaxel	Nivolumab/ ipilimumab
		Untreated	Previously treated		Non-squamous	Squamous			
Neurosensory									
Neutropenia	[redacted]			0.4%	0.3%		16.0%	16.5%	
Neutrophil count decrease								14.8%	
Oedema peripheral/other	[redacted]	0.6%					0.5%		
Pain	[redacted]	1.2%			2.1%		1.5%		
Platelet count decrease								5.8%	
Pleural effusion	[redacted]	3.9%							
Pneumonitis / pneumonia	[redacted]	4.5%		0.5%	3.5%	0.8%	3.0%		
Pulmonary/ respiratory tract infection	[redacted]			0.2%					
Thrombocytopenia							8.4%	4.8%	
Vomiting	[redacted]	0.6%					4.0%		0.3%
White blood cell count decrease								4.3%	
Source	VISION[121]	TA531[77]	TA428[74]	TA520[76]	TA484[75]	TA483[170]	Gadgeel et al, 2020[175]	TA584[79]	Hellmann et al, 2020[171]

Note:
a For pembrolizumab, the reported incidence for diarrhoea was Grade ≥2

Table 43: Grade ≥3 adverse event incidence - chemotherapies

Adverse event	Tepotinib	Docetaxel/ platinum	Gemcitabine/ platinum	Paclitaxel/ platinum	Vinorelbine/ platinum	Docetaxel monotherapy	Docetaxel/ nintedanib	Docetaxel/ gemcitabine	Vinorelbine monotherapy	Pemetrexed/ platinum	Pemetrexed maintenance
Alanine aminotransferase increase	[redacted]		3.0%				10.3 %				0.3%
Alopecia		1.0%	1.0%			0.6%			1.0%	15.8%	
Amylase increase	[redacted]										
Anaemia	[redacted]	7.0%	25.0%		25.0%	1.6%	2.5%	2.5%			6.4%
Asthenia	[redacted]	12.0%			14.0%	1.9%		20.0%	5.0%	3.5%	
Bilirubin increased						3.2%	15.9 %		5.0%		
Cardiac failure	[redacted]							7.5%			
Cough	[redacted]							7.5%			
Diarrhoea	[redacted]	7.0%	4.0%		3.0%	8.1% [a]	34.1 % [a]	5.0%	1.0%	3.0%	0.3%
Dyspnoea	[redacted]		7.0%						2.0%	5.0%	
Fatigue	[redacted]			13.0%		3.6%	2.2%			3.5%	4.7%
Febrile neutropenia				2.0%		4.9%	7.2%	5.0%			1.9%
Hyperglycaemia	[redacted]		6.0%								
Hypertension	[redacted]		1.0%	0.7%							
Hypoalbuminemia	[redacted]										
Hypomagnesemia	[redacted]		7.0%								
Infection	[redacted]	8.0%	5.0%	3.0%	8.0%		6.6%				
Leukopenia	[redacted]		46.0%					2.5%			2.2%
Lipase increase	[redacted]										

Adverse event	Tepotinib	Docetaxel/ platinum	Gemcitabine/ platinum	Paclitaxel/ platinum	Vinorelbine/ platinum	Docetaxel monotherapy	Docetaxel/ nintedanib	Docetaxel/ gemcitabine	Vinorelbine monotherapy	Pemetrexed/ platinum	Pemetrexed maintenance
Lymphocyte count decrease	[redacted]		43.0%								
Nausea	[redacted]	10.0%	27.0%		17.0%	0.3%	1.5%	7.5%	1.0%	8.0%	0.6%
Neuromotor		3.0%	12.0%		6.0%			2.5%			
Neurosensory		4.0%	12.0%		4.0%						0.3%
Neutropenia	[redacted]	74.0%	57.0%	17.0%	78.0%	12.3%	9.1%	27.5%		12.4%	5.8%
Neutrophil count decrease						6.1%					
Oedema peripheral/other	[redacted]										
Pain	[redacted]	1.0%		1.0%	1.0%			12.5%	1.0%	2.0%	1.1%
Platelet count decrease											
Pleural effusion	[redacted]	2.0%			2.0%						
Pneumonitis / pneumonia	[redacted]			3.0%						2.0%	
Pulmonary/ respiratory tract infection	[redacted]							22.5%			
Thrombocytopenia		3.0%	50.0%		4.0%		1.3%	5.0%		6.9%	1.9%
Vomiting	[redacted]	8.0%	23.0%		16.0%	0.6%		2.5%	1.0%	3.0%	0.3%
White blood cell count decrease						3.2%	15.9 %				
Source	VISION[1] [21]	Docetaxel prescribing information [179]	Gemcitabine prescribing label[180]	AVASTIN prescribing information [181]	Docetaxel prescribing information [179]	TA428[7] [4]	TA347 [72]	Casal et al 2007[176]	Vinorelbine prescribing information [182]	Scagliotti et al, 2008[173]	Paz-Ares et al 2013[183]

Note:
a For docetaxel and docetaxel + nintedanib, the reported incidence for diarrhoea was Grade ≥2.

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

In the VISION trial, the EQ-5D-5L, EORTC-QLQ-C30 and EORTC QLQ-LC13 questionnaires were administered to patients to measure HRQL. The questionnaires were to be completed every six weeks from Cycle 1, Day 1 until nine months and every 12 weeks thereafter until disease progression, death or withdrawal of consent. Following progression, questionnaires were continued up to 30 days.

A crosswalk algorithm by van Hout et al. (2012)[184] was used to map the EQ-5D-5L data to EQ-5D-3L responses, and utility values as recommended by NICE.[185] The "eq5dcw" function from the "eq5d" R package was used to obtain the utility values. To estimate EQ-5D utilities, complete responses of all five dimensions from the EQ-5D questionnaire (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) were required.

In total, 973 EQ-5D-5L observations were available from 150 of the 151 patients. Of these, 808 were recorded in the progression-free health state with the remaining 165 recorded post-progression (defined by investigator).

A tabulated summary of the EQ-5D utility values by progression status is provided in Table 44. This table does not account for repeated measures for individual patients (i.e., patients who are progression-free for longer having multiple observations), and so should be interpreted with caution.

Table 44: Summary of utility values by progression status

Health state	Number of patients	Number of observations	Mean	Median
Pre-progression	150	808	0.732	0.767
Post-progression	101	165	0.694	0.735

Linear mixed model (LMM) regressions were fitted to the utility data to support the interpretation of changes in utility according to progression status. The use of LMM enables dependencies within the data (i.e., correlated repeated measurements within patients) to be accounted for when demonstrating the overall mean pattern of change over time. Three regression models were considered:

1. Utility ~ progression

2. Utility ~ progression + baseline observation

3. Utility ~ progression + baseline observation + treatment line

An overview of the statistical goodness-of-fit for each regression is provided in Table 45. AIC and BIC values were used to assess the quality of the model fit. The results of the LMM regressions are provided in Table 46.

Table 45: Statistical goodness-of-fit for LMM regressions

Model	AIC	BIC
1 (progression)	-570.39	-550.87
2 (progression + baseline observation)	-594.99	-570.59
3 (progression + baseline observation + treatment line)	-593.33	-564.05

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayesian Information Criteria

Table 46: LMM regressions output

Coefficient	Value	SE	p-value
Model 1 (progression)			
Progression-free	0.6985	0.0166	<0.001
Post-progression	-0.0656	0.0142	<0.001
Model 2 (progression + baseline observation)			
Progression-free	0.7180	0.0168	<0.001
Post-progression	-0.0817	0.0143	<0.001
Baseline observation	-0.0781	0.0150	<0.001
Model 3 (progression + baseline observation + treatment line)			
Progression-free	0.7077	0.0243	<0.001
Post-progression	-0.0818	0.0143	<0.001
Baseline observation	-0.0782	0.0150	<0.001
Previously treated	0.0191	0.0323	0.5566

Abbreviation: SE, standard error

The inclusion of baseline observation as a covariate was found to improve the model fit (Table 45) and was found to be a statistically significant predictor of utility (indicated by the p-values in Table 46). The inclusion of treatment line (defined as untreated or previously treated) as a covariate did not improve the model fit (Table 45), nor was it found to be a significant predictor of utility, (p-value: 0.5566). Therefore, Model 2 (progression + baseline observation) was selected for inclusion within the cost-effectiveness model. The utility values utilised within the economic model are presented in Table 47.

Table 47: Model utility values

Health state	Mean utility
Pre-progression	0.7180
Post-progression	0.6363

B.3.4.2. Mapping

HRQL was collected using the EQ-5D-5L questionnaire in the VISION study with a crosswalk used to establish EQ-5D-3L responses to derive utility as per the NICE reference case. As such, no mapping techniques were required.

B.3.4.3. Health-related quality-of-life studies

An SLR of published literature was conducted to identify all relevant utility studies for patients with advanced NSCLC harbouring METex14 skipping alterations. No published HRQL studies were identified in the literature for NSCLC patients harbouring METex14 with the exception of those reported from VISION at baseline (see Appendix H).

In order to provide context of utility values of patients with advanced NSCLC, a targeted literature search was conducted to identify reported outcomes in previous NICE submissions for the comparator treatments listed within the final scope (further details are provided in Appendix G). Of the reported HRQL values used within the previous NICE submissions, the utilities for progression-free and progressed were taken forward for the economic model to use within scenario analysis.

- Nafees et al. (2008) is a study reporting health-related quality of life estimates for patients with metastatic NSCLC on second-line treatment.[186] Members of the general public were asked to complete the Visual Analogue Scale (VAS) and standard gamble of health states describing metastatic NSCLC looking at varying progression status and toxicities. This study has been used in many previous NSCLC submissions to inform their health state utility values[71,187] or included in scenario analysis.

- Chouaid et al. (2013) study has also been used in previous NSCLC submissions.[79,188] The study prospectively measured health states in advanced NSCLC with 263 patients from 25 centres including the UK using EQ-5D and EQ-VAS. The other values from previous submissions were mainly based on the data collected from their

pivotal trials with a couple differing based on the final appraisal committee preferences (Table 48).

The utility values for untreated group ranged from 0.85 to 0.71 for the progression-free health state and 0.74 to 0.67 for the progressed state. For the second-line and previously treated values, these ranged from 0.75 to 0.62 and 0.69 to 0.46 for the progression-free and progressed health state, respectively. The VISION utility values (presented in Table 47), sit between the ranges presented in the literature, though there would be an expectation of worse values compared to the untreated group and more in line with the previously treated group. However, the literature value ranges overlap between the untreated and previously treated values and overlap between the progression-free and progressed values, therefore interpretation of the most appropriate 'reference' is unclear. The literature sources are from different NSCLC populations, with generally younger patients compared to METex14 patients and in wildtype NSCLC therefore direct comparison with the values from VISION is not necessarily appropriate. However, this does show that the values derived from VISION are in line with the expected values for patients with NSCLC and clinical experts at the advisory board confirmed that the utilities from VISION appeared reasonable for this patient group.

Table 48: HRQL studies used in previous NSCLC NICE submissions

Source	Utility value (SE)	
	Progression-free	**Progression**
Nafees et al. (2008)[186] (2L)	0.67	0.47
Chouaid et al. (2013)[188]		
1L	0.71 (0.24)	0.67 (0.20)
2L	0.74 (0.18)	0.59 (0.34)
3L/4L	0.62 (0.29)	0.46 (0.38)
TA584[79] – Atezolizumab in combination (1L)		
IMPower	0.71	0.69
TA531[77] – Pembrolizumab (1L) (PD-L1>50%, 1L)	0.85	0.74
Keynote 024		
TA428[74] – Pembrolizumab (PD-L1>50%, 2L+)		
Keynote 010	0.75	0.66
TA484[75] – Nivolumab (non-squamous 2L+)		
CheckMate 057	0.74 (0.23)	0.69 (0.30)
Committee preference	0.71	0.57
TA655[163] – Nivolumab (squamous 2L+)		
CheckMate 017	0.75 (0.23)	0.59 (0.32)
Committee preference	0.69	0.51

Abbreviations: 1L, first-line (untreated); 2L, second-line; 2L+, previously treated; 3L/4L, third/fourth line; HRQL, health-related quality of life; NSCLC, non-small cell lung cancer; SE, standard error

B.3.4.4. Adverse reactions

The impact of Grade ≥3 adverse events on HRQL was explored in the cost-effectiveness analysis. Utility decrements for each of the adverse events included in the analysis (described in Table 42 and Table 43) were sourced from the literature or from previous NSCLC appraisals. Adverse event utility decrements are applied in the model for the expected duration of each adverse event, the data for which were sourced from the VISION study. When an adverse event duration could not be estimated from VISION, the duration was assumed to be the mean of the available duration estimates from VISION or sourced from other NSCLC appraisals. The disutility and expected duration are presented in Table 49.

Table 49: Disutilities of adverse events

Adverse event	Disutility	Duration (days)	Source for disutility	Source for duration
ALT increase	-0.050	54.8	Assumption based on TA347[72]	VISION[121]
Alopecia	-0.045	37.2	Nafees et al. (2008)[186]	Assumed based on mean duration of all AEs in VISION[121]
Amylase increase	-0.050	76.0	Assumed same as ALT increase	VISION[121]
Anaemia	-0.073	3.0	Assumed same as fatigue as per TA181	VISION[121]
Asthenia	-0.073	52.0	Assumed same as fatigue	VISION[121]
Bilirubin increased	-0.050	37.2	Assumed same as ALT increase	Assumed based on mean duration of all AEs in VISION[121]
Cardiac failure	-0.105	9.5	McMurray et al, 2018)[189]	VISION[121]
Cough	-0.046	22.0	Doyle et al. (2008)[190]	VISION[121]
Diarrhoea	-0.047	3.0	Nafees et al. (2008)[186]	VISION[121]
Dyspnoea	-0.050	18.8	Doyle et al. (2008)[190]	VISION[121]
Fatigue	-0.073	212.0	Nafees et al. (2008)[186]	VISION[121]
Febrile neutropenia	-0.090	7.1	Nafees et al. (2008)[186]	TA628[191]
Hyperglycaemia	-0.122	1.0	Palmer et al. (2016)[192] (Currie et al. (2006)[193]	VISION[121]

Adverse event	Disutility	Duration (days)	Source for disutility	Source for duration
Hypertension	-0.030	150.0	Paracha et al. (2018)[194] (Nafees et al. 2016[195])	VISION[121]
Hypoalbuminemia	-0.050	344.1	Assumed same as white blood cell decrease	VISION[121]
Hypomagnesemia	-0.0028	7.0	CADTH 2020[196]	VISION[121]
Infection	-0.050	15.0	Assumption based on TA347[72]	VISION[121]
Leukopenia	-0.090	200.0	Assumed same as neutropenia as per TA520[76]	VISION[121]
Lipase increase	-0.073	38.2	Assumed same as anaemia	VISION[121]
Lymphocyte count decrease	-0.05	46.0	Assumed same as white blood cell decrease	VISION[121]
Nausea	-0.048	10.5	Nafees et al. (2008)[186]	VISION[121]
Neuromotor	-0.150	37.2	Tabberer et al. 2006[197]	Assumed based on mean duration of all AEs in VISION[121]
Neurosensory	-0.150	37.2	Tabberer et al. 2006[197]	Assumed based on mean duration of all AEs in VISION[121]
Neutropenia	-0.090	158.0	Nafees et al. (2008)[186]	VISION[121]
Neutrophil count decrease	-0.090	2.5	Assumed same as neutropenia	TA628[191]
Oedema peripheral/other	-0.085	180.9	Hagiwara et al. (2018)[198]	VISION[121]
Pain	-0.069	31.0	Doyle et al. (2008)[190]	VISION[121]
Platelet count decrease	-0.050	37.2	Assumed same as white blood cell count decrease	Assumed based on mean duration of all AEs in VISION[121]
Pleural effusion	-0.008	125.1	Assumed same as pneumonia	VISION[121]
Pneumonitis / pneumonia	-0.008	19.6	Marti et al. (2013)[199] as per TA655[163] and TA520[76]	VISION[121]
Pulmonary/respiratory tract infection	-0.186	33.9	Hunter et al. (2015)[200] as per TA520[134]	VISION[121]
Thrombocytopenia	-0.003	37.2	Handorf et al. (2012)[201]	Assumed based on mean duration of all AEs in VISION[121]
Vomiting	-0.048	2.0	Nafees et al. (2008)[186]	VISION[121]

Adverse event	Disutility	Duration (days)	Source for disutility	Source for duration
White blood cell count decrease	-0.050	37.2	Assumption based on TA347[72]	Assumed based on mean duration of all AEs in VISION[121]

Abbreviations: AEs, adverse events; ALT: Alanine aminotransferase

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

For the base case, utilities derived from VISION have been used to directly inform the health states in the model for all treatments, with values from the literature and previous NSCLC NICE appraisals tested in scenario analyses (see Table 48). The values derived from VISION are based directly on a relevant METex14 patient population and measure the health states as per the economic model using EQ-5D.

Age-related utility decrements have also been included in the model base case to account for the natural decline in quality of life associated with age. This was done by estimating the utility values of the general population at each age and creating a utility multiplier based upon the algorithm by Ara and Brazier, 2010.[202] This multiplier is applied in each cycle throughout the model time horizon. The algorithm used to estimate the multiplier is shown below:

$$General\ population\ utility\ value = 0.9508566 + 0.0212126 \times male - 0.0002587 \times age - 0.0000332 \times age^2$$

Table 50 summarises the utility values used in the base case analysis.

Table 50: Summary of utility values for cost-effectiveness analysis

Health state	Utility value	Reference in submission (section and page number)	Justification
Progression-free	0.719	Section B.3.4.1, Page 162	EQ-5D values derived from a relevant METex14 patient population
Progressed	0.638		
ALT increase	-0.050	Section B.3.4.4, Page 166	Identified through targeted literature search and based on values used in previous NSCLC appraisals or assumed equivalent
Alopecia	-0.045		
Amylase increase	-0.050		
Anaemia	-0.073		
Asthenia	-0.073		
Bilirubin increased	-0.050		

Health state	Utility value	Reference in submission (section and page number)	Justification
Cardiac failure	-0.105		to a similar adverse event
Cough	-0.046		
Diarrhoea	-0.047		
Dyspnoea	-0.050		
Fatigue	-0.073		
Febrile neutropenia	-0.090		
Hyperglycaemia	-0.122		
Hypertension	-0.030		
Hypoalbuminemia	-0.050		
Hypomagnesemia	-0.003		
Infection	-0.050		
Leukopenia	-0.090		
Lipase increase	-0.073		
Lymphocyte count decrease	-0.05		
Nausea	-0.048		
Neuromotor	-0.150		
Neurosensory	-0.150		
Neutropenia	-0.090		
Neutrophil count decrease	-0.090		
Oedema peripheral/other	-0.085		
Pain	-0.069		
Platelet count decrease	-0.050		
Pleural effusion	-0.008		
Pneumonitis/ pneumonia	-0.008		
Pulmonary/ respiratory tract infection	-0.186		
Thrombocytopenia	-0.003		
Vomiting	-0.048		
White blood cell count decrease	-0.050		

B.3.5. Cost and healthcare resource use identification, measurement and valuation

In line with the NICE reference case, the perspective on costs is that of the NHS and PSS in England. An SLR for health care resource use and cost data relevant to this submission is reported in Appendix I.

B.3.5.1. Intervention and comparators' costs and resource use

B.3.5.1.1. Drug acquisition costs

The unit drug costs for each treatment included within the cost-effectiveness analysis and its source are summarised in Table 51. The majority of the unit drug costs are sourced from the British National Formulary (BNF) with some sourced from the drugs and pharmaceutical electronic market information tool (eMIT). If multiple options were available for each size, the lowest cost per size was taken forward and included in the model. Tepotinib incorporates a confidential discount of [redacted]. As the discounts of the other treatments are unknown, no discounts are applied.

Table 51: Unit costs of each treatment

Treatment	Size	Cost	Source
Tepotinib	60 x 250 mg tablets [a]	[redacted]	Merck
Pembrolizumab	1 x 100 mg vial	£2,630.00	BNF 2021[203]
Nivolumab	1 x 40 mg vial	£439.00	BNF 2021[203]
	1 x 100 mg vial	£1,097.00	
	1 x 240 mg vial	£2,633.00	
Atezolizumab	1 x 1200 mg vial	£3,807.69	BNF 2021[203]
	1 x 840 mg vial	£2,665.38	
Bevacizumab	1 x 100 mg vial	£218.39	BNF 2021[203]
	1 x 400 mg vial	£831.96	
Carboplatin	1 x 150 mg vial	£6.03	eMIT 2021[204]
	1 x 450 mg vial	£13.76	
	1 x 50 mg vial	£3.37	
	1 x 600 mg vial	£24.11	
Cisplatin	1 x 100 mg vial	£8.73	eMIT 2021[204]
	1 x 50 mg vial	£5.38	
Docetaxel	1 x 160 mg vial	£17.95	eMIT 2021[204]
	1 x 20 mg vial	£3.77	
	1 x 80 mg vial	£9.13	
Nintedanib	60 x 100 mg tablets	£2,151.10	BNF 2021[203]
	120 x 100 mg tablets	£2,151.10	
	60 x 150 mg tablets	£2,151.10	
Paclitaxel	1 x 100 mg vial	£7.22	eMIT 2021[204]
	1 x 150 mg vial	£12.41	
	1 x 300 mg vial	£17.66	
	1 x 30 mg vial	£4.41	
Pemetrexed	1 x 100 mg vial	£125.00	BNF 2021[203]
	1 x 500 mg vial	£450.00	
Vinorelbine	1 x 10 mg vial	£29.00	BNF 2021[203]

Treatment	Size	Cost	Source
	1 x 50 mg vial	£139.00	
Gemcitabine	1 x 200 mg vial	£6.40	BNF 2021[203]
	1 x 1600 mg vial	£140.00	
	1 x 2000 mg vial	£26.86	
	1 x 2200 mg vial	£200.00	
Ipilimumab	1 x 200 mg vial	£15,000.00	BNF 2021[203]
	1 x 50 mg vial	£3,750.00	
Crizotinib [b]	60 x 200 mg tablets	£4,689.00	BNF 2021[203]
	60 x 250 mg tablets	£4,689.00	
Brigatinib [b]	28 x 30mg tablets	£1,225.00	BNF 2021[203]
	28 x 90 mg tablets	£3,675.00	
	28 x 180 mg tablets	£4,900.00	

Abbreviations: PAS, patient access scheme; BNF, British National Formulary; eMIT, electronic market information tool
Note: [a] Each pack contains 250mg tablets of tepotinib hydrochloride hydrate equivalent to 225mg of tepotinib.
[b] Drug costs used as subsequent therapies only

The dosing schedule for each treatment was taken from the treatments summary of product characteristics (SmPC). If it was unclear what dose is used for NSCLC patients from the SmPC, alternative sources using published trials or specific NHS dosing for lung cancer was used (see Table 52). Treatment stopping rules are included based on SmPC or NICE guidance. Where guidance suggests 4 to 6 cycles for some chemotherapy regimens, the maximum of 6 cycles has been assumed.

Tepotinib is dosed as 450 mg daily (equivalent to 500 mg of tepotinib hydrochloride hydrate). In the draft SmPC (Appendix C), tepotinib can be reduced to 225 mg (one tablet daily, equivalent to 250 mg tepotinib hydrochloride hydrate) in the case of adverse events of grade ≥ 3, or temporary interruption can also be considered. In the VISION study, dose reductions were allowed for patients with adverse events. In those cases of dose reductions in VISION, doses were reduced to 300mg tepotinib hydrochloride hydrate daily though further reductions were subject to case-by-case decisions. To account for dose reductions, missed doses and treatment interruptions, the relative dose intensity from VISION has been incorporated in the base case. The dose reductions allowed in the VISION study differ to the expected use in clinical practice, however given that dose reductions and interruptions can still be considered, the impact is expected to be similar. Dose intensity was also included for the comparators to account for missing doses or reductions in some treatments, sourced from the literature.

For treatments dependent on patients' BSA or weight, patient-level data from VISION are used with the method of moments technique to calculate the average number of vials that would be required to satisfy one administration of treatment.[205] The method of moments first

derives a log-normal distribution for the patient BSA or weight within the study based upon the mean and standard deviation measured at baseline. It then uses the log-normal distribution to predict what proportion of patients requires each number of vials to administer the required dose. This method assumes that patients only receive whole vials (no vial sharing), and thus accounts for drug wastage. The number of vials needed per administration per patient weight is calculated based on the possible vial combinations of multiple vial sizes. All the possible vial combinations (up to five vials) and their respective doses were calculated; where there were more than one of the same dose, only the cheaper of the options was carried forward. An alternative method is included within scenario analysis using the minimum cost per mg for each treatment (i.e., excluding wastage). For oral therapies, to account for wastage the model calculates when a new pack is required then it is costed for accordingly. If patients come off treatment before the next pack, the cost of the full pack is still costed for.

Carboplatin uses an area under the concentration-versus-time curve (AUC) technique to estimate the dosage.[206] This is calculated as:

$$Dose\ (mg) = Target\ AUC\ \times\ [GFR\ ml/\min + 25]$$

The global filtration rate (GFR) was calculated using the patient-level data from VISION using the Cockcroft and Gault formula:[207]

$$GFR = sex\ \times \frac{140 - age}{Serum\ Creatinine} \times \frac{Weight}{72}$$

Patient's serum creatinine level was assumed to be 0.93 mg/dL based on the mid-range of the typical serum creatinine levels for males and females.[208]

Table 52 presents the treatment regimens with the dosing schedules, dose intensity and cost per treatment cycle. Some comparator treatments may have patient access schemes, however as these are confidential, no discounts are applied.

Table 52: Dosing schedules and cost per dose for each treatment regimen

Treatment regimen	Drug	Dose	Max duration	Dose intensity	Cost per dose/pack	Dosing source	Dose intensity source
Tepotinib		500 mg once daily	-	[redacted]	[redacted]	VISION[121]	VISION[121]
IO monotherapy	Pembrolizumab	200 mg Q3W	2 years	99.2%	£5,218.45	KEYTRUDA SmPC[165]	TA531[77]
	Atezolizumab	1,200 mg Q3W	2 years	97.7%	£3,720.11	Tecentriq SmPC[209]	TA520[76]
	Nivolumab	240 mg Q2W	2 years	99.2%	£2,612.20	OPDIVO SmPC[210]	Assumed same as pembrolizumab
Nivolumab/ ipilimumab	Nivolumab	360 mg Q3W	-	99.2%	£4,136.06	Hellmann et al. (2020)[171]	Assumed same as pembrolizumab
	Ipilimumab	1 mg/kg Q6W	-	99.2%	£7,085.85	Hellmann et al. (2020)[171]	
Docetaxel/ platinum	Docetaxel	75 m^2 Q3W	6 cycles	94.0%	£17.70	Docetaxel SmPC (2021)[211]; NHS (2017)[212]	Fossella et al. (2003)[172]
	Cisplatin	75 m^2 Q3W	6 cycles	94.0%	£13.50	Docetaxel SmPC (2021)[211]; NHS (2017)[212]	
	Carboplatin	AUC 5 Q3W	6 cycles	93.0%	£12.79	NHS (2017)[212]	
Gemcitabine/ platinum	Gemcitabine	1,250 mg/m^2 Q3W day 1 and 8	4 cycles	85.8%	£39.38	Gemcitabine SmPC;[213] NHS (2017)[212]	Scagliotti et al. (2008)[173]
	Cisplatin	80 m^2 Q3W	4 cycles	93.5%	£13.92	Gemcitabine SmPC;[213] NHS (2017)[212]	
	Carboplatin	AUC 5 Q3W	4 cycles	93.5%	£12.86	NHS (2017)[212]	
Paclitaxel/ platinum	Paclitaxel	175 mg/m^2 Q3W	4 cycles	94.0%	£24.89	Paclitaxel SmPC[214]	[206]Assumed same as docetaxel + platinum
	Cisplatin	80 mg/m^2 Q3W	4 cycles	94.0%	£14.00	Paclitaxel SmPC[214]	
	Carboplatin	AUC 5 Q3W	4 cycles	93.0%	£12.79	Carboplatin SmPC	
Vinorelbine/ platinum	Vinorelbine	25 mg/m^2 day 1 and 8 Q3W	4 cycles	78.0%	£105.81	NHS (2017)[212]	Fossella et al. (2003)[172]
	Cisplatin	80 mg/m^2 Q3W	4 cycles	78.0%	£11.61	NHS (2017)[212]	
	Carboplatin	AUC 5 Q3W	4 cycles	78.0%	£10.73	NHS (2017)[212]	

Treatment regimen	Drug	Dose	Max duration	Dose intensity	Cost per dose/pack	Dosing source	Dose intensity source
Docetaxel monotherapy	Docetaxel	75 m^2 Q3W	6 cycles	98.7%	£18.59	Docetaxel SmPC (2021)[211]; NHS (2017)[212]	TA347[72]
Docetaxel/ nintedanib	Docetaxel	75 m^2 Q3W	-	98.1%	£18.47	Docetaxel SmPC (2021)[211]; NHS (2017)[212]	TA347[72]
	Nintedanib	200 mg twice daily days 2-21 Q3W	-	91.2%	£1,961.80	Nintedanib SmPC	
Docetaxel/ gemcitabine	Docetaxel	75 m^2 Q3W day 8	6 cycles	98.0%	£18.45	Casal et al. (2007)[176]	Casal et al. (2007)[176]
	Gemcitabine	1,000 mg/m^2 Q3W day 1 and 8	6 cycles	98.0%	£101.33	Casal et al. (2007)[176]	
Vinorelbine monotherapy	Vinorelbine	30 mg/m^2 day 1 and 8 Q3W	4 cycles	93.0%	£147.98	NHS (2017)[212]	Kang et al. (2019)[177]
Pemetrexed/ platinum	Pemetrexed	500 mg/m^2 Q3W	4 cycles	94.8%	£859.98	NHS (2017)[212]	Scagliotti et al. (2008)[173]
	Cisplatin	75 m^2 Q3W	4 cycles	95.0%	£13.65	NHS (2017)[212]	
	Carboplatin	AUC 5 Q3W	4 cycles	95.0%	£13.07	NHS (2017)[212]	
Pemetrexed maintenance	Pemetrexed	500 mg/m^2 Q3W	-	93.7%	£850.00	Alimta SmPC[215]	Paz-Ares et al. (2013)[183]
Pembrolizumab/ pemetrexed/ platinum [a]	Pembrolizumab	200 mg Q3W	2 years	95.6%	£5,028.56	KEYTRUDA SmPC;[165] Gandhi et al. (2018)[216] (KEYNOTE-089)	TA683[164]
	Pemetrexed	500 mg/m^2 Q3W	-	95.6%	£867.24	Alimta SmPC;[215] Gandhi et al. (2018)[216] (KEYNOTE-089)	
	Cisplatin	75 m^2 Q3W	4 cycles	95.6%	£13.73	Alimta SmPC;[215] Gandhi et al. (2018)[216] (KEYNOTE-089)	
	Carboplatin	400 mg/m^2 Q3W	4 cycles	95.6%	£24.53	Carboplatin SmPC;[206] Gandhi et al. (2018)[216] (KEYNOTE-089)	
Atezolizumab/ bevacizumab/	Atezolizumab	1,200 mg Q3W	2 years	94.0%	£3,579.23	Tecentriq SmPC;[209] Socinski et al. (2018)[178] (IMPower150)	TA584[79]

Treatment regimen	Drug	Dose	Max duration	Dose intensity	Cost per dose/pack	Dosing source	Dose intensity source
carboplatin/ paclitaxel [a]	Bevacizumab	15 mg/kg Q3W	2 years	93.8%	£2,040.65	AVASTIN SmPC; Socinski et al 2018 (IMPower150)	
	Carboplatin	AUC 6 Q3W	4 cycles	93.8%	£19.22	Tecentriq SmPC;[209] Socinski et al. (2018)[178] (IMPower150)	
	Paclitaxel	200 mg/m^2 Q3W	4 cycles	93.8%	£27.26	Tecentriq SmPC;[209] Socinski et al. (2018)[178] (IMPower150)	

Abbreviations: AUC, area under the concentration versus time curve; PAS, patient access scheme; Q2W, every two weeks, Q3W, every 3 weeks; Q6W, every 6 weeks; SmPC, summary of product characteristics

Notes: [a] Immunotherapies in combination with chemotherapies are included as a comparator for the untreated population, presented in Appendix N.

For platinum regimens, the split between carboplatin and cisplatin was based on the real-world cohort data which showed that of the patients having platinum therapy, 84.4% were on carboplatin. This split is applied to all platinum-based regimens and in line with clinical expert opinion who estimated that approximately 80-90% of patients have carboplatin over cisplatin. In scenario analysis, pemetrexed maintenance treatment is applied to some patients after they complete four cycles of chemotherapy (docetaxel, vinorelbine, paclitaxel, gemcitabine or pemetrexed) plus platinum treatment in line with the JMEN study.[217] It this scenario, it is assumed that 50% of patients who finish chemotherapy plus platinum go onto pemetrexed maintenance treatment based on clinician expert opinion.

B.3.5.1.2. Administration costs

Treatment administration costs are based on NHS reference costs 19/20[218] in line with the HRG codes from the National Tariff Chemotherapy Regimens List 17/18.[219] These are also consistent with previous NSCLC appraisals. For some chemotherapy with platinum regimens requiring multiple administrations per cycle (e.g., gemcitabine), a separate administration cost is applied to that dose where chemotherapy is given alone without platinum (e.g., on Day 8). Different administration costs are given for cisplatin and carboplatin based on the National Tariff Chemotherapy Regimens List 17/18, therefore the overall administration cost is weighted based on the estimated proportion of patients receiving cisplatin versus carboplatin (84.4%).

For oral treatment the cost of 12 minutes of pharmacy time was assumed, in line with TA406[220] and preferred assumptions of the committee in TA395.[221]

Table 53: Cost per administration

Treatment regimen	Drug	Cost per administration	Currency code
Tepotinib		£10.40	PSSRU 2020. Hospital based scientific and professional staff – Band 6 – radiologist cost per working hour (12 minutes)[222]
IO monotherapy	Pembrolizumab	£295.92	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance (DCRDN)
	Atezolizumab		
	Nivolumab		
Nivolumab/ ipilimumab	Nivolumab	£295.92	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance (DCRDN)
	Ipilimumab	£428.26 (in combination with nivolumab)	SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (DCRDN)

Treatment regimen	Drug	Cost per administration	Currency code
Docetaxel/ platinum	Docetaxel	£345.15	-
	Cisplatin		SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (DCRDN)
	Carboplatin		SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance (DCRDN)
Gemcitabine/ platinum	Gemcitabine	£363.37 (day 8 only)	SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle (DCRDN)
	Cisplatin	£345.15	SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (DCRDN)
	Carboplatin		SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance (DCRDN)
Paclitaxel/ platinum	Paclitaxel	£428.26	SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (DCRDN)
	Cisplatin		
	Carboplatin		
Vinorelbine/ platinum	Vinorelbine	£363.37 (day 8 only)	SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle (DCRDN)
	Cisplatin	£428.26	SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (DCRDN)
	Carboplatin	£295.92	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance (DCRDN)
Docetaxel monotherapy	Docetaxel	£295.92	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance (DCRDN)
Docetaxel/ nintedanib	Docetaxel	£295.92	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance (DCRDN)
	Nintedanib	£10.40	PSSRU 2020. Hospital based scientific and professional staff – Band 6 – radiologist cost per working hour (12 minutes)[222]
Docetaxel/ gemcitabine	Docetaxel	£295.92 (day 1)	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance (DCRDN)
	Gemcitabine	£363.37 (day 8)	SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (DCRDN)
Vinorelbine monotherapy	Vinorelbine	£295.92	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance (DCRDN)

Treatment regimen	Drug	Cost per administration	Currency code
Pemetrexed/ platinum	Pemetrexed	£345.15	-
	Cisplatin		SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (DCRDN)
	Carboplatin		SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance (DCRDN)
Pemetrexed maintenance	Pemetrexed	£295.92	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance (DCRDN)
Pembrolizumab/ pemetrexed/ platinum [a]	Pembrolizumab	£428.26	SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (DCRDN): Assumed same as TA584[79]
	Pemetrexed		
	Cisplatin		
	Carboplatin		
Atezolizumab/ bevacizumab/ carboplatin/ paclitaxel [a]	Atezolizumab	£428.26	SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance (DCRDN): As per TA584[79]
	Bevacizumab		
	Carboplatin		
	Paclitaxel		

Note: Platinum based regimens are weighted based the real-world cohort data assuming [redacted]% on carboplatin versus cisplatin. [a] Immunotherapies in combination with chemotherapies are included as a comparator for the untreated population, presented in Appendix N.

B.3.5.2. Health-state unit costs and resource use

Disease monitoring resource use costs are based on a health technology assessment for adult patients with advanced or metastatic NSCLC by Brown et al. (2013)[223] and are consistent with the source used in other NSCLC appraisals.[72,77,79,82,164] The disease monitoring resource use is split by health state; progression-free and post-progression. Clinicians explained that disease monitoring doesn't usually change by progression status, but is mainly dependant on the treatment status, therefore, progression-free costs were applied to all patients in the progression-free health state and to the proportion of patients who go onto subsequent treatment. Patients who have progressed and do not receive subsequent treatment acquire the progressed disease costs. This approach is also consistent with previous NSCLC appraisals.[72,77,82,164]

Table 54 presents the resource use for monitoring and disease management in the progression-free and progressed health state and unit costs. The unit costs were sourced from NHS reference costs 19/20[218] or taken from Brown et al.[223] The estimated per week monitoring and disease management costs were £79.11 and £143.88 per week, respectively, for the progression-free and progressed periods.

Table 54: Disease monitoring resource use frequencies and costs

Resource	Progression-free	Progressed	Unit	Source	Unit cost	Source
Outpatient visit	9.61	7.91	Per annum	Big Lung Trial[224]	£166.20	NHS reference costs 19-20.[218] Consultant led, non-admitted face-to-face attendance, first. 800 clinical oncology
Chest radiography	6.79	6.5	Per annum	Big Lung Trial[224]	£29.65	Brown et al. (2013)[223]
CT scan (chest)	0.62	0.24	Per annum	Big Lung Trial[224]	£118.64	NHS reference costs 19-20. Outpatient. RD24Z[218]
CT scan (other)	0.36	0.42	Per annum	Big Lung Trial[224]	£111.58	NHS reference costs 19-20. Outpatient. RD26Z[218]
ECG	1.04	0.88	Per annum	Big Lung Trial[224]	£177.05	NHS reference costs 19-20. Clinical oncology 800. EY51Z[218]
Community nurse visit	8.7	8.7	Visits per annum	NICE guidelines report CG81 (Appendix 1)[225]	£68.00	PSSRU 2020. Nurses. Cost per working hour. Band 8a[222]
Clinical nurse specialist	12	12	Hours contact per annum	NICE guidelines report CG81 (Appendix 1)[225]	£81.00	PSSRU 2020. Nurses. Cost per working hour. Band 8b[222]
GP surgery	12	0	Consultations per annum	NICE guidelines report CG81 (Appendix 1)[225]	£39.00	PSSRU 2020. General practitioner. Per surgery consultation lasting 9.22 minutes[222]
GP home visit	0	29.09	Per annum	Marie Curie report[226]	£100.62	PSSRU 2020. General practitioner. Cost per minute assuming 23.4 minutes[222]
Therapist visit	0	26.09	Per annum	NICE guidelines report CG81 (Appendix 1)[225]	£49.00	PSSRU 2020. Community occupational therapist[222]

Abbreviations: CT, computerised tomography; ECG, electrocardiogram; GP, general practitioner

B.3.5.2.1. Testing for METex14 skipping alterations

Next generation sequencing (NGS) is routinely done in clinical practice in most centres for various NSCLC mutations, including ALK, EGFR and ROS1 within the non-squamous population.[59] This was confirmed by the clinical experts at the advisory board (see Section B.3.2). [redacted]. As NGS testing is already performed for non-squamous patients in most centres, we expect there will be very minimal costs associated with the addition of METex14 skipping alterations testing for non-squamous patients, and so this was not included in the model.

However, clinical experts confirmed that most centres do not routinely test for genetic driver mutations in squamous patients in line with ESMO guidelines, and as such, reimbursement for tepotinib in squamous patients could be associated with additional costs for the NHS through the additional testing of squamous patients. Therefore, the cost associated with METex14 skipping alterations testing in squamous patients was applied to the tepotinib arm as a one-off cost at the start of the model. The total cost is calculated using the expected incidence rate of METex14 skipping alterations in squamous patients and the cost of NGS.

Table 55 presents the inputs to calculate the total cost of METex14 skipping alterations tests per patient in the model. A scenario assuming no additional cost for METex14 skipping alterations testing is also included (see Section B.3.8.3).

Table 55: METex14 alteration testing costs per patient for tepotinib

	Value	Source
Incidence rate of METex14 skipping alterations in squamous patients	1.6%	Sands et al. (2020);[227] Lam et al. (2018)[228]
Cost of NGS per patient	£352.86	Hamblin et al. (2017)[229]
Proportion of squamous patients	9.3%	VISION[121]
Total cost per METex14 patient	£2,047.07	Calculation: (1/1.6%)*£352.86*9.3%

Abbreviations: NGS, next generation sequencing

B.3.5.3. Adverse reaction unit costs and resource use

As discussed in Section B.3.3.5, the adverse events considered are those grade ≥3 occurring in greater than 5% of patients in either treatment arm. The unit costs associated with the management of these adverse events were sourced from NHS reference costs

19/20[218] in line with costs used in previous NSCLC submissions.[72,76,79] Table 56 summarises the costs associated with each adverse event.

Table 56: Adverse event costs included in the model

Adverse event	Cost per event	Source
ALT increase	£1,757.19	Total HRG's - Non-Malignant, Hepatobiliary or Pancreatic Disorders - weighted average GC17A-K
Alopecia	£192.90	WF01A - Non-Admitted Face-to-Face Attendance, Follow-up - consultant led - medical oncology (service code 370)
Amylase increase	£192.90	WF01A - Non-Admitted Face-to-Face Attendance, Follow-up - consultant led - medical oncology (service code 370)
Anaemia	£1,454.72	Total HRG's - Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia - weighted average SA01G-K
Asthenia	£1,757.19	Assumed same as fatigue as per TA584[79]
Bilirubin increased	£1,757.19	Total HRG's - Non-Malignant, Hepatobiliary or Pancreatic Disorders - weighted average GC17A-K
Cardiac failure	£2,461.50	Total HRG's - Cardiac Valve Disorders - weighted average EB06A-D
Cough	£684.44	Total HRG's - Other Respiratory Disorders - weighted average DZ19H-N
Diarrhoea	£1,363.17	Total HRG's - Gastrointestinal Infections - weighted average FD01A-J
Dyspnoea	£684.44	Total HRG's - Other Respiratory Disorders - weighted average DZ19H-N
Fatigue	£1,454.72	Assumed same as anaemia as per TA347[72]
Febrile neutropenia	£2,880.63	Non-elective long stay - Agranulocytosis - weighted average SA35A-E
Hyperglycaemia	£1,165.97	Total HRG's - Diabetes with Hyperglycaemic Disorders - weighted average KB02H-K
Hypertension	£192.90	WF01A - Non-Admitted Face-to-Face Attendance, Follow-up - consultant led - medical oncology (service code 370)
Hypoalbuminemia	£1,757.19	Total HRG's - Non-Malignant, Hepatobiliary or Pancreatic Disorders - weighted average GC17A-K
Hypomagnesemia	£1,757.19	Total HRG's - Non-Malignant, Hepatobiliary or Pancreatic Disorders - weighted average GC17A-K
Infection	£1,873.01	Total HRG's - Infections or Other Complications of Procedures - weighted average WH07A-G
Leukopenia	£705.52	Assumed same as white blood cell decrease
Lipase increase	£192.90	WF01A - Non-Admitted Face-to-Face Attendance, Follow-up - consultant led - medical oncology (service code 370)

Adverse event	Cost per event	Source
Lymphocyte count decrease	£705.52	Assumed same as white blood cell decrease
Nausea	£181.73	Total outpatient - General medicine (300)
Neuromotor	£182.59	Total outpatient - Pain management (191)
Neurosensory	£182.59	Total outpatient - Pain management (191)
Neutropenia	£705.52	Non-elective short stay - weighted average SA35A-E
Neutrophil count decrease	£705.52	Assumed same as white blood cell decrease
Oedema peripheral/other	£589.49	Total HRG's - Unspecified Oedema - weighted average WH10A-B
Pain	£999.82	Total HRG's - Unspecified Pain - weighted average WH08A-B
Platelet count decrease	£705.52	Assumed same as white blood cell decrease
Pleural effusion	£1,811.41	Total HRG's - Pleural Effusion - weighted average DZ16H-R
Pneumonitis / pneumonia	£1,904.55	Total HRG's - Lobar, Atypical or Viral Pneumonia - weighted average DZ11K-V
Pulmonary/respiratory tract infection	£1,498.40	Total HRG's - Pulmonary Embolus - weighted average DZ09J - DZ09Q
Thrombocytopenia	£705.52	Non-elective short stay - Agranulocytosis - weighted average SA35A-E
Vomiting	£181.73	Total outpatient - General medicine (300)
White blood cell count decrease	£705.52	Non-elective short stay - Agranulocytosis - weighted average SA35A-E

Abbreviations: HRG, Healthcare resource group

The unit cost of each adverse event is applied to the incidence rate of the adverse event for each treatment (Table 42 and Table 43), which is applied as a one-off upfront cost to each treatment arm in the model. The total costs of adverse events per treatment is presented in Table 57.

Table 57: Total adverse event cost per treatment

Treatment	Total cost
Tepotinib	£924.06
Immunotherapy	£233.32
Chemotherapy	£557.79

B.3.5.4. Miscellaneous unit costs and resource use

B.3.5.4.1. Subsequent treatments

Subsequent treatments were included in the model as an average cost per patient, which is applied as a one-off cost to patients leaving the progression-free health state. In the base case, the average subsequent treatment cost was based on the same efficacy source used

to derive the survival for each treatment to ensure that any benefit associated with a subsequent therapy in the efficacy is also captured within the costs. Subsequent treatment data from VISION were used to derive the subsequent therapy costs for tepotinib and subsequent treatment data from the real-world data sets were used to inform the comparator arms.

Subsequent treatment data from the real-world cohort datasets were not clearly presented. Treatments were listed in one cell per patient, and it was unclear whether these referred to combination treatments versus monotherapies or multiple doses, as such, assumptions were required to extract the data. For the model, each treatment listed is costed separately. For example, if one patient has docetaxel plus cisplatin for their subsequent treatment then this is costed separately in the model as one incidence of docetaxel and one incidence of cisplatin. Repeated subsequent treatments were counted once, e.g., if it is reported a patient had “cisplatin, docetaxel, docetaxel” only one incidence of docetaxel and one incidence of cisplatin was taken for the model. This approach ensures that doses of treatments were not counted as separate subsequent treatment periods, however, this could also underestimate the costs of subsequent treatments if a patient did have multiple rounds of the same treatment (e.g., docetaxel plus cisplatin followed by docetaxel monotherapy) and could overestimate administration costs if a patient had combination treatment instead of individual treatments (e.g., docetaxel plus gemcitabine versus docetaxel followed by gemcitabine). Subsequent treatments from VISION were better reported, however the same approach was taken to extract the data (separately by treatment instead of by combination) to be consistent.

Given that both VISION and the real-world data sets are not specifically UK based, some subsequent treatments listed are not routinely used for NSCLC patients in clinical practice or are not available in the UK. These treatments were categorised as ‘other’ and re-distributed within their subsequent treatment category (e.g., cabozantinib is only licensed for the treatment of renal cell, hepatocellular and thyroid carcinoma,[230,231] so is re-distributed between the other MET inhibitors). Investigational products were re-distributed to all included treatment categories.

Experts at the advisory board noted the differences between the distributions from the real-world data compared to what would be used in UK practice, particularly the aggressive treatment patterns (i.e., re-treatment of immunotherapy, or subsequent targeted or MET inhibitors). Therefore, scenarios are presented where UK based subsequent treatment distributions are considered. In this scenario, the distributions of treatments used in clinical

practice estimated by clinical experts were used and only subsequent immunotherapies, chemotherapies and platinum-based chemotherapy options are considered.

- For immunotherapy, it is assumed that no patients will receive subsequent immunotherapy, therefore all these patients are proportionally re-distributed to the chemotherapy regimens.

- For tepotinib it is assumed that the distribution of treatments from first-line and second-line would not be changed (with the exception of immunotherapy in combination with chemotherapy which are only available in untreated patients) therefore both immunotherapies and chemotherapies are included.

- For chemotherapy, the distribution of previously treated estimates are used for this scenario.

It is important to note that the modelled overall survival is based on the initial treatments and subsequent treatment distributions used in the base case, therefore the scenario considering UK based distributions only impact the costs and not the difference in survival efficacy, and so is an unfair comparison. It is unclear how the differences in these distributions will impact the survival. In addition to exploring UK based distributions, another scenario assuming the same number of treatment lines between tepotinib and comparators are explored. All subsequent treatment scenarios are presented in Appendix P.

Table 58 presents the subsequent treatment distributions and costs used in the model. The full list of subsequent treatments including those categorised as ‘other’ and ‘investigational’ are presented in Appendix P.

Table 58: Subsequent treatments and costs

Treatment category	Treatment	Tepotinib (VISION) N=151	Immunotherapy (real-world cohort data) N=150	Chemotherapy (real-world cohort data) N=152	Mean duration (weeks)	Total cost [a]	Source for duration
Patient who had at least one subsequent treatment		[redacted]	[redacted]	[redacted]			
Immunotherapy	Pembrolizumab	[redacted]	[redacted]	[redacted]	23.4	£43,336	TA428[74]
	Atezolizumab	[redacted]	[redacted]	[redacted]	14.8	£20,222	TA520[76]
	Nivolumab	[redacted]	[redacted]	[redacted]	25.3	£37,110	TA484,[75] TA483[170]
Chemotherapy	Pemetrexed	[redacted]	[redacted]	[redacted]	15.0	£14,124	Scagliotti et al. (2008)[173]
	Vinorelbine	[redacted]	[redacted]	[redacted]	12.0	£3,453	Fossella et al. (2003)[172]
	Paclitaxel	[redacted]	[redacted]	[redacted]	15.0	£2,274	Sandler et al. (2006)[174]
	Docetaxel	[redacted]	[redacted]	[redacted]	18.0	£1,888	Fossella et al. (2003)[172]
	Gemcitabine	[redacted]	[redacted]	[redacted]	15.0	£3,418	Scagliotti et al. (2008)[173]
Platinum	Cisplatin	[redacted]	[redacted]	[redacted]	15.0	£2,216	Average of values reported in Fossella et al. (2003);[172] Sandler et al. (2006);[174] and Scagliotti et al. (2008)[173]
	Carboplatin	[redacted]	[redacted]	[redacted]	15.0	£1,548	
Targeted	Brigatinib	[redacted]	[redacted]	[redacted]	153.4	£188,267	TA670[232]
	Nintedanib	[redacted]	[redacted]	[redacted]	18.26	£9,211	TA347[72]
MET inhibitor	Crizotinib	[redacted]	[redacted]	[redacted]	97.4	£106,802	Shaw et al. (2019)[233]
Total weighted cost per progressed patient		**£26,638**	**£34,619**	**£51,616**			

Note:
a Includes administration costs

B.3.5.4.2. Terminal care

A cost associated with terminal care is applied to patients who enter the death state as a one-off cost. The resource use frequencies are based on a health technology assessment for adult patients with advanced or metastatic NSCLC by Brown et al. (2013)[223] and is consistent with the source used in other NSCLC appraisals.[74,77,79,82,164]

Table 59 presents the resource use and unit care costs associated with the terminal care costs. All costs have been inflated to reflect 2020 costs using the NHS cost inflation index resulting in a total terminal care cost of £4,478.80 per patient.[222]

Table 59: Resource use and unit costs for terminal care

Resource	Frequency	% patients	Unit cost	Source
Community nurse visit	28 hours	27.0%	£81.00 per hour	PSSRU 2020. Nurses cost per working hour Band 8a[222]
GP home visits	7 visits	27.0%	£100.62 per visit	PSSRU 2020. General practitioner. Cost per minute assuming 23.4 minutes. Including direct care staff with qualifications[222]
Macmillan nurse	50 hours	27.0%	£45.36 per hour	Assumed to be 66.7% of community nurse cost (as per TA428, TA531, TA584, TA600 & TA683)[74,77,79,82,164]
Drugs and equipment	As required	27.0%	£616.60	Brown et al. (2013)[223] (2009/10 costs uplifted to 2020 costs)
Terminal care in hospital	9.66 days	56.0%	£3,931.49	TA683/TA600[82,164] (2016/17 uplifted to 2020 costs)
Terminal care in hospice	9.66 days	17.0%	£4,671.31	Assumed to be 25% increase to hospital cost (as per TA428, TA531, TA584, TA600 & TA683)[74,77,79,82,164]
		Total weighted cost	**£4,478.80**	

B.3.6. Summary of base-case analysis inputs and assumptions

B.3.6.1. Summary of base-case analysis inputs

A table summarising the full list of variables and distributions are provided in Appendix Q.

B.3.6.2. Assumptions

The key assumptions of the economic analysis are described in Table 60.

Table 60: Summary of key model assumptions

Topic	Assumption	Justification/reason
Cycle length	Model cycle length of 1 week is appropriate	A weekly cycle length is assumed to be sufficiently short enough to represent the frequency of clinical events and interventions, and is aligned with the administration of the multiple treatments included within the model (treatment cycles in weeks).
Time horizon	A lifetime time horizon of 30 years is appropriate	The economic model runs for 30 years to reflect the maximum lifetime of patients based on a starting age of 73. The impact of varying time horizon on the results was tested in sensitivity analysis.
Indirect treatment comparison	TTNTD/ToT was used as a proxy for PFS for patients who had a missing PFS event in the real-world data set.	This approach was preferred over reducing patient numbers. The PFS only sensitivity analysis shows consistent results with the main ITC.
Comparators	Comparator treatments are grouped into either 'immunotherapy' or 'chemotherapy' categories and applied the same efficacy.	None of the comparator treatments have been assessed in studies of METex14-specific populations. As such the efficacy of these comparator treatments have been assessed in studies including wider NSCLC population. Incorporating clinical trial data for the comparators in wildtype NSCLC to inform the efficacy versus tepotinib would create a comparison between two different patient populations, due to the expected differences in patient characteristics and prognosis in the METex14 population. As such, comparator data relied on studies using real-world retrospective studies in this specific population. However, given the rarity of patients with METex14 skipping mutations patient numbers in these studies were too small to split out each treatment regimen, and so were grouped together by treatment class / mechanism of action, which was supported by clinical data and clinical expert opinion.
	ToT data for the comparators was based on values from the literature extrapolated using an exponential distribution capped at PFS.	ToT from the real-world cohort data was limited therefore alternative approaches were considered. It is expected that patients will stop treatment upon progression, therefore a cap was applied to ensure that ToT remained equal or below PFS. Other assumptions are tested in scenario analysis.
	Dose intensity was included in the base case to account for missing doses or reductions. For treatments where dose intensity was	The assumptions ensure that all treatments have a dose intensity value. Paclitaxel and platinum have moderately low usage in the chemotherapy arm and the dose intensity assumed for nivolumab

Topic	Assumption	Justification/reason
	not reported, the dose intensity of a similar treatment was assumed: Nivolumab is assumed to have the same dose intensity as pembrolizumab. Paclitaxel + platinum is assumed to have the same dose intensity as docetaxel + platinum.	was close to 100% therefore these assumptions have relatively low impact on the results.
Efficacy	Individual models have been fit to each treatment arm.	Log cumulative hazard plots showed some support for the proportional hazard assumption. However, given the availability of patient-level data for each treatment, the reliance on the proportional hazard assumption was deemed unnecessary and therefore, independent models were deemed more appropriate. In addition, independent models allow the tepotinib arm to remain the same between both comparisons (i.e., versus immunotherapy and chemotherapy).
	Identification of the most appropriate survival curves describing OS, PFS and ToT	Extensive analyses have been undertaken to identify appropriate survival curves describing the efficacy of each treatment, with reference to the guidance from the NICE DSU. The approach and identified survival extrapolations have been validated by clinical and health economic experts. However, to address the uncertainty around these parameters, scenario analyses have been conducted by applying alternative assumptions around extrapolations.
	3.2 months was deemed an appropriate cut-off for the piece-wise models for immunotherapy PFS curves.	Median PFS was 3.2 months allowing enough information in the remaining data set to fit parametric curves, and the shape of the smoothed hazard plot becomes more constant over time following the turning point around 3.2 months (Figure 39D). The piecewise models provided a much-improved visual fit to the data and were included as options in the economic model.
Utilities	Health state utility values were assumed the same for each treatment.	Comparative data were not available to compare treatment effects of HRQL. The utilities derived from VISION were used for all treatments, and separate disutilities were applied to account for treatment toxicities. Given the lack of adverse event data for the comparator

Topic	Assumption	Justification/reason
		treatments, this is likely to underestimate the benefit for tepotinib.
Adverse events	Adverse events for the comparators was taken from published literature in wildtype NSCLC and assumed applicable for the METex14 population.	No adverse event data were available from the real-world cohort study for the comparators. Relying on adverse events from the literature is limited due to the lack of reporting on certain adverse events, compared to tepotinib where all adverse events reported from VISION can be included. As such, this approach is conservative for tepotinib.
	Mean duration of some adverse events were assumed to be the mean of all adverse event durations from VISION.	Not all adverse events in the model were reported in VISION and therefore the mean duration could not be estimated. These assumptions have negligible impact on results.
Resource use	METex14 testing cost applied to only squamous patients.	Clinical experts confirmed that testing is routine practice for non-squamous patients and [redacted].
Subsequent treatments	Subsequent treatment cost was based on the same efficacy source used to derive the survival for each treatment.	This approach was to ensure consistency between the efficacy and costs given the benefit of some subsequent treatments are incorporated within the OS survival. To not include efficacy and costs together from the data could create unfair and inappropriate comparisons. However, UK based distributions are tested in scenario analysis.

Abbreviations: DSU, Decision Support Unit; HRQL, health related-quality of life; ITC, indirect treatment comparison; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; ToT, time on treatment; TTNTD, time to next treatment or death.

B.3.7. Base-case results

B.3.7.1. Base-case incremental cost-effectiveness analysis results

Table 61 presents the base case incremental cost-effectiveness results for tepotinib versus the comparators including a confidential commercial discount of [redacted] for tepotinib. Results for the subgroups are presented in Section B.3.1. Despite the limitations of the evidence and conservative assumptions (i.e., not in favour of tepotinib), the model demonstrated that tepotinib was cost effective versus chemotherapy at the £50,000 willingness to pay (WTP) threshold, based on end-of-life criteria for the chemotherapy group (i.e., patients who are contraindicated or unsuitable for immunotherapy) and is predicted to be more effective and less costly versus immunotherapy (dominating). In comparison to chemotherapy, tepotinib

incurs an incremental QALY gain of [redacted] and incremental costs of [redacted] resulting in an ICER of £19,512. Compared to immunotherapy, tepotinib has incremental QALY gain of [redacted] and a cost reduction of [redacted]. Immunotherapy is strictly dominated in fully incremental analyses (Table 62).

Table 61: Base-case pairwise results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NMB [a]
Tepotinib	[redacted]	2.85	[redacted]					
Chemotherapy	[redacted]	1.99	[redacted]	[redacted]	0.86	[redacted]	£19,512	£12,808
Immunotherapy	[redacted]	2.84	[redacted]	[redacted]	0.01	[redacted]	Dominant	£22,267

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years
Notes:
a Willingness-to-pay threshold is £30,000 versus immunotherapy and £50,000 versus chemotherapy

Table 62: Base-case fully incremental analysis

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)	Incremental ICER (extended dominance)
Chemotherapies	[redacted]	[redacted]				
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£19,512	£19,512
Immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Strictly dominated

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

B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed within the cost-effectiveness model for 1,000 iterations. The mean incremental costs and QALYs from tepotinib and comparators are displayed in Table 63. The visual results of the PSA runs are displayed in Figure 46 and Figure 47. The results of the probabilistic results are consistent with the deterministic results.

Table 63: Mean results of PSA (1,000 runs) and comparison with deterministic results

Technology	Total costs		Total QALYs		ICER (£)		NMB [a]	
	Det.	PSA	Det.	PSA	Det.	PSA	Det.	PSA
Versus chemotherapies								
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]				
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£19,512	£21,689	£12,808	£12,074
Versus immunotherapies								
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]				
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant	£22,267	£21,687

Abbreviations: DET, deterministic; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Notes:
a Willingness-to-pay threshold is £30,000 versus immunotherapy and £50,000 versus chemotherapy

Figure 46: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus chemotherapy

Abbreviations: QALYs, quality-adjusted life years

Figure 47: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus immunotherapy

Abbreviations: QALYs, quality-adjusted life years

Figure 49 and Figure 49 present the cost-effectiveness acceptability curves for tepotinib versus chemotherapy and immunotherapy respectively, based on the 1,000 PSA iterations

at different willingness-to-pay (WTP) thresholds. At the £30,000 WTP threshold, the probability of tepotinib being cost-effective is 80.1% and 98.0% compared to chemotherapy and immunotherapy, respectively. At the £50,000 WTP threshold (based on tepotinib qualifying for end-of-life criteria, Section B.2.13.1), tepotinib is 91.8% likely to be cost-effective versus chemotherapy.

Figure 48: Cost-effectiveness acceptability curve – tepotinib versus chemotherapy

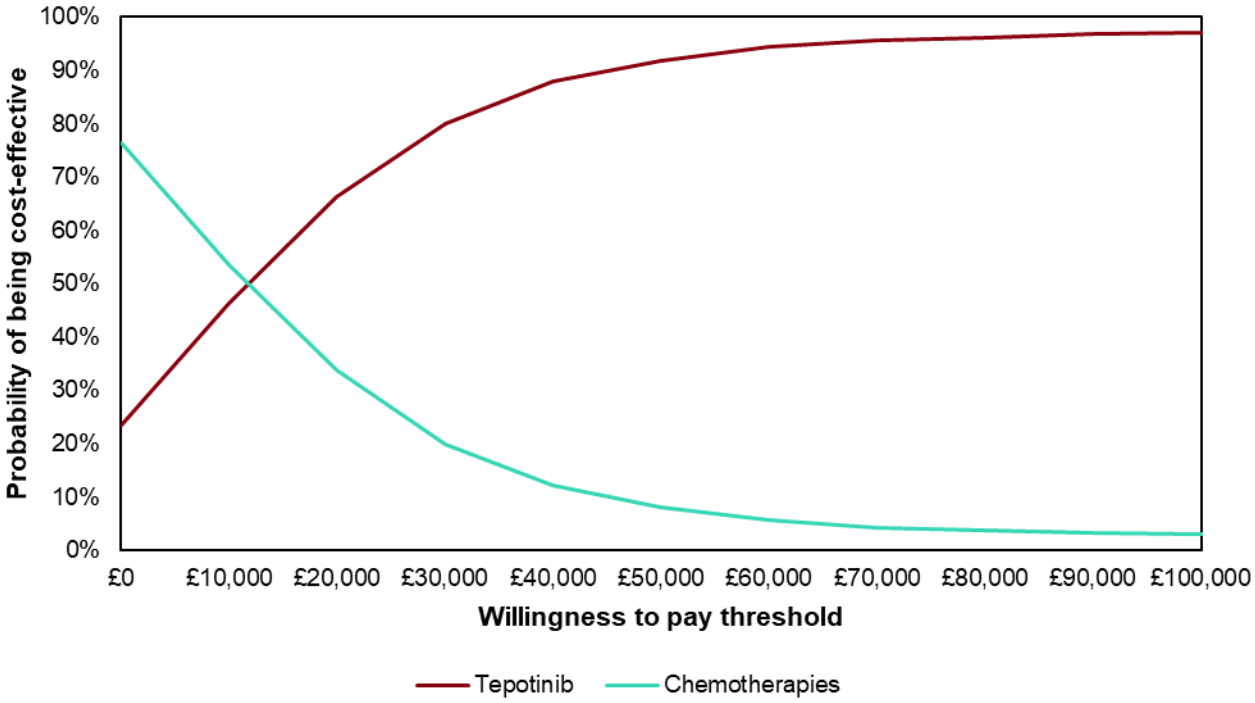
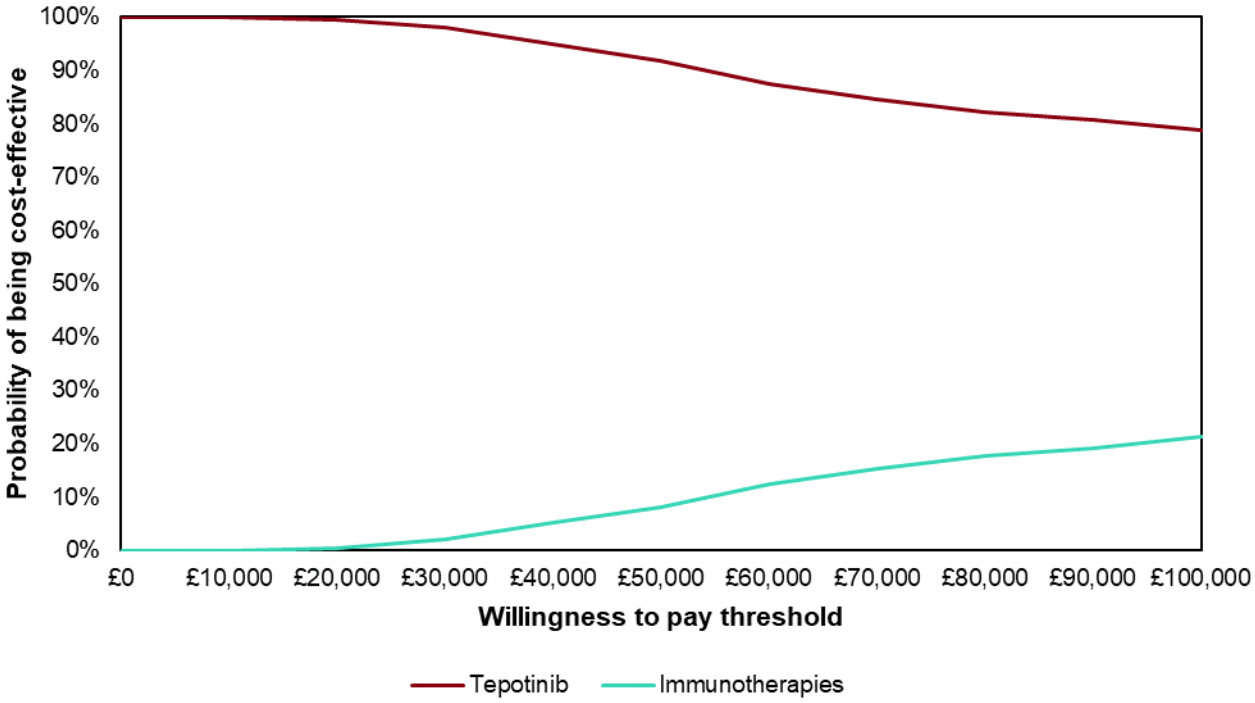


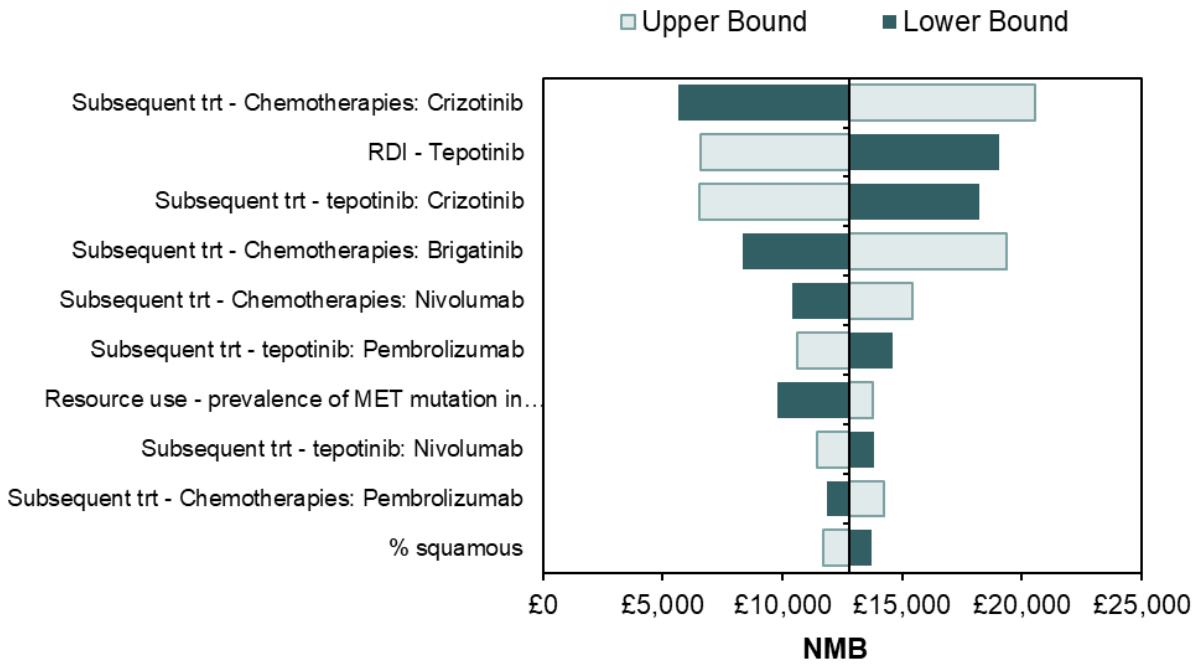
Figure 49: Cost-effectiveness acceptability curve – tepotinib versus immunotherapy



B.3.8.2. Deterministic sensitivity analysis

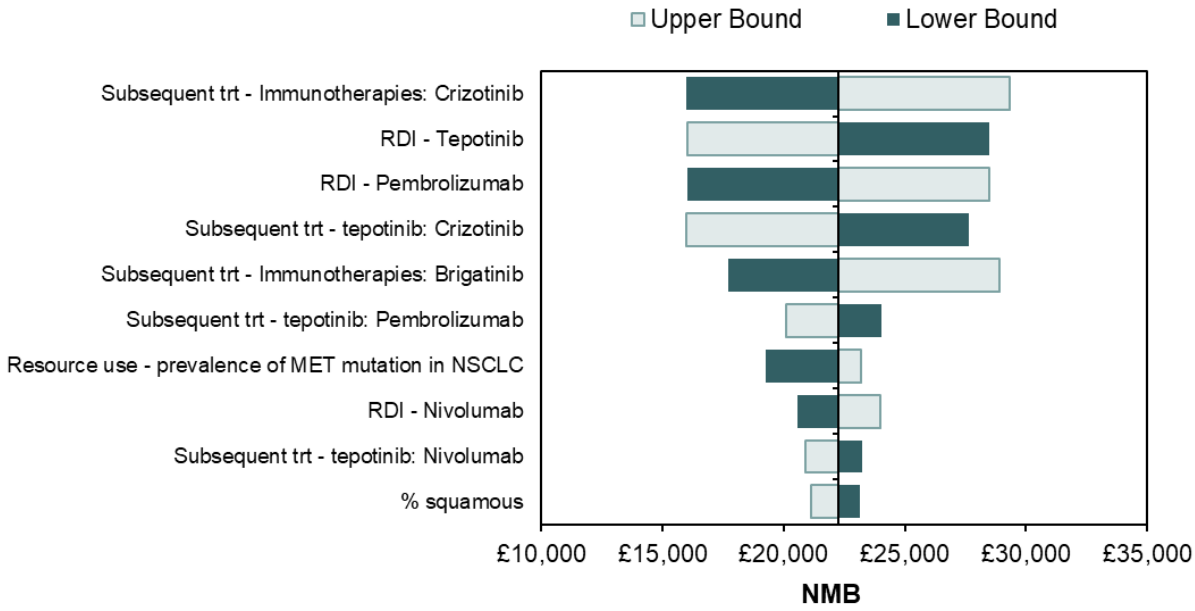
Figure 50 and Figure 51 present the tornado diagrams showing the parameters with the greatest impact on the net monetary benefit (NMB) results with descending sensitivity from one-way sensitivity analysis (OWSA), when their values were set to their upper and lower limits of the confidence intervals presented in Appendix Q. NMB is presented instead of the ICER due to potential crossing of ICERs between the cost-effectiveness plane quadrants making interpretation difficult. The inputs which had the most impact are mainly associated with treatment costs; subsequent treatment distributions, RDI and MET mutation test costs. The input that had the most impact was the proportion of patients receiving crizotinib as subsequent therapy after the comparator treatment. All results resulted in tepotinib remaining cost-effective at the £30,000 and £50,000 thresholds.

Figure 50: Tornado diagram showing OWSA results on the NMB versus chemotherapy (WTP=£50,000)



Abbreviations: OWSA, one-way sensitivity analysis; NMB, net monetary benefit; RDI, relative dose intensity

Figure 51: Tornado diagram showing OWSA results on the NMB versus immunotherapy (WTP=£30,000)



Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis; RDI, relative dose intensity

B.3.8.3. Scenario analysis

Table 64 and Table 65 presents the scenario analyses performed to assess structural uncertainty within the model. All model settings were varied to explore the impact on results. For the survival curves, only the plausible scenarios are presented below. Clinical experts advised that they would not expect tepotinib to have worse outcomes compared to immunotherapy and chemotherapy, hence any curves which predicted a large decrement in survival were excluded from scenario analyses. Furthermore, any implausibly pessimistic or optimistic curves for either treatment arm were excluded in addition to any curve which provided a poor fit to the data.

The results show that for all plausible scenarios, tepotinib remained dominant over immunotherapy at the £30,000 WTP threshold and mainly cost-effective versus chemotherapy at the £50,000 WTP threshold.

Using UK based subsequent treatment scenarios had the largest impact on the ICER versus chemotherapy, however, it is important to note that these scenarios are biased against tepotinib, as the scenarios only vary the impact of the costs and not the efficacy, which models the benefit of the subsequent treatment distribution observed from the real-world cohort data for the chemotherapy arm. Patients in the real-world cohort arms had subsequent immunotherapies or often a subsequent MET inhibitor (mostly crizotinib) so not acknowledging the costs together with associated efficacy from the same source limits these scenarios.

Table 64: Results of scenario analysis versus chemotherapy

Parameter	Base case	Scenario	Tepotinib versus Chemotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB [a]
Time horizon	30 years	10 years	[redacted]	[redacted]	[redacted]	£22,778	£8,019
		20 years	[redacted]	[redacted]	[redacted]	£19,627	£12,412
Discount rates	3.5%	0.0%	[redacted]	[redacted]	[redacted]	£19,378	£17,185
		6.0%	[redacted]	[redacted]	[redacted]	£19,247	£10,773
Weight data source	All patients	European patients	[redacted]	[redacted]	[redacted]	£19,516	£12,807
Drug wastage	Include	Exclude	[redacted]	[redacted]	[redacted]	£17,957	£13,461
Dose intensity	Include	Exclude	[redacted]	[redacted]	[redacted]	£36,287	£5,761
Pemetrexed maintenance	Exclude	Include	[redacted]	[redacted]	[redacted]	£10,050	£16,874
AE disutility	Include	Exclude	[redacted]	[redacted]	[redacted]	£18,429	£14,043
MET mutation testing	Include	Exclude	[redacted]	[redacted]	[redacted]	£14,639	£14,856
Subsequent treatment	VISION/real-world data	UK based distribution	[redacted]	[redacted]	[redacted]	£85,128	-£14,758
		UK based distribution matching number of subsequent lines	[redacted]	[redacted]	[redacted]	£90,877	-£17,173
Utility source	VISION	Nafees et al, 2008[186]	[redacted]	[redacted]	[redacted]	£20,385	£11,909
		Chouaid et al, 2013 - 1L[188]	[redacted]	[redacted]	[redacted]	£19,879	£12,420
		Chouaid et al, 2013 - 2L[188]	[redacted]	[redacted]	[redacted]	£18,715	£13,703
		Chouaid et al, 2013 - 3L/4L[188]	[redacted]	[redacted]	[redacted]	£22,244	£10,229
		TA428 – Pembrolizumab[74]	[redacted]	[redacted]	[redacted]	£18,583	£13,859
		TA484 – Nivolumab[75]	[redacted]	[redacted]	[redacted]	£19,057	£13,309
		TA484 - Nivolumab (committee preference)[75]	[redacted]	[redacted]	[redacted]	£19,436	£12,891
		TA584 - Atezolizumab in combination[79]	[redacted]	[redacted]	[redacted]	£19,950	£12,347

Parameter	Base case	Scenario	Tepotinib versus Chemotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB [a]
		TA531 – Pembrolizumab[77]	[redacted]	[redacted]	[redacted]	£16,396	£16,800
		TA655 – Nivolumab[163]	[redacted]	[redacted]	[redacted]	£18,444	£14,025
		TA655 - Nivolumab (committee preference)[163]	[redacted]	[redacted]	[redacted]	£19,848	£12,453
Tepotinib OS parametric curve	Log-logistic	Exponential	[redacted]	[redacted]	[redacted]	£35,021	£2,419
		Gen Gamma	[redacted]	[redacted]	[redacted]	£30,338	£3,839
		Log-normal	[redacted]	[redacted]	[redacted]	£18,989	£13,731
Tepotinib PFS parametric curve	Log-normal	Gen Gamma	[redacted]	[redacted]	[redacted]	£18,966	£13,162
		Gompertz	[redacted]	[redacted]	[redacted]	£18,682	£13,342
		Log-logistic	[redacted]	[redacted]	[redacted]	£18,823	£13,250
Tepotinib ToT parametric curve	Gen Gamma	Exponential	[redacted]	[redacted]	[redacted]	£17,256	£13,756
		Gompertz	[redacted]	[redacted]	[redacted]	£22,012	£11,758
		Log-logistic	[redacted]	[redacted]	[redacted]	£36,166	£5,812
		Log-normal	[redacted]	[redacted]	[redacted]	£31,958	£7,580
		Weibull	[redacted]	[redacted]	[redacted]	£16,971	£13,876
Chemotherapy OS parametric curve	Weibull	Exponential	[redacted]	[redacted]	[redacted]	£20,500	£11,446
		Gompertz	[redacted]	[redacted]	[redacted]	£29,011	£4,832
		Log-logistic	[redacted]	[redacted]	[redacted]	£33,164	£3,208
		Log-normal	[redacted]	[redacted]	[redacted]	£29,114	£4,781
Chemotherapy PFS parametric curve	Spline – 1 knot odds	Gen Gamma	[redacted]	[redacted]	[redacted]	£19,846	£12,744
		Weibull	[redacted]	[redacted]	[redacted]	£20,056	£12,600
		Spline - 2 knot odds	[redacted]	[redacted]	[redacted]	£19,711	£12,777
		Spline - 3 knot odds	[redacted]	[redacted]	[redacted]	£19,688	£12,592
		Spline - 1 knot hazard	[redacted]	[redacted]	[redacted]	£19,206	£13,063

Parameter	Base case	Scenario	Tepotinib versus Chemotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB [a]
		Spline - 1 knot normal	[redacted]	[redacted]	[redacted]	£20,863	£12,038
		Spline - 2 knot normal	[redacted]	[redacted]	[redacted]	£20,377	£12,408
Chemotherapy ToT	Literature (capped at PFS)	Same as PFS	[redacted]	[redacted]	[redacted]	£19,448	£12,835
		Using HR (PFS vs ToT)	[redacted]	[redacted]	[redacted]	£20,017	£12,596

Abbreviations: AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-years; ToT, time on treatment
Notes:
a Willingness-to-pay threshold is £50,000 versus chemotherapy

Table 65: Results of scenario analysis versus immunotherapy

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB [a]
Time horizon	30 years	10 years	[redacted]	[redacted]	[redacted]	Dominant	£22,430
		20 years	[redacted]	[redacted]	[redacted]	Dominant	£22,243
Discount rates	3.5%	0.0%	[redacted]	[redacted]	[redacted]	Dominant	£21,596
		6.0%	[redacted]	[redacted]	[redacted]	Dominant	£22,656
Weight data source	All patients	European patients	[redacted]	[redacted]	[redacted]	Dominant	£22,283
Drug wastage	Include	Exclude	[redacted]	[redacted]	[redacted]	Dominant	£23,016
Dose intensity	Include	Exclude	[redacted]	[redacted]	[redacted]	Dominant	£15,402
Pemetrexed maintenance	Exclude	Include	[redacted]	[redacted]	[redacted]	Dominant	£22,267
AE disutility	Include	Exclude	[redacted]	[redacted]	[redacted]	Dominant	£22,194
MET mutation testing	Include	Exclude	[redacted]	[redacted]	[redacted]	Dominant	£24,314
		UK based distribution	[redacted]	[redacted]	[redacted]	Dominant	£7,402

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB [a]
Subsequent treatment	VISION/real-world data	UK based distribution matching number of subsequent lines	[redacted]	[redacted]	[redacted]	Dominant	£7,159
Utility source	VISION	Nafees et al, 2008[186]	[redacted]	[redacted]	[redacted]	Dominant	£23,576
		Chouaid et al, 2013 - 1L[188]	[redacted]	[redacted]	[redacted]	Dominant	£21,781
		Chouaid et al, 2013 - 2L[188]	[redacted]	[redacted]	[redacted]	Dominant	£23,071
		Chouaid et al, 2013 - 3L/4L[188]	[redacted]	[redacted]	[redacted]	Dominant	£23,082
		TA428 – Pembrolizumab[74]	[redacted]	[redacted]	[redacted]	Dominant	£22,381
		TA484 – Nivolumab[75]	[redacted]	[redacted]	[redacted]	Dominant	£21,932
		TA484 - Nivolumab (committee preference)[75]	[redacted]	[redacted]	[redacted]	Dominant	£22,978
		TA584 - Atezolizumab in combination[79]	[redacted]	[redacted]	[redacted]	Dominant	£21,551
		TA531 – Pembrolizumab[77]	[redacted]	[redacted]	[redacted]	Dominant	£22,696
		TA655 – Nivolumab[163]	[redacted]	[redacted]	[redacted]	Dominant	£23,171
		TA655 - Nivolumab (committee preference)[163]	[redacted]	[redacted]	[redacted]	Dominant	£23,421
Tepotinib OS parametric curve	Log-logistic	Log-normal	[redacted]	[redacted]	[redacted]	Dominant	£22,736
Tepotinib PFS parametric curve	Log-normal	Gen Gamma	[redacted]	[redacted]	[redacted]	Dominant	£22,540
		Gompertz	[redacted]	[redacted]	[redacted]	Dominant	£22,682
		Log-logistic	[redacted]	[redacted]	[redacted]	Dominant	£22,611
Tepotinib ToT parametric curve	Gen Gamma	Exponential	[redacted]	[redacted]	[redacted]	Dominant	£23,214
		Gompertz	[redacted]	[redacted]	[redacted]	Dominant	£21,216
		Log-logistic	[redacted]	[redacted]	[redacted]	Dominant	£15,270
		Log-normal	[redacted]	[redacted]	[redacted]	Dominant	£17,038
		Weibull	[redacted]	[redacted]	[redacted]	Dominant	£23,334

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB [a]
Immunotherapy OS parametric curve	Spline - 1 knot normal	Exponential	[redacted]	[redacted]	[redacted]	Dominant	£29,560
		Gompertz	[redacted]	[redacted]	[redacted]	Dominant	£28,873
		Weibull	[redacted]	[redacted]	[redacted]	Dominant	£26,643
		Spline - 2 knot odds	[redacted]	[redacted]	[redacted]	Dominant	£27,612
		Spline - 3 knot odds	[redacted]	[redacted]	[redacted]	Dominant	£28,218
		Spline - 1 knot hazard	[redacted]	[redacted]	[redacted]	Dominant	£28,586
		Spline - 2 knot normal	[redacted]	[redacted]	[redacted]	Dominant	£29,305
		Spline - 3 knot normal	[redacted]	[redacted]	[redacted]	Dominant	£29,946
Immunotherapy PFS parametric curve	Piecewise - Log-logistic	Gen Gamma	[redacted]	[redacted]	[redacted]	Dominant	£18,791
		Piecewise - Exponential	[redacted]	[redacted]	[redacted]	Dominant	£24,104
		Piecewise - Gen Gamma	[redacted]	[redacted]	[redacted]	Dominant	£22,689
		Piecewise - Log-logistic	[redacted]	[redacted]	[redacted]	Dominant	£22,267
		Piecewise - Log-normal	[redacted]	[redacted]	[redacted]	Dominant	£22,506
		Piecewise – Weibull	[redacted]	[redacted]	[redacted]	Dominant	£23,759
Immunotherapy ToT	Literature (capped at PFS)	Same as PFS	[redacted]	[redacted]	[redacted]	Dominant	£34,763
		Using HR (PFS vs ToT)	[redacted]	[redacted]	[redacted]	Dominant	£22,944

Abbreviations: AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-years; ToT, time on treatment

Notes:

a Willingness-to-pay threshold is £30,000 versus immunotherapy

B.3.8.4. Summary of sensitivity analyses results

The probabilistic results remain consistent with the deterministic results for comparisons of tepotinib to chemotherapy and immunotherapy. The OWSA identified parameters that had the biggest impact on the NMB and qualified the impacts of taking extreme values of each parameter on the cost-effectiveness results. The OWSA showed that the cost-effectiveness results were not overly sensitive to these parameters, with all results consistently showing tepotinib remaining cost effective versus the comparators. A wide range of scenario analyses were performed on key model assumptions and alternative choices to test the robustness of base case results. The majority of the results remained under the £30,000 and £50,000 threshold, with only limited scenarios resulting in a greater ICER compared to chemotherapy. Tepotinib remained dominant over immunotherapy for all scenarios.

The cost-effectiveness acceptability curve based on 1,000 runs estimates that the probability of tepotinib being cost-effective at the £30,000 WTP threshold is 80.1% and 98.0% compared to chemotherapy and immunotherapy, respectively. At the £50,000 WTP threshold, tepotinib is 91.8% likely to be cost-effective versus chemotherapy.

B.3.1. Subgroup analysis

The results of the cost-effectiveness analysis for the untreated and previously treated sub-populations are presented below.

As discussed in Section B.3.2.3, immunotherapy in combination with chemotherapy is a key comparator for the untreated population and is therefore included in the untreated populations results. Data were limited for this comparator, therefore the interpretation of the results should be interpreted with caution (see Appendix N for details). Other assumptions informing the cost-effectiveness analyses for these subgroups are also described in Appendix N with subgroup ITC results presented in the ITC report within Appendix L.

Table 66 and Table 68 present the pairwise results for the untreated and previously treated population, and Table 67 and Table 69 present the fully incremental results for the untreated and previously treated population, respectively. Tepotinib remained cost-effective between all comparisons at the £30,000 and £50,000 WTP thresholds for the untreated and previous treated subgroups, respectively.

In the untreated sub-population, tepotinib was cost-effective versus chemotherapy with an ICER of £23,354. Immunotherapy and immunotherapy in combination with chemotherapy

was estimated to produce greater QALYs than tepotinib but remained a higher cost, therefore the ICERs sits within the South-West (SW) quadrant showing that immunotherapy and immunotherapy in combination with chemotherapy is not cost-effective versus tepotinib at the £30,000 threshold.

In the previously treated subgroup, compared to chemotherapy and immunotherapy, the ICER was £18,176 and £24,823 respectively.

Table 66: Base-case results – untreated population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NMB [a]
Tepotinib	[redacted]	3.20	[redacted]					
Chemotherapy	[redacted]	2.42	[redacted]	[redacted]	0.78	[redacted]	£23,354	£2,495
Immunotherapy	[redacted]	3.45	[redacted]	[redacted]	-0.25	[redacted]	£418,802 (SW)	£54,539
Immunotherapy plus chemotherapy	[redacted]	3.79	[redacted]	[redacted]	-0.60	[redacted]	£186,293 (SW)	£55,919

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years; SW, South-West
Note: [a] NMB is set to £30,000

Table 67: Base-case fully incremental analysis – untreated population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)	Incremental ICER (extended dominance)
Chemotherapies	[redacted]	[redacted]				
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£23,354	£23,354
Immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	£418,802	Extendedly dominated
Immunotherapy plus + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,345	£186,293

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

Table 68: Base-case results – previously treated population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NMB [a]
Tepotinib	[redacted]	2.61	[redacted]					
Chemotherapy	[redacted]	2.00	[redacted]	[redacted]	0.60	[redacted]	£18,176	£3,617
Immunotherapy	[redacted]	1.87	[redacted]	[redacted]	0.74	[redacted]	£24,824	£2,119

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years
Note:
a NMB is set to £50,000

Table 69: Base-case fully incremental analysis – previously treated population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)	Incremental ICER (extended dominance)
Immunotherapies	[redacted]	[redacted]				
Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	£44,475	Extendedly dominated
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£18,176	£24,824

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

B.3.2. Validation

B.3.8.5. Validation of cost-effectiveness analysis

Clinical validation was sought for the ITC and cost-effectiveness analysis consisting of individual interviews with two clinical experts, and then an advisory board involving four clinical experts and two UK HTA experts. The four clinical experts were leading medical and clinical lung cancer oncologists from a range of centres across the UK to provide a variety of expert perspectives. They all had extensive experience in treatment of NSCLC, as well as with oncogenic mutation driven cancers. The two HTA experts were from UK universities with relevant and vast experience in NICE committees and HTA submissions in oncology.

The following key aspects were discussed and validated:

- The model structure and appropriateness to the decision problem
- The approach used to model comparators and distributions
- The approach to inform the efficacy of tepotinib to the comparators
- Extrapolation of survival beyond the observed period
- Validity of model inputs such as costs and utilities
- Subsequent treatment usage

In addition to clinical validation of model inputs, the cost-effectiveness model was quality assured by a health economist not involved in the model building who reviewed the model for coding errors, inconsistencies, and plausibility of inputs. The model was also subject to stress testing of extreme scenarios to test for known modelling errors and questioning of results.

Both internal and external data sources were used to validate the model survival projections.

B.3.8.6. Internal validation

PFS, OS and ToT Kaplan-Meier data from the efficacy source were compared to the PFS, OS and ToT outputs from the model (see Appendix J). For tepotinib, the model survival projections appear in line with the observed trial data, until around four-years due to the long tails of the Kaplan-Meier data caused by the low numbers at risk. OS for chemotherapy looks in line between the observed data and modelled curves, however PFS looks

underestimated after 2.5 years due to the long tail in the Kaplan-Meier data. For immunotherapy, the model projections look consistent with the real-world data until around 3 years where the Kaplan-Meier data drops suddenly to zero. This is not reflected in the modelled projections as it is likely caused by low patient numbers and censoring.

Overall, the modelled curves look in line with the observed data.

B.3.8.7. External validation

There are no long term published data on the outcomes of advanced NSCLC patients harbouring METex14 skipping alterations, and long-term data in advanced NSCLC in the wider population are limited due to the changing landscape of treatments available.

Therefore, external data sources used for validation of the comparator arms in the economic analysis include a range of published data sources:

- Real-world retrospective studies for patients with NSCLC with METex14 skipping alterations treated with immunotherapy or chemotherapy (Awad et al, Sabari et al and Guisier et al)[49,51,85]
    - Awad et al is a retrospective study of 148 patients with METex14 skipping alterations, across multiple treatment lines. The study describes outcomes seen in a real-world METex14 skipping alterations population treated with different treatments (predominantly chemotherapy), focussing on whether a MET inhibitor improves outcomes. 34 patients included in the study did not receive a MET inhibitor.[49]
    - Sabari et al is also a retrospective study consisting of 147 patients with METex14 skipping alterations investigating the response to immunotherapies. Of the 147 patients, 24 had been treated with immunotherapy across multiple lines.[51]
    - The Guisier et al. study has a similar objective to Sabari et al., although it investigates the effectiveness of immunotherapy in a range of genetic mutations (not just MET). Of the 107 patients in the study, 30 had METex14 skipping alterations.[85]
- Recent trial data in the wider advanced NSCLC population (KEYNOTE-024,[234] KEYNOTE-189,[175] KEYNOTE-042,[235] KEYNOTE-010[236] and CheckMate 017/057[237]

- KEYNOTE-024 is a Phase III randomised controlled trial of pembrolizumab versus platinum-based chemotherapy (carboplatin or cisplatin plus gemcitabine or pemetrexed or paclitaxel) in PD-L1≥50% advanced first-line NSCLC patients.[234]

- 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.[175]

- KEYNOTE-042 is a Phase III randomised controlled trial comparing first-line pembrolizumab monotherapy versus chemotherapy (carboplatin plus pemetrexed or paclitaxel) in patients with advanced NSCLC who are PD-L1 positive (>1%).[235]

- 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.[236]

- 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.[237]

- Real-world studies of older patients with wildtype advanced NSCLC treated with immunotherapy or chemotherapy (Cramer van der Welle et al, Gajra et al, and Arias Ron et al).[161,162,238]

    - Cramer-van der Welle et al compares real-world clinical outcomes of immunotherapy for patients with Stage IV NSCLC compared to clinical trial data using data from six Dutch hospitals for both first-line and second line outcomes (n=83 first-line, n=141 second-line).[238]

    - Gajra et al is a study which pooled data from three first-line clinical trials for advanced NSCLC treated with chemotherapy to compare outcomes of the older patients (≥ 70 years; n=736) versus younger patients (<70 years; n=270).[161]

    - Arias Ron et al is a study which investigated the efficacy and safety of nivolumab in older patients with pre-treated advanced NSCLC in Galician

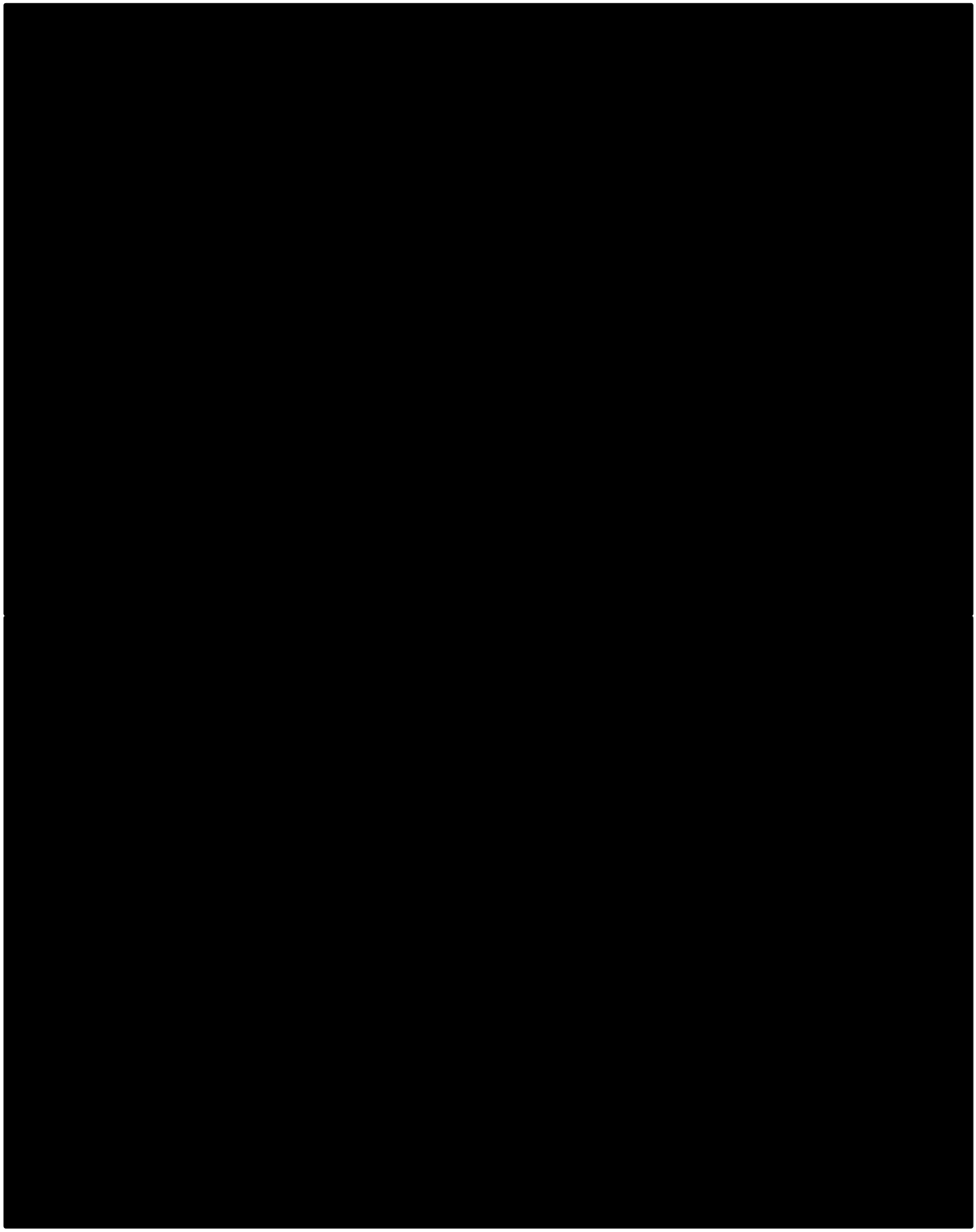
hospitals. Of the 188 patients included in the study, only 38 patients were ≥70 years old.[162]

Figure 52 and Figure 53 presents the chemotherapy projected survival from the model compared to external sources for OS and PFS, respectively.

The chemotherapy OS curve from the model projects higher survival in comparison to all chemotherapy arms in the published clinical trials until around three years when the survival then projects lower estimates in comparison to KEYNOTE-189.[49] Based on the mix of untreated and previously treated patients, and a generally older cohort, the modelled chemotherapy OS would be expected to sit more closely with the previously treated published data (i.e., KEYNOTE-010[236] and CheckMate 057/017[237]). Additionally, the modelled OS looks overestimated when compared to the real-world study Awad et al, and study from Gajra et al.[161] of older patients. PFS looks mostly in line with the external sources as they all project similar outcomes when naively compared, though looks slightly over what would be expected from one year and into the long-term in comparison.

Overall, OS looks substantially overestimated when comparing against external sources for chemotherapy (clinical trials in wildtype NSCLC and published real-world studies in METex14 skipping alterations patients). As confirmed from internal validation (see Section B.3.8.6), the curves appeared to fit the observed data well, therefore the high estimates of survival are mainly driven by the real-world data as opposed to the curve selected. This could be largely due to subsequent treatments which will differ by study and will be dependent on the time period of the studies. Clinical experts at the advisory board noted the aggressive subsequent treatment usage in the real-world data sets (e.g., high use of targeted MET inhibitors) which is likely having an impact on the survival. Subsequent treatments from the published METex14 skipping alterations studies are not available therefore it is not possible to compare appropriately what impact subsequent treatments may be having. Given the apparent impact these treatments could be having on the efficacy, it is considered important to therefore apply the costs of these treatments when considering the cost-effectiveness as per the model's base case.

Figure 52: External validation – chemotherapy – OS



Abbreviations: 1L, first-line; 2L+, second-line plus; OS, overall survival
A: Model survival projections versus clinical trials. **B:** Model survival projections versus real-world data

Figure 53: External validation – chemotherapy – PFS

Abbreviations: 1L, first-line; 2L+, second-line plus; PFS, progression-free survival

Figure 54 and Figure 55 present the immunotherapy model survival projections compared to external sources for OS and PFS, respectively.

In comparison to the clinical studies, the OS for the immunotherapy group projects lower survival compared to the pembrolizumab arm in KEYNOTE-024[234] and more in line with KEYNOTE-042.[235] Given that the KEYNOTE-024[234] and 042[235] populations are in first-line PD-L1 positive NSCLC without METex14 skipping alterations or other oncogenic driver mutations (which generally respond more favourably to immunotherapy compared to METex14 skipping alterations population) and younger (median age 64.5 years and 63.0 years respectively), the survival for the METex14 skipping alterations immunotherapy group is expected to be lower. In comparison to the previously treated clinical trials (KEYNOTE-010[236] and CheckMate 057/017[237]), the METex14 skipping alterations immunotherapy group survival projects better outcomes. Although the immunotherapy model survival contains a mix of untreated and previously treated patients (hence the expectation of outcomes to appear better than a purely previously treated group), given the expectation of poorer outcomes for METex14 skipping alterations patients, and an older cohort, the survival would be expected to be either in line or lower than the immunotherapy arms from the published clinical trials in the previously treated group.

Compared to real-world data, the projected OS for the METEx14 skipping alterations immunotherapy group appears in line with the two METex14 skipping alterations population sources (Guisier et al.[85] and Sabari et al.[51]), although underestimated compared to Sabari et al.[51] for the first two years and overestimated from one year compared to Guisier et al..[85] The model's immunotherapy OS curve sits consistently on the first-line real-world outcomes presented in Cramer-van der Welle et al.[238], however, compared to a wildtype NSCLC population, outcomes for a METex14 skipping alterations population are expected to be closer to the second-line projections. The Ron et al.[162] data does not seem plausible in comparison to the other data sources, which is likely due to the small patient numbers within this data set (n=38), as such, comparison to this study is limited.

The immunotherapy PFS curve looks as expected compared to the immunotherapy arms from the clinical trials. In comparison to real-world data, the PFS curve looks consistent with Guisier et al.,[85] Cramer-van der Welle et al.[238] (second-line). However, Sabari et al.[51] presents extremely poor PFS for patients treated with immunotherapy, therefore the model projection looks overestimated in comparison.

Overall, the projected OS for the immunotherapy groups looks optimistic compared to the external sources where as PFS looks as anticipated.

Figure 54: External validation – immunotherapy – OS

Abbreviations: 1L, first-line; 2L, second-line; OS, overall survival
A: Model survival projections versus clinical trials. **B:** Model survival projections versus real-world data

Figure 55: External validation – immunotherapy – PFS

Abbreviations: PFS, progression-free survival
A: Model survival projections versus clinical trials. **B:** Model survival projections versus real-world data

B.3.3. Interpretation and conclusions of economic evidence

The economic analysis performed is based on a *de novo* economic model with a structure designed to reflect the advanced NSCLC pathway in a simplistic form while still capturing the relevant health outcomes. The model structure is consistent with previous NSCLC appraisals and brought together the most relevant efficacy and safety clinical data, using robust statistical techniques to establish the comparative efficacy of tepotinib versus immunotherapy and chemotherapy in patients with advanced NSCLC harbouring METex14 skipping alterations.

The inclusion of the retrospective real-world cohort data addresses the limitations of the available literature-based evidence for specific comparators, particularly due to the lack of published data in the METex14 skipping alterations population. The availability of patient-level data for both the tepotinib trial and the real-world cohort data meant that the patient populations could be adjusted to account for any differences. In addition, the inclusion and exclusion criteria in VISION could be applied to patients in the real-world cohort to allow for a fairer comparison.

The main limitation of the model is the lack of direct comparative efficacy with the comparators. However, analysis has been conducted utilising the most appropriate available

data, with all appropriate statistical adjustments being made (informed and validated by clinical expert feedback) in order to perform an unbiased comparison. The comparison is likely to underestimate the benefit for tepotinib, due to the aggressive subsequent treatments which are used in the real-world cohorts, and as a result overestimating the overall survival for the comparator arms compared to UK clinical practice. A second limitation is the small patient numbers in the comparator arms, which does not allow for analysis to be conducted for tepotinib versus each specific treatment or treatment combination separately. However, the approach used in the model, which groups the comparators by treatment class was supported by clinical and HTA experts, and available literature.

No previous economic analysis was identified through the systematic literature review in the advanced NSCLC harbouring METex14 skipping alterations population; therefore, the modelling assumptions or results could not be externally validated with previous studies. However, the model structure, key assumptions and modelling options were validated with clinical and health economic experts and compared to clinical trials and real-world data. The model structure and inputs are also consistent with the breadth of available previous NSCLC appraisals, with some of the previously used data utilised in the current analysis. Similarly, the survival extrapolations used are compared to published data, where they appear more favourable to the comparators.

Despite these limitations and conservative assumptions (i.e., not in favour of tepotinib), the model demonstrated that tepotinib was cost effective versus chemotherapy and is predicted to be more effective and less costly versus immunotherapy (dominating) in the base case population. Tepotinib is the first treatment to be appraised specifically for patients harbouring METex14 skipping alterations and will be the first treatment licensed to treat these patients in the UK. Existing treatment options leave substantial unmet need for patients with METex14 skipping alterations, where currently patients are treated for wildtype NSCLC, in which treatments are known to respond poorly, particularly immunotherapies. Tepotinib represents a novel treatment offering a cost-effective alternative to chemotherapy-based and immunotherapy-based treatment options. This is particularly important as it will offer patients a targeted treatment, which are already available for cancers with EGFR, ALK and ROS1 oncogenic drivers. In addition, tepotinib will also offer patients an oral drug option, where currently only infusions, which require frequent hospital visits, are available. This reduces the burden for patients, frees capacity within the NHS and allows cost offsets. In the budget impact analysis, tepotinib was also shown to be cost saving for the NHS.

Furthermore, tepotinib is licensed across all lines of therapy, and is shown to be cost-effective in both the untreated and previously treated groups. This would allow clinicians the flexibility to choose the most appropriate treatment strategy for specific patients.

Overall, tepotinib represents a cost-saving and cost-effective treatment that can replace current non-targeted therapies for patients with NSCLC harbouring METex14 skipping alterations and addresses the critical unmet need for a therapy that improves survival outcomes and maintains HRQL in this patient population.

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B.5. Appendices

The following appendices are provided as standalone documents:

Appendix C Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D Identification, selection and synthesis of clinical evidence

Appendix E Subgroup Analysis

Appendix F Adverse reactions

Appendix G Identification, selection and synthesis of cost-effectiveness evidence

Appendix H Identification, selection and synthesis of health-related quality-of-life evidence

Appendix I Identification, selection and synthesis of cost and healthcare resource identification, measurement, and valuation

Appendix J Clinical outcomes and disaggregated results from the model

Appendix K Checklist of confidential information

Appendix L Indirect treatment comparison

Appendix M: Proportional hazard assumption

Appendix N: Cost-effectiveness analysis for subgroups

Appendix O: Comparator literature time on treatment

Appendix P: Subsequent treatments

Appendix Q: Base-case analysis inputs

Appendix R: VISION: Cohort A+C Data

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

August 2021

File name	Version	Contains confidential information	Date
ID3761_Tepotinib company response to ERG clarification letter_18Aug21_redacted	1	Yes	18 August 2021

Section A: Clarification on effectiveness data

Literature searches

A1. Priority question. Please justify the use of highly specific search strategies with focus on only patients with METex14 skipping alterations in non-small cell lung cancer (NSCLC).

a. **Please explain why the search strategies did not include search terms for the drug name 'tepotinib'.**

The search terms were already restricted to the specific population of patients with NSCLC harbouring METex14 skipping alterations. Therefore, the addition of intervention terms would have unnecessarily further restricted the search results.

b. **Please confirm that the top-up search conducted in appendix 1 (page 311) for (met adj1 mutation) was not conducted for the cost-effectiveness searches in appendix 2.**

The top-up search was conducted to support the indirect treatment comparison (ITC). However, as part of the response to the clarification questions, records have been re-screened for economic and health-related quality of life outcomes and none were considered eligible for inclusion.

c. **Please provide the date ranges of the databases searched in appendix 1; Tables 72 to 81, e.g. Medline: 1946- 22 January 2020.**

For the Initial Review and Update Review 1, searches in each of the databases (Medline, EMBASE, EBM Reviews - Cochrane Central Register of Controlled Trials; EBM Reviews - Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects, NHS Economic Evaluations – NHS EED, and the HTA Database) were conducted on 22 January 2020:

- Medline – 1946 to January 2020 [Initial Review] and August 2020 [Update Review 1])
- Embase – 1974 to January 2020 [Initial Review] and August 2020 [Update Review 1])

- The Cochrane Central Register of Controlled Trials (CENTRAL) – 1991 to January 2020 (or August 2020)
- The Cochrane Database of Systematic Reviews (CDSR) – 2005 to January 2020 (or August 2020)
- Database of Abstracts of Reviews of Effectiveness (DARE) – 1991 to 2015 (historical database)
- Health Technology Assessment (HTA) Database – 2001 to 2016 (historical database)

For Update Review 2 the searches were conducted in June 2021:

- Medline – 1946 to June 11, 2021
- Embase – 1974 to June 11, 2021
- The Cochrane Library: The Cochrane Central Register of Controlled Trials (CENTRAL) and The Cochrane Database of Systematic Reviews (CDSR) – to 8 June 2021

For conference searches, no time restriction was applied to the Initial Review. Update Review 1 and Update Review 2 searched only new annual conferences that had occurred since the Initial Review.

d. Please provide the search terms used for ClinicalTrials.gov searches, see appendix 1; Tables 77, 83, and 88.

The search strategy for the Initial Review and Update Review 1 was as follows:

- Condition or disease – Non-small cell lung cancer
- Other terms – MET exon 14
- Status: All, except Suspended, Terminated, or Withdrawn

This information has been added to Appendix D.

For Update Review 2 the search strategy was as follows:

- Other terms - Tepotinib
- Status: All, except Suspended, Terminated, or Withdrawn

No new studies were identified vs the Initial Review or Update Review 1.

The searches were rerun in clinicaltrials.gov to align with the prior searches on 10 August 2021 (refer to Appendix 1 of this document).

e. Please confirm the search dates provided in the ClinicalTrials.gov searches (Tables 83 and 88), as both are labelled 'As of 24 September 2020.

The search date for Update Review 1 for the ClinicalTrials.gov search was 24 September 2020 and the search date for Update Review 2 for the ClinicalTrials.gov search was 8 June 2021. This has been corrected in Appendix D – thank you for highlighting.

f. Please confirm whether Tables 89 and 90 (appendix 1) are mis-labelled. Is Table 89 the Medline search and Table 90 the Embase search? Please also confirm the date range for each.

Thank you for highlighting this. The tables were mis-labelled: Table 89 reports the Medline search and Table 90 reports the Embase search. In Medline, the searches were conducted on 22 June 2021 for date range 1946 to 21 June 2021. In Embase, the searches were conducted on 22 June 2021 for date range 1974 to 21 June 2021. This has been corrected in Appendix D.

g. Please provide details of the 'targeted literature search' (company submission, page 164) conducted to identify reported outcomes in previous National Institute for Health and Care Excellence (NICE) submissions for the comparator treatments. The company submission states that details are provided in appendix H, but they do not appear to be reported in this appendix.

The targeted literature search that was conducted to identify reported outcomes in previous National Institute for Health and Care Excellence (NICE) submissions for the comparator treatments was reported in Appendix G (refer to Appendix G, Section

G.1.2, Health technology assessment websites). This has been corrected in Document B.

This supplementary search of the NICE website was performed to identify prior health technology assessment (HTA) submissions in NSCLC, as no cost-effectiveness analyses in the METex14 skipping alterations population were identified in the database searches. The search used term “non-small-cell lung cancer” and was filtered by published guidance. Prior technology appraisals were eligible for inclusion if they had assessed any of the listed comparators in the tepotinib decision problem with no date restriction **or** any technology appraisal in non-small-cell lung cancer indication published in the last three years. Terminated appraisals were excluded. Refer to Appendix G (Section G.1.2) for summary results of included technology appraisals.

h. **According to appendix D, the Cochrane Database of Systematic Reviews (CDSR) was searched three times between 22 January and 8 June 2021 for prognostic, clinical, humanistic, epidemiological, and economic evidence, yet systematic reviews were ineligible as per Table 1, therein. Please explain this ambiguity.**

The highlighted ambiguity is acknowledged. The bibliographies of systematic reviews were, however, searched for references to other potentially relevant studies. Although this was documented in the review protocol, it is noted that this was not aligned with the PICO criteria that stated the exclusion of systematic reviews with no allowance that the bibliographies of systematic reviews meeting other eligibility criteria would be scrutinised for other potentially relevant studies.

A2. According to appendix F, no studies were identified that reported additional adverse reactions. It appears that some relevant studies were omitted. Please justify this omission or include all relevant studies.

The studies listed below were in indications other than NSCLC harbouring METex14 skipping alteration population, hence these studies were not included in Appendix F. Safety data from the listed publications have, however, been provided below for the requested publications for completeness. The majority were not captured in the searches given the search terms used.

1. **Decaens, T. et al. Safety profile of tepotinib in patients with advanced solid tumors: Pooled analysis of phase I and II data. Annals of Oncology, Volume 30, v181 – v182**

Table 1. Treatment-related (TR)AEs

	N=228	
	Any Grade ≥10%	**Grade ≥3 ≥2%**
Any TRAE, n (%)	172 (75.4)	52 (22.8)
Peripheral oedema	77 (33.8)	8 (3.5)
Diarrhoea	45 (19.7)	4 (1.8)
Fatigue	34 (14.9)	3 (1.3)
Nausea	29 (12.7)	0 (0)
Decreased appetite	27 (11.8)	0 (0)
Increased lipase	13 (5.7)	9 (3.9)
Increased AST	11 (4.8)	5 (2.2)

Abbreviations: AST, aspartate aminotransferase; TRAE, treatment related adverse event
Pooled analysis of clinical trialsNCT01014936, NCT01832506, NCT01988493, NCT02115373, NCT02864992

These data were also reported in two abstract publications Paik et al. (2020) and Xiong et al. (2021), these studies were listed as excluded study citations as the population was mixed and included participants from the broader NSCLC population.

2. **Decaens T, Barone C, Assenat E, Wermke M, Fasolo A, Merle P, Blanc JF, Grando V, Iacobellis A, Villa E, Trojan J, Straub J, Bruns R, Berghoff K, Scheele J, Raymond E, Faivre S. Phase 1b/2 trial of tepotinib in sorafenib pretreated advanced hepatocellular carcinoma with MET overexpression. Br J Cancer. 2021 Apr 6.**

Table 2. Phase 2: TRAEs of any grade and Grade ≥3

Event	**Tepotinib**	
	Any grade	**Grade ≥3**
≥1 AE of any cause,[a] n (%)	48 (98.0)	28 (57.1)
≥1 TRAE, n (%)	41 (83.7)	14 (28.6)
TRAE in ≥5% of patients, n (%)		
Peripheral oedema	19 (38.8)	3 (6.1)
Asthenia	11 (22.4)	0
Fatigue	9 (18.4)	0
Diarrhoea	8 (16.3)	0
Nausea	7 (14.3)	0

Event	Tepotinib	
	Any grade	Grade ≥3
Ascites	6 (12.2)	2 (4.1)
Hypoalbuminaemia	5 (10.2)	0
Decreased appetite	4 (8.2)	0
Vomiting	4 (8.2)	0
Blood creatinine increased	3 (6.1)	1 (2.0)
Lipase increased	3 (6.1)	3 (6.1)
Pruritus	3 (6.1)	0

a Treatment-related adverse events are defined as events that occur within the day of first dose of trial treatment, up until 33 days after last dose of treatment

3. **Falchook GS, Kurzrock R, Amin HM, Xiong W, Fu S, Piha-Paul SA, Janku F, Eskandari G, Catenacci DV, Klevesath M, Bruns R, Stammberger U, Johne A, Bladt F, Friese-Hamim M, Girard P, El Bawab S, Hong DS. First-in-Man Phase I Trial of the Selective MET Inhibitor Tepotinib in Patients with Advanced Solid Tumors. Clin Cancer Res. 2020 Mar 15;26(6):1237-1246.**

Table 3. TRAEs

	Regimen 1		Regimen 2		Regimen 3		Total	
	(n ¼ 42)		(n ¼ 45)		(n ¼ 62)		(N ¼ 149)	
	Any Grade	Grade2:3	Any Grade	Grade2:3	Any Grade	Grade2:3	Any Grade	Grade2:3
TRAE[a]	14 (33.3)	1 (2.4)	23 (51.1)	3 (6.7)	39 (62.9)	9 (14.5)	76 (51.0)	13 (8.7)
Peripheral oedema	1 (2.4)	0	2 (4.4)	0	16 (25.8)	3 (4.8)	19 (12.8)	3 (2.0)
Fatigue	3 (7.1)	0	5 (11.1)	0	11 (17.7)	2 (3.2)	19 (12.8)	2 (1.3)
Decreased appetite	2 (4.8)	0	0	0	10 (16.1)	0	12 (8.1)	0
Nausea	1 (2.4)	0	2 (4.4)	1 (2.2)	6 (9.7)	0	9 (6.0)	1 (0.7)
Vomiting	2 (4.8)	0	2 (4.4)	1 (2.2)	5 (8.1)	1 (1.6)	9 (6.0)	2 (1.3)
Lipase increased	1 (2.4)	1 (2.4)	4 (8.9)	2 (4.4)	1 (1.6)	0	6 (4.0)	3 (2.0)
Rash	0	0	2 (4.4)	0	2 (3.2)	0	4 (2.7)	0
AST increased	1 (2.4)	0	0	0	3 (4.8)	1 (1.6)	4 (2.7)	1 (0.7)
Diarrhoea	0	0	1 (2.2)	0	3 (4.8)	0	4 (2.7)	0
ALT increased	0	0	0	0	3 (4.8)	2 (3.2)	3 (2.0)	2 (1.3)
Anemia	0	0	0	0	3 (4.8)	0	3 (2.0)	0
Blood creatinine increased	0	0	0	0	3 (4.8)	0	3 (2.0)	0
Constipation	0	0	0	0	3 (4.8)	0	3 (2.0)	0

	Regimen 1		Regimen 2		Regimen 3		Total	
	(n ¼ 42)		(n ¼ 45)		(n ¼ 62)		(N ¼ 149)	
	Any Grade	Grade2:3	Any Grade	Grade2:3	Any Grade	Grade2:3	Any Grade	Grade2:3
Transaminases increased	0	0	0	0	3 (4.8)	0	3 (2.0)	0
Peripheral neuropathy	1 (2.4)	0	1 (2.2)	0	1 (1.6)	0	3 (2.0)	0
Renal failure	2 (4.8)	0	0	0	1 (1.6)	0	3 (2.0)	0
Oedema	0	0	0	0	1 (1.6)	1 (1.6)	1 (0.7)	1 (0.7)
Amylase increased	1 (2.4)	1 (2.4)	0	0	0	0	1 (0.7)	1 (0.7)
Hypoalbuminemia	0	0	0	0	2 (3.2)	1 (1.6)	2 (1.3)	1 (0.7)
Hyponatremia	0	0	0	0	2 (3.2)	1 (1.6)	2 (1.3)	1 (0.7)

Abbreviation: AST, aspartate transaminase; treatment emergent adverse events

a For any-grade treatment-related TEAEs, events occurring in >2 patients with any regimen are reported; for treatment-related TEAEs grade 3 or higher, all events are shown

4. **Ryoo BY, Cheng AL, Ren Z, Kim TY, Pan H, Rau KM, Choi HJ, Park JW, Kim JH, Yen CJ, Lim HY, Zhou D, Straub J, Scheele J, Berghoff K, Qin S. Randomised Phase 1b/2 trial of tepotinib vs sorafenib in Asian patients with advanced hepatocellular carcinoma with MET overexpression. Br J Cancer. 2021 May 10.**

Table 4. TRAEs reported in ≥10% of patients (Phase 2 study; safety analysis set)

Patients with TRAEs, n (%)	Tepotinib		Sorafenib	
	n = 45		n = 44[a]	
	Any grade	Grade ≥ 3[b]	Any grade	Grade ≥ 3[b]
Overall	37 (82.2)	13 (28.9)	43 (97.7)	20 (45.5)
Diarrhoea	16 (35.6)	2 (4.4)	14 (31.8)	3 (6.8)
Oedema peripheral	11 (24.4)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	9 (20.0)	2 (4.4)	11 (25.0)	0 (0.0)
PPES	8 (17.8)	1 (2.2)	27 (61.4)	3 (6.8)
Decreased appetite	8 (17.8)	0 (0.0)	12 (27.3)	0 (0.0)
Blood creatinine increased	6 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)
AST increased	5 (11.1)	2 (4.4)	10 (22.7)	3 (6.8)
Hypoalbuminaemia	5 (11.1)	0 (0.0)	2 (4.5)	0 (0.0)
ALT increased	4 (8.9)	0 (0.0)	7 (15.9)	0 (0.0)
Amylase increased	3 (6.7)	2 (4.4)	5 (11.4)	1 (2.3)
Blood bilirubin increased	2 (4.4)	1 (2.2)	8 (18.2)	2 (4.5)
Alopecia	1 (2.2)	0 (0.0)	10 (22.7)	0 (0.0)
Lipase increased	1 (2.2)	0 (0.0)	5 (11.4)	4 (9.1)

Patients with TRAEs, n (%)	Tepotinib		Sorafenib	
	n = 45		n = 44[a]	
Hypertension	0 (0.0)	0 (0.0)	11 (25.0)	6 (13.6)
Dermatitis acneiform	0 (0.0)	0 (0.0)	5 (11.4)	0 (0.0)

ALT alanine aminotransferase, AST aspartate aminotransferase, PPES, palmar–plantar erythrodysesthesia syndrome

a One patient did not receive treatment

b Grade ≥3 treatment-related adverse events (in ≥2 patients) also included ascites (4.4%) and hyperglycaemia (4.4%) for tepotinib, and increased gamma-glutamyl transferase (4.5%) for sorafenib.

5. **Shitara K, Yamazaki K, Tsushima T, Naito T, Matsubara N, Watanabe M, Sarholz B, Johne A, Doi T. Phase I trial of the MET inhibitor tepotinib in Japanese patients with solid tumors. Jpn J Clin Oncol. 2020 Aug 4;50(8):859-866.**

Table 5. TEAEs (any cause)

Patients with TEAE n (%)	Tepotinib 215 mg OD (n=3)	Tepotinib 300 mg OD (n=3)	Tepotinib 500mg OD (n=6)	Total (n=12)
Any TEAE	2	3	6	11 (91.7)
Any treatment related TEAE	1	1	3	5 (41.7)
Ay serious TEAE	0	3	1	4 (33.3)
Any related serious TEAE	0	0	0	0
Any Grade ≥3 TEAE	0	3	4	7 (58.3)
Any related Grade ≥3	0	0	3	3 (25.0)
TEAE leading to treatment discontinuation	0	0	0	0
TEAE leading to death[a]	0	0	1	1 (8.3)
Related TEAE leading to death	0	0	0	0
Related TEAE of special interest[b]	0	0	2	2 (16.7)

OD, once daily; TEAE, treatment emergent adverse event

a Primary reason for death was disease progression

b Defined as lipase or amylase elevation of Grade ≥3

Table 6. TRAEs

TEAE, n (%)	Tepotinib 215 mg OD (n=3)	Tepotinib 300 mg OD (n=3)	Tepotinib 500mg OD (n=6)	Total (n=12)
Any grade				
Amylase increase	0	0	2	2 (16.7)
Lipase increase	0	0	2	2 (16.7)

TEAE, n (%)	Tepotinib 215 mg OD (n=3)	Tepotinib 300 mg OD (n=3)	Tepotinib 500mg OD (n=6)	Total (n=12)
Serum creatinine increase	0	0	1	1 (8.3)
Hypoalbuminemia	0	0	2	2 (16.7)
Decreased appetite	1	0	0	1 (8.3)
Hyponatraemia	0	0	1	1 (8.3)
Nausea	0	0	1	1 (8.3)
Stomatitis	0	0	1	1 (8.3)
Vomiting	0	0	1	1 (8.3)
Fatigue	1	1	0	2 (16.7)
Dysgeusia	1	0	1	2 (16.7)
Acneiform dermatitis	0	0	1	1 (8.3)
Grade 3/4				
Lipase increase (Grade 4)	0	0	2	2 (16.7)
Hyponatraemia (Grade 3)	0	0	1	1 (8.3)

OD, once daily; TEAE, treatment emergent adverse event

Systematic literature review

A3. Please provide the full systematic review report mentioned in section D.1.1.4 of the company submission.

The full systematic literature review report mentioned in Section D.1.1.4 was provided in the reference pack, in a separate Data on File reference folder.

Please note that this report contains the methods and results for the Initial Review and Update Review 1. Update Review 2 was updated for this appraisal and is only documented in Appendix D.

A4. Please justify the application of eligibility criteria:

a. **There are 81 studies excluded based on outcomes being outside of the PICO (population, intervention, comparator(s), outcome(s)) but some of these appear to report outcomes within the NICE scope. For example, the study by David S. et al. (J Clin Oncol 38: 2020, suppl; abstr TPS3663) includes safety and tolerability which are within the scope. Please revise**

the list of excluded studies or provide appropriate reasons for exclusion. If needed, provide information on studies providing relevant evidence.

A total of 79 studies were excluded on “Outcomes not in PICO”. These studies were rescreened as requested. Refer to Appendix 2 of this document for tabulated summary. Some adjustments were made to reasons for exclusion (highlighted in orange in the table in Appendix 2), but no studies were judged to have been incorrectly excluded from the review.

The study Hong et al. J Clin Oncol 38: 2020, suppl; abstr TPS3663 does indeed state that its primary endpoint was the incidence of disease limiting toxicities and refers to relevant secondary endpoints (ORR blinded by independent central review, PFS and OS (dose expansion only)); however, no data were reported within the abstract hence the study was excluded on outcomes (no results reported for relevant outcomes).

b. **According to section D.1.3.2 (Excluded studies: clinical), the study by Smit EF, Felip E (1415TiP INSIGHT 2: Tepotinib + osimertinib in patients (pts) with EGFR-mutant NSCLC having acquired resistance to first-line osimertinib due to MET amplification (METamp). Ann Oncol 2020; 31(S4): S894) has an invalid reason for exclusion. Please provide a correct reason for exclusion.**

The study by Smit et al. (2020) was excluded as it did not meet the population criterion “patients with advance non-small cell lung cancer with METex14 skipping alterations”. The study included people with **EGFR-mutant NSCLC** having acquired resistance to first-line osimertinib due to **MET amplification (METamp)**, and this is a separate indication/population. The reason for exclusion as stated is therefore accurate: “Indication/ population not in PICO (e.g. other than NSCLC)”. The example in brackets was provided for illustrative purposes only. However, this has been adjusted to reflect exactly why the population criterion was not met. As this reason for exclusion appeared elsewhere in the list of excluded studies, this has also been adjusted where relevant elsewhere in the list of excluded studies reported in the appendices (Section D.1.3.2: p.44, p.45, p.46).

c. **According to section D.1.4. (Table 5: Summary of publications included in the ITC [indirect treatment comparison], the studies by Kato et al. 2021,**

Hur et al. 2020, and Gow et al. 2017 are all excluded from the ITC with the same reason i.e., Asian population. However, the VISION study which presents the efficacy results for the submission to NICE recruited patients originated from Japan, South Korea or Taiwan. Please explain this discrepancy.

The VISION study was conducted at approximately 120 treatment sites in Austria, Belgium, China, France, Germany, Israel, Italy, Japan, the Netherlands, Poland, South Korea, Spain, Switzerland, Taiwan, and the United States of America (USA). Demographics by race and geographic region of participants included in the VISION study are reported in Table 12, Document B of the company submission, and below for reference. Unlike the studies referred to that were excluded from the ITC, the VISION study included participants from a broad range of countries.[1]

Table 7. VISION: Baseline characteristics by race

	Overall	1L	2L+
	N=152 (100%)	N=69 (100%)	N=83 (100%)
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Not collected at site	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Geographic region, n (%)			
Europe	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]

- Kato et al. (2021) included seven Asian participants treated with immunotherapy. In addition to just being from an Asian population, the sample size was too low for inclusion in the MAIC analysis.[2]

- Gow et al. (2017) included 27 lung adenocarcinoma patients and 1 squamous cell carcinoma patient with METex14 skipping alterations, and all were recruited from East Asian sites. In addition to being exclusively from an Asian population, it was unclear what treatments the participants received so could not be included in the MAIC analysis.[3]

- The study by Hur et al.[4] focused on the treatments and outcomes in a group of 20 METex14 skipping alterations patients, who received chemotherapy. Profound differences were noted between the patients enrolled and those in the VISION study, for example, only 15 were Stage IV, all were from Korea, while ECOG performance status for 19 patients is given only as '0-2', with a further patient ECOG 3. Substantial differences between this study and VISION make it inappropriate for the MAIC analysis.

d. According to section D.1.1.2, only studies published as a peer-reviewed publication or abstract in the English language were eligible. Please discuss the potential biases arising from narrowing the inclusion criteria.

It was specified that only studies "… published as a peer-reviewed publication or abstract in the English language" were eligible for inclusion. Indeed, the reliance on English-language studies may not represent all of the evidence, and excluding languages other than English (LOE) may introduce a language bias. Such bias may lead to an over- or underestimation of an intervention's effectiveness.

The literature searches were not restricted by language, but the language exclusion was applied during screening per PICO. It is unclear what proportion of the studies excluded at title/abstract stage may have been excluded on language; however, none of the studies were excluded at full text due to LOE.

A5. According to section D.1.6 of the company submission, quality assessment for clinical evidence studies was conducted using the *"adapted Downs and Black adapted checklist"*.

Please provide a justification for the selection of this tool; and how (and by whom) it was adapted.

The Downs and Black checklist[5] was selected as it is considered appropriate for assessing both randomised and non-randomised studies. The amended Downs and Black was selected from a previously published review (see PDF provided <Downs-Black-Modified.pdf>), given that all studies included were non-randomised studies, and the power calculation between treatment arms was not possible to conduct.[5]

The questionnaire typically includes 27 questions: Question 11 was originally considered to cover an important risk of bias but should have been excluded in line with the typical questionnaire. Therefore the only adjustment was to the scoring of the final question regarding the power (as documented below):

- Question 5 “”are the distributions of principal confounders in each group of subjects to be compared clearly described?”: Instead of rating according to whether a list of principal confounders was provided, partially provided, or not provided, the study was assessed based on whether the list was provided or not. The maximum score was therefore 1 not 2 (yes 1, no 0).

- Question 28 “Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?”: the maximum score was 1 (rather than 5). Instead of rating according to an available range of study powers, the study was assessed based on whether the study had performed a power calculation or not (yes 1 no 0).

A6. Please provide details regarding the data extraction process.

a. **Please clarify whether a third researcher was involved in case of any disagreements in the extracted data**.

A third researcher was not involved in case of any disagreements in the extracted data. As outlined in the methods in the systematic literature review report, two reviewers were involved in the data extraction process; one author (AGa) in the first review and (AGe) in the update review [Update Review 1]) independently extracted data from all the included publications, and the same publications were extracted once again by another author (HE in the Initial Review, PC in Update Review 1). AGa and HE/AGe and PC extracted the data autonomously, meaning that two separate data extraction sheets were generated. The reviewers then compared both data extraction sheets. Finally, one uniform data extraction sheet was generated. The same process was followed in Update Review 2.

b. **According to section D.1.1.2, details of the interventions are missing. Please provide this information.**

No specific interventions were listed in the protocol. The intervention criterion allowed for any pharmacotherapy at any line of therapy for the clinical review and no restrictions were placed on interventions for the prognostic, humanistic, epidemiological, or economic reviews (refer to Appendix D, Section D.1.1.2, Table 1, p.19).

Treatments assessed in each of the included studies is reported in Table 2 “Clinical outcomes studies in NSCLC patients with METex14 skipping alterations” (refer to Appendix D, Table 2, p.28).

Decision problem

A7. According to Table 33 of the company submission, docetaxel + gemcitabine or gemcitabine monotherapy or vinorelbine monotherapy are comparators outside the NICE scope. Please justify their incorporation in efficacy and economic models.

Docetaxel plus gemcitabine, gemcitabine monotherapy and vinorelbine monotherapy are included within the efficacy data taken from the real-world cohort data. Within the all-patients group, one patient within the real-world cohort data had docetaxel plus gemcitabine as their treatment from second-line. Clinical expert opinion stated that although docetaxel and gemcitabine are unlikely to be given together in clinical practice, it is possible if treatment options are low. Within the previously treated group, one patient had gemcitabine monotherapy and two patients had vinorelbine monotherapy.

Although not listed within the final scope, these treatments are sometimes given to patients with NSCLC and hence still part of the clinical pathway.[6] As the preference is to match the comparator costs with the efficacy as closely as possible, these treatments were included within the comparator groupings economic model and costed for within the economic analysis. Other treatments which were in the real-world cohort data but not in the NICE scope and not available in the UK, such as spartalizumab, were costed as different treatments within the NICE scope. Treatments which were in the real-world cohort data and not in the NICE scope but available in the UK for other indications, such as crizotinib, were costed for within the

economic analysis to match the comparator costs with the efficacy as closely as possible.

Furthermore, when presented to clinical experts at the advisory board, they agreed that the chemotherapy groupings were appropriate (included those described above), based on expectation of similar efficacy and safety, and so these products were retained in the efficacy analysis to increase the numbers for patients treated with chemotherapy.[7]

Clinical evidence

A8. Priority question. In several sections (relating to both, clinical as well as cost effectiveness), the company submission refers to clinical expert opinion.

Please report on the methods sought to gather the clinical experts' opinions as well as the results of this process, and refer to this throughout the provided documentation, e.g. details on the validation of factors for balancing between studies in section B.2.9.6 of the company submission.

Merck conducted two main sets of meetings to obtain clinical expert opinions on a variety of topics.

The first meetings were to obtain expert input on the clinical variables thought to be prognostic and/or predictive in patients with NSCLC harbouring METex14 skipping alterations, in order to conduct the propensity score weighting between VISION and the real-world cohort data. The way clinical input was incorporated into the indirect comparison is described in Section 5.2 of the ITC report (Appendix L). *"The approach taken to expert input was to review a list of the possible covariates with the first expert via videoconference. Input was taken on the most important factors to be included in matching, and the order of importance of the variables (in case it was not possible to match on all). This ranking was then used to prepare a weighted analysis. With the second clinician (again via videoconference) the list was presented for any changes they would like to make – instead however they concurred with the variables, and the ordering of variables."*

The interactions described were conducted via videoconference, with screen sharing to allow presentation of results. These variables and weighting were then validated

separately at an advisory board with four additional clinical experts (described below).

The second main interaction was with four clinical experts and two leading health economic experts, at a 4.5 hour virtual advisory board. Extensive minutes from this meeting have been provided to NICE separately. In summary, key aspects of the disease area, clinical trial data, ITC, economic model and survival modelling were presented and discussed, and the experts provided feedback and opinions on each. For each topic, Merck asked a set of pre-defined questions which the experts discussed and answered, and consensus was gained where possible. Follow up questions were also sent out to the experts where the clinical experts provided estimated treatment mixes and market shares in NSCLC for 1L and 2L, based on the NICE scope. They answered questions on the utilities in the model, the adverse event profile of tepotinib and treatment costs and resource use in advanced NSCLC.

Merck also has a consultancy agreement with separate leading oncologists who provide additional feedback on key areas related to the NICE submission when required. These experts have been engaged recently in relation to questions from this Clarification Letter, and information from these are reported in the relevant sections of this document.

A9. Please provide further justification for the categorisation of the tumour expression of PD-L1 ≥50% versus ≤50%, i.e. the proportion score.

As defined in the decision problem, (B.1.1 of company submission) PD-L1 expression determines the treatments patients without genetic driver mutations are eligible for.[8] Previously untreated patients with PD-L1 tumour proportion score ≥50% are eligible for pembrolizumab or atezolizumab monotherapy, regardless of histology (atezolizumab monotherapy has recently been recommended by NICE), whereas patients with PD-L1 tumour proportion score <50% are not eligible for these. Both groups of patients (PD-L1<50% and PD-L1≥50%) with non-squamous histology are eligible for pembrolizumab in combination with chemotherapy, atezolizumab plus bevacizumab with carboplatin and paclitaxel, or platinum-based chemotherapy with or without pemetrexed maintenance.

For patients with PD-L1 tumour proportion score <50% and squamous histology, platinum-based chemotherapy is still available, although pembrolizumab in combination with carboplatin and paclitaxel is currently only available on the Cancer Drugs Fund (CDF). Similarly for previously treated patients, PD-L1 expression determines what treatment patients can receive, along with histology, comorbidities, contraindications, overall performance status and previous treatments.

It is important to note that PD-L1 expression determines treatment eligibility for patients without genetic driver mutations. For patients with genetic driver mutations, such as EGFR-mutant, ALK positive or ROS1 positive advanced NSCLC, their mutation status is the primary determinant of what treatment they are eligible for. Targeted therapies are now the standard of care for patients with EGFR-mutant, ALK positive or ROS1 positive advanced NSCLC.[8] Advanced NSCLC with METex14 skipping alterations is now considered to represent another group of patients who would benefit from a targeted treatment option.

A10. Please clarify how the Best Overall Response (BOR) was defined and operationalised. Furthermore, please specify who carried out the independent evaluations, e.g. BOR in section B.2.6.3 of the company submission.

The study protocol and IAP defines Best Overall Response (BOR) in line with the definition as provided by RECIST 1.1. (Eisenhauer et al. 2009;[9] section Appendix III of the study protocol). Independent assessment of tumour imaging was performed by an independent service provider, i.e. Calyx's Medical Imaging (a former business of Parexel). The independent assessment of imaging data of the VISION trial by Calyx formed the basis for the evaluation of efficacy in the VISION trial including the primary endpoint, namely objective response. Respective independent response results per patient by Calyx were shared with IQVIA data management and the BOR assessment results were derived as defined by RECIST 1.1.

A11. Please specify whether patients with Eastern Cooperative Oncology Group (ECOG) status above 1 would be offered tepotinib.

In clinical practice, patients with ECOG above 1 could be offered tepotinib, as the expected marketing authorisation [redacted].

For example, the Early Access to Medicines Scheme (EAMS) [redacted]. The decision to treat patients above ECOG 1 is driven by the fitness of the patient and this would be based on the clinical assessment by the oncologist for treatment rather than mandated in the license. This is potentially important for tepotinib as it is an oral treatment. For comparators at first line (chemotherapy, immunotherapy or immunotherapy in combination with chemotherapy) patients who are less well might be less able to tolerate the infusions, and burdensome side effect and toxicity profiles of chemotherapy. As such, tepotinib could offer a beneficial oral targeted treatment option for these patients.

A12. For all effectiveness outcomes (sections B.2.6.1 to B.2.6.7) results are split into 1L versus 2L+. Please specify which lines of anticancer therapy were used and provide all relevant results.

In VISION Cohort A (N=152), there were [redacted] patients who were previously untreated ([redacted]%). Among those who were previously treated (N=[redacted], [redacted]%), [redacted] ([redacted]%) had one prior therapy (and so had tepotinib as second-line treatment), [redacted] ([redacted]%) had two prior therapies (and so had tepotinib as third-line treatment) and [redacted] ([redacted]%) had three prior therapies (and so had tepotinib as fourth-line treatment).[10]

Results by previously untreated (1L) and previously treated (2L+) are reported in Document B, Section B.2.6 and Appendix R.

A13. As per Figure 4 of appendix E (subgroups of objective response rate [ORR]), the data consistently show better efficacy in Asian patients (race and geographic region) compared with White Caucasians or those from North America.

a. Please elaborate on those differences.

As reported in Appendix E, patients of Asian race demonstrated marginally higher ORR compared to White Caucasians. Patients from Asia (geographical region) also demonstrated marginally higher ORR compared to those from Europe or North America. However it is worth noting the small N numbers from these subgroups (N=[redacted] for Asian race, N=[redacted] for Asian geographical region, in VISION Cohort A). In the relevant figures in Appendix E, the confidence intervals cross in all instances between the race and geographic region subgroups.[1]

When looking at the larger Cohort A + C subgroup analysis for ORR (Figure 5, Appendix E), similar trends are seen with the larger patient numbers (N=[redacted] for Asian race, N=[redacted] for Asian geographical region), although the numerical differences between races and regions are even less pronounced. The confidence intervals still cross between each of the race subgroups and each of the geographic region subgroups.

METex14 is a rare oncogenic driver mutation, and in this specific patient population, the ORR with tepotinib is similar across the various geographical regions, and across race groups, demonstrating the benefit of tepotinib as a targeted treatment in patients with METex14 skipping alterations.

b. Please provide relevant results for these subgroups for all outcomes.

Results for the Asian subgroups (race and geographic region) in other outcomes are not available to provide as the VISION study was not designed and powered to assess differences in these outcomes for subgroups such as race and geographic region.

A14. According to Table 11 of the company submission, a proportion of recruited patients in the VISION study originated from Japan, South Korea, or Taiwan.

Please explain how these populations are generalisable to the United Kingdom (UK) clinical settings.

VISION was an international clinical trial that was conducted at approximately 120 treatment sites in Austria, Belgium, China, France, Germany, Israel, Italy, Japan, the Netherlands, Poland, South Korea, Spain, Switzerland, Taiwan, and the United States of America (USA).

METex14 skipping alterations are a rare mutation and so the large number of countries covered, including those from Asia, allowed for recruitment of a large number of patients (so far up to [redacted] patients in Cohort A+C at the 1 February 2021 data cut). The large number of patients recruited from various global countries also ensured adequate patient recruitment from different geographical and racial populations. VISION included [redacted]% of patients from Asian countries, however over [redacted]% were from

Europe alone (in Cohort A), and as discussed in A13 and Appendix E of the company submission, ORR rates are similar across regions and race, supporting the overall generalisability of VISION to the UK population.[1]

As described in Section B.1.3.2 of Document B, patients with METex14 skipping alterations have a number of specific characteristics which differentiate them from other types of NSCLC (wildtype or other genetic driver mutations), including older age and predominantly non-squamous histology, and these characteristics are observed across geographical regions and race, as reported in the SLR report.[11] This supports the generalisability of the patient population across geographic regions and race, in line with the specific METex14 skipping alterations population.

A15. According to Table 8 of the appendix E, patients with tissue biopsy (T+) had better outcomes, i.e. overall survival, progression free survival (PFS) and duration of response.

Please explain and discuss the differences.

Liquid (L+) and tissue biopsy (T+) are complementary approaches for the identification of actionable gene alterations in NSCLC.[12,13] Tissue biopsy has been associated with higher sensitivity and is considered the 'gold-standard', however, there are limitations to tissue sampling which liquid biopsy may overcome.[12]

As noted, there are numerical differences between the outcomes for patients with METex14 skipping alterations detected by T+ and for those detected by L+, with a trend for better outcomes in the T+ group. This comparison between the T+ and L+ group in VISION is being explored in an upcoming abstract and presentation, to be presented at the 2021 World Conference on Lung Cancer, September 8 – 14, 2021, virtual event.[14] – *Please note this reference is unable to be shared until the conference.*

- In Cohort A + C, [redacted] patients with positive detection of METex14 skipping by L+, and [redacted] by T+, were enrolled. [redacted] patients had positive detection of MET exon 14 skipping by both L+ and T+.

- A large proportion of patients enrolled ([redacted]%) were positive for METex14 skipping by T+ and negative by liquid biopsy, indicating higher sensitivity for T+.

- Baseline demographics were broadly consistent between patients enrolled by liquid (n=[redacted]) or tissue biopsy (n=[redacted]). For example, median age was [redacted] years versus [redacted] years respectively, with very similar smoking history, histology subtypes, and previous lines of therapy. However, a higher proportion of T+ patients had ECOG PS 0 ([redacted]% versus [redacted]%), and a higher proportion of T+ patients were Asian ([redacted]%) compared to L+ ([redacted]%).

- Patients enrolled by liquid biopsy had a worse prognosis, with a higher tumour load (see below) and more brain metastases ([redacted]% versus [redacted]%).

  - Median tumour load of target lesions: [redacted]_mm (range, [redacted]) for L+ versus [redacted]_(range, [redacted]) for T+.

  - L+ (N=[redacted]); [redacted]% had ≥3 target lesions, [redacted]% had ≥3 non-target lesions, documented non-target lesions: N=[redacted].

  - T+ (N=[redacted]): [redacted]% had ≥3 target lesions, [redacted]% had ≥3 non-target lesions, documented non-target lesions: N=[redacted].

- Objective response rate with tepotinib was [redacted]% in patients enrolled by liquid biopsy and [redacted]% in patients enrolled by tissue biopsy. Although ORR was consistent between patients in L+ and T+ populations, time-dependent end points were more favourable in the T+ population as noted above and in Appendix E.

- Across Cohorts A and C, [redacted] patients received at least one dose of tepotinib, and were analysed for safety. Incidence of treatment-related AEs was consistent across the L+ and T+ populations, but any-cause AEs (treatment emergent AEs) were reported in a larger proportion of L+ patients, suggesting a population with a worse prognosis.

  - Serious any-cause AEs: [redacted]% in L+ versus [redacted]% in T+

- Grade ≥3 any-cause AEs: [redacted]% in L+ versus [redacted]% in T+
- Grade ≥4 any cause AEs: [redacted]% in L+ versus [redacted]% in T+
- Any cause AEs leading to death: [redacted]% in L+ versus [redacted]% in T+

As noted above, there are a number of differences between the T+ and L+ patient groups in VISION which might explain the differences noted. The L+ patients had characteristics associated with a worse prognosis, such as higher tumour load and more brain metastases. These patients also had a higher incidence of AEs considered unrelated to tepotinib, which is in line with a worse overall prognosis. The T+ group had a higher proportion of patients with ECOG PS 0, and a higher proportion were Asian.

[redacted] particularly in the treatment-naïve setting, and likely reflect that patients enrolled through liquid biopsy had a worse prognosis.

A16. ORRs by histological classification (adenocarcinoma or squamous) are different.

Does the UK clinical population have similar rates of adenocarcinoma/squamous cell carcinoma as in the VISION study? Please provide supporting references.

In VISION Cohort A (February 2021 data cut), [redacted]% of patients (N=[redacted]) had adenocarcinoma, [redacted]% (N=[redacted]) had squamous cell carcinoma, and [redacted]% (N=[redacted]) had sarcomatoid. Similar rates were seen in the larger Cohort A + C group.

There are very limited UK-specific prevalence data for patients with METex14 skipping alterations reporting histology subtype. The only study Merck identified is Benafif et. al. 2021 (presented at BTOG 2021). In this study, 27/30 patients (90%) had adenocarcinoma histology, 1/30 (3.3%) had adenosquamous, and 1/30 (3.3%) had sarcomatoid. Based on the limited published data for METex14 skipping alterations in the UK, the rates of adenocarcinoma/squamous seem similar between

the published evidence and VISION study. However, given the low patient numbers reported here, there are limitations to this analysis. Merck are aware of ongoing studies in the UK in patients with METex14 skipping alterations, as well as the ongoing EAMS for tepotinib, so more data for UK patients will become available in the coming years.

In larger studies outside of the UK reporting on the histology subtypes of patients with METex14 skipping alterations, the rates of different subtypes appear to be similar to VISION. In the SLR report (provided separately), which pooled data from up to 29 studies, adenocarcinoma histology was present in 72% (mean) and 79% (median) of METex14 skipping alterations patients; squamous was present in 9% (mean) and 3% (median); and sarcomatoid was present in 13% (mean) and 3% (median).[11]

When looking at a single study with the largest patient numbers reporting on histology subtype (Schrock et. al. 2016; N=298),[15] 68.8% were adenocarcinoma, 8.4% were squamous and 3% were sarcomatoid. These rates are also similar to VISION, although VISION does appear to have marginally higher rates of adenocarcinoma compared to this study.

Overall, the rates of different histology subtypes in VISION appears to be similar to the wider METex14 skipping alterations NSCLC population reported across a wide range of studies. This was confirmed with clinical experts at the advisory board who agreed that the patient characteristics in VISION were generally reflective of the METex14 skipping alterations population, including for histology.[7]

A17. Please clarify whether any additional variables were able to be matched on in the indirect treatment comparison (ITC), in addition to prior treatment experience, age, metastatic/stage IV disease, sex, histology and history of smoking.

For any variables available but not matched please explain why these were not matched. If available, please provide additional ITC results based on the variables not previously matched.

As described in the ITC report (Appendix L), the variables selected for matching were those deemed clinically relevant, for example age and sex. Similarly, how

characteristics were included was taken from clinical expert opinion; e.g., mean age rather than age above or below 70.

Although additional variables were available should clinicians have felt they were clinically relevant (such as height, weight, or stage) the clinical experts elected to include only the selected variables.

Given the lack of rationale for including any further characteristics, and clinical support for not, particularly given the small sample sizes (and likely missing data which reduce sample sizes further), the ITC has not been rerun to include further variables.

A18. In section B.2.9.3, the company states that *"this approach was considered reasonable given the expected similar outcomes in efficacy within the treatment classes in NSCLC, supported by the literature"*.

Please clarify whether any studies have been conducted to show that chemotherapies used for NSCLC are equally effective, or whether this approach has only been taken for previous NICE submissions.

As reported in Section B.2.9.3 of the company submission, the grouping of comparators has been used in previous NSCLC NICE submissions, such as TA531 where the comparator arm was comprised of a mix of chemotherapy and platinum-based chemotherapy regimens.[16] Additionally, this approach has been used in other NICE oncology submissions (TA517, TA502 and TA541)[17-19] where the comparators comprised a basket of chemotherapies. These were considered appropriate given the assumption of similar efficacy. As such, this approach was considered reasonable given the expected similar outcomes in efficacy within the treatment classes in NSCLC.

However, this approach is also supported by a number of studies which show similar efficacy between chemotherapy regimens in NSCLC:

- Pilkington et al 2015[20] evaluated clinical effectiveness of chemotherapy treatments recommended by NICE for the first-line treatment of advanced NSCLC based on a systematic search of randomised control trials published from 2001 to 2010. Relative treatment effects for OS and PFS were estimated

using standard meta-analysis and mixed treatment comparison methodology. A total of 23 RCTs were included: 18 trials compared platinum-based chemotherapy, two compared pemetrexed and three compared gefitinib. There were no statistically significant differences in OS between any of the four third-generation chemotherapy regimens (paclitaxel, docetaxel, gemcitabine, vinorelbine) in combination with platinum agents for squamous and non-squamous disease (see Table 1 and 2 within publication).

- Horita et al 2017[21] reports a systematic literature review of chemotherapy regimens for advanced NSCLC based on randomised control trials with outcomes analysed using the frequentist weighted least squares approach random-model network meta-analysis. The authors concluded that a number of platinum-based chemotherapy regimens did not have statistically significant poorer OS and were acceptable first-choice regimens.

- Zhu et al 2013[22] used data from SEER-Medicare to identify first-line chemotherapy agents administered to patients with Stage IIIB or IV NSCLC diagnosed between 2000 to 2007. Crude median survival demonstrated similar survival between the paclitaxel/gemcitabine/docetaxel and carboplatin (8.0, 7.3 and 7.5 months, respectively). Multivariate Cox proportional hazard models demonstrated only slight inferior survival for paclitaxel plus carboplatin compared to docetaxel/gemcitabine plus carboplatin.

In addition to the above, in the previous NICE submission TA658 (previously TA557), the company conducted a network meta-analysis including various chemotherapies for NSCLC. The results demonstrated that for the majority of chemotherapy regimens versus other chemotherapy regimens, non-statistically significant differences were seen for OS and PFS (see company submission Table 42 and Table 43 for TA658).[23]

No evidence was found for previously treated chemotherapy regimens, however, clinical opinion sought in the early stages of the submission development confirmed that for different chemotherapies, similar efficacy would be expected in this setting.

A19. Please update Table 22 to include post-weighting bias amounting for all variables, rather than P values, which are affected by both the degree of

difference in each variable as well as the number of participants within each category.

We believe the ERG may in this case be asking for the standardised mean differences (SMD), which are already provided in Table 23 and Table 24 of Document B. The SMD gives a measure of difference that is unaffected by sample size. Mean values are also provided in the table such that if desired, the ERG are able to calculate the mean difference before and/or after weighting.

A20. In section B.2.9.7.1, the company states that *"all characteristics with the exception of one looked balanced between tepotinib and the immunotherapy data"*: Please give the definition of "balanced" here and provide evidence to support the view that these characteristics are balanced.

As described in Section 5.2 of the ITC report (Appendix L), the generally accepted definition of balanced at baseline is p-values and standardised mean differences (SMDs) where values of >0.1 and <0.1 are generally deemed to be measures of acceptable similarity in data.[12] In addition to these statistical tests, values were presented to clinicians to judge whether the groups appeared similar; it is unlikely (even in an RCT) values will be perfectly balanced between groups, however large differences in multiple characteristics could be indicative of a biased comparison.

In this instance, Table 24 of the submission shows the area where there is an SMD and p-value difference (only for one characteristic) as 3/151 tepotinib patients had non-metastatic disease, compared to all the immunotherapy patients who had metastatic disease. Although extremely small in number, this reaches statistical significance. It was not, however, thought to be clinically significant according to the clinical experts, especially given the low numbers who had non-metastatic disease.

A21. Please clarify what the effective sample sizes were for the real-world cohorts in the indirect comparisons after weighting with propensity scores. Please note that by *"effective sample size"* we refer to the effective sample size for weighted samples, e.g. using Kish's effective sample size, rather than that used in Table 24 of Document B, which the ERG does not recognise as an "effective sample size" but rather the "weighted sample size".

Thank you for highlighting this. The ERG is correct, what was labelled as 'ESS' in the tables is more correctly the weighted sample size (WSS). This has been corrected within Document B. Sample size, and [accurate] expected sample size (ESS), for each of the comparisons when data is reweighted to match the tepotinib data is provided in Table 8.

Table 8. Effective sample size by overall, naive and experienced cohorts

Group	Overall n (ESS)	Untreated n (ESS)	Previously treated n (ESS)
VISION	151 (151.0)	69 (69.0)	82 (82.0)
Immunotherapy	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]

Abbreviations: ESS, effective sample size

A22. Please include confidence intervals in Figures 24 to 27 in document B of the company submission.

The requested plots are provided in Figure 1 to Figure 4 and have been added to the revised Document B.

Figure 1. Chemotherapy PFS weighting

Figure 2. Chemotherapy OS weighting

Figure 3. Immunotherapy only PFS weighting

Figure 4. Immunotherapy only OS weighting

A23. Please elaborate on how non-interventional studies were conducted and/or included to inform the comparator efficacy data (section B.2.2 of the company submission).

The following text has been added to Section B.2.2 of the company submission and the ITC report provided separately has been clearly signposted in Document B, section B.2.2:

"Non-interventional studies investigating patient characteristics, treatment patterns and effectiveness outcomes in patients with advanced NSCLC harbouring METex14 skipping alterations were also conducted and included in the indirect comparisons and cost-effectiveness analysis to inform the comparator efficacy data (Table 7). For further detail please see Section B.2.9 and the indirect treatment comparison report (Appendix L) provided separately.

Study	0015	0035	COTA	Wong et al
Country	USA	Israel, The Netherlands, Taiwan, USA	USA and Canada	Canada
Study type	Non-interventional real world	Non-interventional real world retrospective	Data source based on EMR	Non-interventional real world

	retrospective cohort study based on EMR data	cohort study, based on EMR data	data sourced from COTA Healthcare	retrospective review
Study period	01 Jan 2004 to 30 Sept 2019	01 Jan 2010 to 30 Sept 2018	15 Aug 2008 to 10 Feb 2020	Jan 2016 to Sept 2019
N (before application of inclusion criteria)	39 with MET alterations	86 with MET alterations	202	41[a]
Treatment lines	76	165	680	NR

Abbreviations: NR, not reported; OS, overall survival; PFS, progression free survival; RR, response rate; ToT, time on treatment; TTNTD, time to next treatment or death

Notes:

a Data was available for 41 patients, though not all received treatment

Missing information and documents

A24. According to appendix F, safety results are only available for the VISION study. It is unclear why other relevant studies were omitted, e.g. Paik PK et al. Ann Oncol 2020; 31: S494-S495 or Xiong W et al. J Thoracic Oncol 2021; 16: S36).

Please provide the adverse event details for studies other than VISION, or justify their exclusion.

Safety results have been provided for the studies requested in clarification question A2.

The cited studies – Paik et al. Ann Oncol 2020; 31: S494-S495 or Xiong et al. J Thoracic Oncol 2021; 16: S36 – included participants from Cohort A of the VISION study along with participants from broader population (e.g. solid tumours), hence they were not aligned with PICO and initially excluded.

A25. According to Table 2 of appendix D (Clinical outcomes studies in NSCLC patients with METex14 skipping alterations), VISION is referred to as a two-arm interventional trial, whereas elsewhere in the company submission, a single-arm trial is referred to.

Please clarify this discrepancy.

VISION was an open-label, Phase 2 study, which administered tepotinib once daily in patients with locally advanced or metastatic NSCLC (advanced NSCLC) with a

confirmed METex14 skipping mutation. This has been corrected in Table 2 of Appendix D.

A26. The Wong et al. real-world dataset does not exclude any participants.

Please clarify whether this is due to the inclusion/ exclusion criteria of Wong et al. matching those of VISION or whether there are other reasons, e.g. insufficient data to exclude participants from Wong et al.

The ERG is correct; after merging into the dataset, no Wong et al.[24] patients were excluded, and all were eligible for inclusion in the final ITC. This is likely as the patients included in the Wong et al. publication had already been filtered by the authors to be those with advanced NSCLC and the correct mutation. This is in contrast to the (raw) datasets in the Merck conducted studies (0015, 0035 and COTA). In these studies patients were included from the beginning of their treatment, with other patients with different mutations also included – who then had be excluded to match the criteria for the VISION study. Therefore, the likely reason for the lack of patients being excluded from Wong et al. was that these steps had already been taken previously.

A27. Please include VISION in Table 19 of document B.

VISION data have been added to Table 20 of Document B (also reported below). Please note that this information is also provided in Table 11 and Table 12 of the data on file ITC report (Appendix L) provided in the reference pack.

Please also note that the reported n (%) for treatment experienced has been corrected (aligned to the ITC report provided), as the values reported in the submitted Document B were reflective of the n (%) untreated.

Table 20. Comparator baseline patient characteristics prior to weighting, compared to the VISION dataset

Characteristic	VISION	Chemotherapy	Immunotherapy
n	[redacted]	[redacted]	[redacted]
Study (%)			
0015	[redacted]	[redacted]	[redacted]
0035	[redacted]	[redacted]	[redacted]
COTA	[redacted]	[redacted]	[redacted]
Wong et al.	[redacted]	[redacted]	[redacted]

Characteristic	VISION	Chemotherapy	Immunotherapy
VISION	[redacted]		
Age (mean, (SD))	[redacted]	[redacted]	[redacted]
Age over 75 (%)	[redacted]	[redacted]	[redacted]
Treatment Experienced (%)	[redacted]	[redacted]	[redacted]
Male (%)	[redacted]	[redacted]	[redacted]
Race			
Asian	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
History of smoking (%)	[redacted]	[redacted]	[redacted]
ECOG			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Stage (%)			
IIIB	[redacted]	[redacted]	[redacted]
IIIB/C	[redacted]	[redacted]	[redacted]
IIIC	[redacted]	[redacted]	[redacted]
IV	[redacted]	[redacted]	[redacted]
IVA	[redacted]	[redacted]	[redacted]
IVB	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Metastatic disease; (%)	[redacted]	[redacted]	[redacted]
Histology			
Adenocarcinoma	[redacted]	[redacted]	[redacted]
Squamous	[redacted]	[redacted]	[redacted]
Sarcomatoid	[redacted]	[redacted]	[redacted]
Others	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; SD, standard deviation

Section B: Clarification on cost-effectiveness data

Literature searches

B1. Please confirm that the searches conducted to identify cost-effectiveness studies (appendix G) are the same searches as those conducted in appendix D, but with a cost effectiveness filter.

The searches to identify prior cost-effectiveness studies were re-run; however, they used the same population terms as those reported in Appendix D and applied a cost-effectiveness filter. It is accepted that this largely repeats work that was reported for the systematic review documented in Appendix D; however, title/abstracts retrieved were screened per the eligibility criteria specified in Appendix G (Section G.1.1.2).

Time to event analysis

B2. Priority question. It was reported in the company submission that clinical expert advice was that time to next treatment or death (TTNDT) would be a conservative estimate of PFS. Please supply information and data in support of this assumption.

Time to next treatment or death (TTNTD) was calculated for the Cohort A patients from VISION in order to form a comparison to progression-free survival (PFS) for the same set of patients. Figure 5 presents the PFS (by investigator definition as used in the economic model) and TTNTD curves from Cohort A of the VISION February 2021 data-cut. Summary statistics for both endpoints are provided in Table 9. While not statistically significantly different (p=0.15), median TTNTD is shown to be greater than median PFS ([redacted] versus [redacted], respectively), thus, providing evidence that the assumption to use TTNTD as a proxy for missing PFS data is likely to be conservative, if this trend holds true for the real-world cohort comparator data.

Figure 5: Kaplan-Meier curves of PFS and TTNTD for all VISION patients

Abbreviations: p, p-value; PFS, progression-free survival; TTNTD; time to next treatment or death.

It was considered that the extension in TTNTD over PFS may be caused by patients discontinuing tepotinib due to progression and not going on to receive a subsequent therapy, therefore the TTNTD is uplifted by the OS time for these patients. Of the 151 ITT patients, 60 received a subsequent therapy so an exploratory analysis was performed to compare the outcomes in this patient group. Figure 6 provides a comparison of PFS and TTNTD between the 60 patients who went on to receive a subsequent therapy. The KM curves are closer than those seen in Figure 5 however, TTNTD continues to be greater (median of [redacted] versus median PFS of [redacted]) and the difference remains insignificant (p=0.17). Summary statistics for both endpoints are provided in Table 9.

Figure 6: Kaplan-Meier curves of PFS and TTNTD for all VISION patients who received a subsequent treatment

Abbreviations: p, p-value; PFS, progression-free survival; TTNTD; time to next treatment or death.

Table 9 presents the summary statistics for PFS and TTNTD from VISION for all ITT patients and patients who received a subsequent therapy only. Both the median and restricted mean survival time (RMST) are greater for TTNTD compared to PFS (by investigator definition).

Table 9: Summary statistics of PFS and TTNTD from VISION

	PFS	TTNTD
All patients	[redacted]	[redacted]
Patients with event, n (%)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
RMST	[redacted]	[redacted]
Patients with subsequent treatments only	[redacted]	[redacted]
Patients with event, n (%)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
RMST	[redacted]	[redacted]

Note: PFS refers to investigator definition.
Abbreviations: CI, confidence interval; n, number; PFS, progression-free survival; RMST, restricted mean survival time; TTNTD; time to next treatment or death.

In addition to the evidence from VISION, clinical experts at the advisory board stated that they would expect PFS to be shorter than TTNTD given the delay from progression to actually receiving treatment.[7]

B3. Priority question. Please provide the median, mean and 95% confidence interval (CI) for overall survival (OS), PFS and time on treatment (ToT) for each treatment using the company-preferred survival models in section B.3.3 of the company submission side-by-side with the same data from the Kaplan-Meier curves derived from the primary ITC (based on the propensity score matched populations).

Table 10 presents the summary statistics of OS, PFS and ToT for each treatment using the company-preferred survival models and the Kaplan-Meier estimates. The values for immunotherapy and chemotherapy are based on the propensity score weighted populations. The overall analysis set for the economic and survival modelling comprised 151 patients; one patient was excluded from ITT efficacy analyses due to insufficient METex14 skipping alteration data at the time. This ITT data was taken forward for the efficacy data applied in the cost-effectiveness model.

Table 10: Summary statistics of OS, PFS and ToT for tepotinib, immunotherapy and chemotherapy from the KM estimate and the company-preferred survival model

	OS		PFS		ToT	
	KM	Model	KM	Model	KM	Model
Tepotinib, n	[redacted]		[redacted]		[redacted]	

	OS		PFS		ToT	
	KM	Model	KM	Model	KM	Model
Patients with event, n (%)	[redacted]	-	[redacted]	-	[redacted]	-
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RMST [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy, n (weighted)	[redacted]	-	[redacted]	-	-	-
Patients with event, n (%)	[redacted]	-	[redacted]	-	-	-
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	-	-
RMST [a]	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Immunotherapy, n (weighted)	[redacted]	-	[redacted]	-	-	-
Patients with event, n (%)	[redacted]	-	[redacted]	-	-	-
Median (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	-	-
RMST [a]	[redacted]	[redacted]	[redacted]	[redacted]	-	-

Note: PFS refers to investigator definition. [a] RMST for PFS and OS capped by maximum immunotherapy time (35.1 months for OS and 32.9 months for PFS). RMST for ToT capped by VISION max time (50.6 months)
Abbreviations: CI, confidence interval; n, number; OS, overall survival; PFS, progression-free survival; RMST, restricted mean survival time; ToT, time on treatment; TTNTD; time to next treatment or death.

B4. Priority question. Please explain the methods used to elicit clinical expert opinion and how the responses were used to inform the selection of models to fit to the time to event data and the distribution of treatments used in UK clinical practice (both as immunotherapy and chemotherapy comparators to tepotinib and also as subsequent treatments). Please provide the clinical expert responses.

As part of the advisory board, discussed in A8 and as part of the meeting report provided to NICE, we presented the different survival curves to the clinical experts, for the line agnostic population, for chemotherapy, immunotherapy, and tepotinib groups. We asked the experts how many patients they expected to be alive/progression free/on treatment for each group, at different time points. We also asked for feedback on which curves were plausible or not, and which were most likely, based on their knowledge and how many patients they would expect to be alive or progression free at certain long term timepoints. These responses described in the meeting report are provided below.

Chemotherapy: PFS

- The clinical experts agreed a very small proportion of patients will remain progression free for an extended period of time, even on chemotherapy, as there are always some responders.
    - It is reasonable to assume 0.2% will be progression free at 10 years so, we can rule out 0.0% PFS at 10 years. 1% PFS at 5 years sounds about right.
- Line of therapy differences
    - 1L likely to be better than 2L+.
    - 2L+ patients are likely to progress very quickly on chemotherapy, so exponential could capture best for 2L+.
- The clinical experts agreed it is important to validate against long term published data for chemotherapies.
- Finally, one clinical expert mentioned that curves will be different for platinum doublet chemotherapy versus single agent docetaxel.

Immunotherapy: PFS

- Expect a small number of patients to be long term responders (1-4% at 5 years).
- Curve preferences for clinical experts:
    - Can rule out Gompertz (too high), as well as exponential and Weibull (too low).
- Line of therapy differences
    - Would not expect results to be too different by line, maybe slightly better at 1L due to PD-L1 expression selection at 1L, but not much. IO works well across lines.

Chemotherapy: OS

- We could use long-term KEYNOTE-10 data to validate.
- Given the age of patients, 0% at 20 years is possible.
- One expert stated that we'd expect 5-year survival around 5%, but a greater plateau would be expected vs. all the extrapolations listed (closer to log logistic, log normal or gen gam) in the long term to reflect the long-term IO benefit.
    - Another expert expected a slightly higher percentage at 5 years

    - It was discussed that we would need to ensure we apply background mortality.
- It is hard to be certain of the OS extrapolations, given 1) uncertainty/lack of data in the METex14 population 2) the confounding factors with the OS data, particularly the subsequent treatments. Some patients in the chemotherapy group also had IO at some point which will impact long term OS.
    - One expert said we have to consider this in the context of poorer responses to IO in the METex14 population though.

Immunotherapy: OS

- Again, the clinical experts stated that these extrapolations underestimate the plateau. They seem steep at 5-8 years, where they would expect fewer patients to die then.
- All patients have IO treatment in this group, so we'd expect higher survival than the chemotherapy group. Therefore, the more optimistic curves should be selected to reflect the long-term IO benefit. However, it would be good to validate against 5-year IO data.

Tepotinib PFS

- The clinical experts agreed that it is reasonable to assume based on other targeted treatments, that the higher estimates would be used for PFS (gen gam, gompertz, log-logistic, log normal)
- One HTA expert said that AIC and BIC are not that useful here, as the scores are very close.

Tepotinib OS

- It was discussed that it is harder to estimate OS because of subsequent treatments and treatment sequencing.
- Curve preferences for clinical experts:
    - All estimates plausible.
    - Wouldn't expect tepotinib to be lower than IO, so at least similar. Based on what we observed in the KM OS data, we would expect similar over the long term. Although there might be a small group who respond well to IO in the long term, more than tepotinib.
    - It was agreed the top 2 are the most likely (log logistic, log normal)

Tepotinib - time on treatment

- Expect to be similar to PFS. Small proportion will continue on treatment for 5+ years.

Subsequent treatments

- It was discussed that it was hard to derive conclusions on the observed OS and extrapolations, based on what patients would likely receive at subsequent lines of therapy.
- The comparator cohorts received a wide range of treatments (some not in UK clinical practice), so a clear understanding around the subsequent treatments is required. As most these data are from the US, the treatment approaches tend to be more aggressive, e.g. immunotherapy after a previous immunotherapy, as well as other MET inhibitors.

B5. The median OS for chemotherapy estimated from the real-world data was worse than the estimated median OS for tepotinib.

Please provide published evidence to support the estimated median OS in chemotherapy derived from the propensity score matched real-world data for the target population.

Section B.3.2 describes the validation of the real-world data for chemotherapy and immunotherapy, including external validation comparing to published studies. The comparison of the estimated median OS in chemotherapy from the real-world data compared to published evidence is described below.

External sources used for this validation consists of:

- Real-world retrospective studies for patients with NSCLC with METex14 skipping alterations treated with immunotherapy or chemotherapy
    - Awad et al 2019[25] is a retrospective study of 148 patients with METex14 skipping alterations, across multiple treatment lines. The study describes outcomes seen in a real-world METex14 skipping alterations population treated with different treatments, focussing on whether a MET inhibitor improves outcomes. 34 patients included in the study did not receive a MET inhibitor (predominantly chemotherapy).

- Hur et al.[4] is a retrospective analysis of patients with METex14 skipping alterations in Korea diagnosed between January 2015 and July 2017 (N=20), including those who were treated with first-line chemotherapy. Please note this was not included in the initial validation section of the dossier.

- Recent trial data in the wider advanced NSCLC population (KEYNOTE-024,[26] KEYNOTE-189,[27] KEYNOTE-042,[28] KEYNOTE-010[29] and CheckMate 017/057[30]

  - KEYNOTE-024 is a Phase III randomised controlled trial of pembrolizumab versus platinum-based chemotherapy (carboplatin or cisplatin plus gemcitabine or pemetrexed or paclitaxel) in PD-L1≥50% advanced first-line NSCLC patients.[26]

  - 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 non-squamous advanced NSCLC.[27]

  - KEYNOTE-042 is a Phase III randomised controlled trial comparing first-line pembrolizumab monotherapy versus chemotherapy (carboplatin plus pemetrexed or paclitaxel) in patients with advanced NSCLC who are PD-L1 positive (>1%).[28]

  - 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.[29]

  - 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.[30]

- A real-world study of older patients with wildtype advanced NSCLC treated with chemotherapy: Gajra et al .[31] which pooled data from three first-line clinical trials for advanced NSCLC treated with chemotherapy to compare outcomes of the older patients (≥ 70 years; n=736) versus younger patients (<70 years; n=270).

The median OS from each study is reported in Table 11 below. In Figure 52 of Document B, the Kaplan-Meier graphs are also presented.

Table 11. Median overall survival by trial

Study	Population	N	Line of therapy	Treatment	Median OS (95% CI)
Real-world cohort data derived using propensity scoring	Advanced NSCLC harbouring METex14 skipping alterations	66 (before weighing) 152 (after weighting)	1L, 2L+	Mixture of chemotherapy regimens	[redacted]
Awad et al 2019[25]	Advanced NSCLC harbouring METex14 skipping alterations	34	1L, 2L+	Platinum based regimens (64%) and/or pemetrexed based regimens (61%)	8.1 months (5.3, NR)
Hur et al[4]	Advanced NSCLC harbouring METex14 skipping alterations		1L	Mixture of chemotherapy regimens	9.5 months (6.5, 23.1)
Gajra et al, 2018[31]	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)
KEYNOTE-024[26]	Advanced NSCLC with PD-L1 >50%	151	1L	Platinum-based chemotherapy regimens	13.4 months (9.4, 18.3)
KEYNOTE-189[27]	Advanced NSCLC	206	1L	Pemetrexed and platinum	10.7 months (8.7, 13.6)
KEYNOTE-042[28]	Advanced NSCLC with PD-L1 >1%	615	1L	Platinum-based chemotherapy regimens	12.1 months (11.3, 13.3)
KEYNOTE-010[29]	Advanced NSCLC	309	2L	Docetaxel	8.4 months (7.6, 9.5)
CheckMate 017/057[30]	Advanced NSCLC	427	2L	Docetaxel	8.1 months (7.2, 9.2)

Overall, the median OS from the real-world data used for the ITC appears to be overestimated when comparing against external sources for chemotherapy, including substantially higher than the other studies specifically in the METex14 skipping alterations population. When compared to the clinical trial data in advanced NSCLC, the median OS from the real-world cohort chemotherapy group is higher, regardless of line of therapy, PD-L1 expression and specific treatment. As the real-world cohort data is a mixture of 1L and 2L+ patients, it could be expected that the median OS would be between the median OS of the 1L and 2L studies, but it is higher than the 1L studies.

Clinical experts at the advisory board noted the aggressive subsequent treatment usage in the real-world data sets (e.g., high use of targeted MET inhibitors) which is likely having an impact on the survival observed. Therefore this conservative estimation compared to tepotinib should be taken into consideration during the decision making process in the chemotherapy comparisons.

B6. In section B.2.9.7.3 of the company submission (page 99), it states that the median PFS for chemotherapy was 3.9 months. In section B.3.3.2 (page 148), it states that a cut-off time of 3.2 months was selected for piece-wise modelling of chemotherapy PFS and that one reason for this was that this was the median PFS for chemotherapy.

Please clarify this apparent inconsistency.

There is a discrepancy in the original text which has been revised in the updated Document B (pages 148-149). Piece-wise parametric curves were only implemented for immunotherapy PFS as spline models provided a suitable visual fit to the chemotherapy data (CS Doc B, Figure 41).

B7. Table 37 of the company submission (page 148) only refers to piece-wise parametric curves with respect to immunotherapy, not chemotherapy.

Please clarify whether there is an error in the Table or in the text and please clarify the use of piece-wise modelling for both chemotherapy and immunotherapy to model PFS.

Piece-wise parametric modelling was only implemented for immunotherapy PFS.

Figure 39 in Document B of the company submission presents the diagnostic plots of PFS for immunotherapy and chemotherapy. The plots indicated that parametric models were unlikely to provide a good fit to the observed data due to a lack of flexibility to capture the underlying shape of the hazard function. Parametric models provided an extremely poor visual fit to the immunotherapy PFS data and provided a reasonably poor visual fit to the chemotherapy PFS (shown in Figure 40 [CS Doc B]). Therefore, spline models were fit to the data for both comparators, resulting in a range of reasonable curves to choose between for chemotherapy (Figure 41 [CS Doc B]). However, a poor visual fit to the immunotherapy PFS data remained when extrapolating with spline models, thus a piecewise modelling approach was undertaken in order to more accurately capture the observed data.

Comparators

B8. Priority question. Please clarify how the real-world treatment distribution presented in Table 33 was derived.

a. **Why do some combination therapies in Table 33 (page 125) differ from those listed in Tables 20 and 21 of the company submission (pages 91 to 92)? Please explain.**

Tables 21 and 22 of the company submission present the distribution of treatments received by the real-world cohort for immunotherapy and chemotherapy. Some of these treatments are not used in UK practice (e.g., durvalumab) while others were not specific about the treatment received (e.g., “immunotherapy”). Table 34 presents the treatment distributions following the redistribution of those that were either not specific or, not used in UK practice to treatments that are. The distributions in Table 34 are the proportions implemented within the economic model.

Table 12 and Table 13 below present the original treatments from the real-world cohort detailing what these are categorised as within the economic model to inform the costs.

Table 12: Re-distributions of immunotherapies for the economic model

Original treatment	Model treatment category	Immunotherapy (n=51)	
		Frequency	Percent
Pembrolizumab	Pembrolizumab	[redacted]	[redacted]
Immunotherapy [a]	Other	[redacted]	[redacted]
Nivolumab	Nivolumab	[redacted]	[redacted]
Ipilimumab & nivolumab	Ipilimumab + nivolumab	[redacted]	[redacted]
Durvalumab [a]	Other	[redacted]	[redacted]
Spartalizumab [a]	Other	[redacted]	[redacted]

Note: [a] The 'other' category are re-distributed proportionally between the remaining treatments

Table 13: Re-distributions of chemotherapies for the economic model

Original treatment	Model treatment category	Chemotherapy (n=66)	
		Frequency	Percent
Carboplatin & pemetrexed	Pemetrexed + platinum	[redacted]	[redacted]
Platinum doublet [a]	Other	[redacted]	[redacted]
Bevacizumab, carboplatin & pemetrexed	Pemetrexed + platinum	[redacted]	[redacted]
Carboplatin & paclitaxel	Pemetrexed + platinum	[redacted]	[redacted]
Docetaxel	Docetaxel	[redacted]	[redacted]
Pemetrexed	Pemetrexed + platinum	[redacted]	[redacted]
Cisplatin & pemetrexed	Pemetrexed + platinum	[redacted]	[redacted]
Pemetrexed & bevacizumab	Pemetrexed + platinum	[redacted]	[redacted]
Bevacizumab, cisplatin & pemetrexed	Pemetrexed + platinum	[redacted]	[redacted]
Carboplatin [a]	Other	[redacted]	[redacted]
Carboplatin & gemcitabine	Gemcitabine + platinum	[redacted]	[redacted]
Cisplatin & etoposide	Docetaxel + platinum	[redacted]	[redacted]
Cisplatin & gemcitabine	Gemcitabine + platinum	[redacted]	[redacted]
Cisplatin & vinorelbine	Vinorelbine + platinum	[redacted]	[redacted]
Everolimus [a]	Other	[redacted]	[redacted]
Gemcitabine & vinorelbine	Docetaxel + gemcitabine	[redacted]	[redacted]
Vinorelbine	Vinorelbine monotherapy	[redacted]	[redacted]

Note: [a] The 'other' category are re-distributed proportionally between the remaining treatments

b. Was the distribution presented in Table 33 based on the original real-world data set or based on the propensity score adjusted population data set?

The treatment distribution presented in Table 34 (based on the updated dossier table numbers) is based on the propensity score adjusted population data set.

c. **If the Table 33 distribution was based on the original real-world data set, please present the treatment distribution based on the propensity score matched population data set.**

The treatment distribution presented in Table 34 (based on the updated dossier table numbers) is based on the propensity score adjusted population data set.

B9. Priority question. The table in "Treatment costs" (cells D97:S115) in the Excel model presents UK clinical practice treatment mix distribution for untreated and treated populations. These data do not appear to be presented anywhere in the company submission.

a. **Please provide tables of these data.**

Table 14 and Table 15 present the treatment distributions for the comparators in the untreated and previously treated populations implemented in the economic model. The treatment distributions are based on the propensity score weighted real world cohort, redistributed to reflect treatments that are used in UK practice.

Table 14: Comparator treatment distributions for the untreated patient population

Category	Treatment	Real-world data (base case)	UK clinical practice (scenario)
Immunotherapy	Pembrolizumab	[redacted]	[redacted]
	Atezolizumab	[redacted]	[redacted]
	Nivolumab	[redacted]	[redacted]
	Nivolumab + ipilimumab	[redacted]	[redacted]
Chemotherapy	Docetaxel + platinum	[redacted]	[redacted]
	Gemcitabine + platinum	[redacted]	[redacted]
	Paclitaxel + platinum	[redacted]	[redacted]
	Vinorelbine + platinum	[redacted]	[redacted]
	Pemetrexed + platinum	[redacted]	[redacted]
	Docetaxel monotherapy	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]
	Docetaxel + gemcitabine [a]	[redacted]	[redacted]
	Gemcitabine monotherapy [a]	[redacted]	[redacted]
	Vinorelbine monotherapy [a]	[redacted]	[redacted]

Table 15: Comparator treatment distributions for the previously treated population

Category	Treatment	Real-world data (base case)	UK clinical practice (scenario)
Immunotherapy	Pembrolizumab	[redacted]	[redacted]
	Atezolizumab	[redacted]	[redacted]
	Nivolumab	[redacted]	[redacted]
	Nivolumab + ipilimumab	[redacted]	[redacted]
Chemotherapy	Docetaxel + platinum	[redacted]	[redacted]
	Gemcitabine + platinum	[redacted]	[redacted]
	Paclitaxel + platinum	[redacted]	[redacted]
	Vinorelbine + platinum	[redacted]	[redacted]
	Pemetrexed + platinum	[redacted]	[redacted]
	Docetaxel monotherapy	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]
	Docetaxel + gemcitabine [a]	[redacted]	[redacted]
	Gemcitabine monotherapy [a]	[redacted]	[redacted]
	Vinorelbine monotherapy [a]	[redacted]	[redacted]

Notes: [a] These treatments were not listed within the NICE final scope however are included as they are incorporated within the efficacy and therefore costed for.

b. Please explain how these data were derived.

As described in Appendix P, the UK clinical practice treatment distributions were informed by UK clinical opinion (N=3), as follow up questions to the advisory board in May 2021. Clinicians were asked to provide market share estimates per subgroup of the available treatments listed in the NICE scope with an option to add others not listed. For the model, a number of steps were then taken to estimate the distribution of treatments in the required format:

1. The average distributions of the three clinical responses were first re-weighted to exclude non comparators; best supportive care, and pembrolizumab plus carboplatin plus paclitaxel as it is in the CDF.

2. The treatments were then weighted based on the proportion of patients who are untreated vs previously treated, and squamous versus non-squamous using the proportions from the VISION data. Patients who were PD-L1 ≥50% versus PD-L1 < 50% was estimated from Aggarwal et al, 2016[32] using pooled data from KEYNOTE 001, 010 and 024.

B10. Priority question. Please present the 1st and 2nd line distribution characteristics of the propensity score matched populations for immunotherapy and chemotherapy.

Please find the requested tabulations in the accompanying Excel workbook.

B11. Priority question. Please provide the details of the method used to derive the distribution of treatments for the untreated population reported in Tables 29 and 47, appendix N, sections N.1.1.2 and N.1.2.2. (pages 142 to 143 and 206 to 207, respectively).

The treatment distributions for the untreated and previously treated populations were based on the propensity score weighted data sets.

Treatments received by patients in the real-world cohort that were either not considered UK practice or were not specific about the treatment received (e.g., "immunotherapy"), were re-weighted to other treatments within the same treatment class. For instance, durvalumab was redistributed between the included immunotherapy regimens. The proportion of patients assigned to each treatment was then calculated after redistribution.

Table 16 provides an example of the calculations used to derive the treatment distribution proportions. The example uses the weighted immunotherapies from the untreated population ([redacted]). The calculation used to redistribute non-UK practice/non-specific treatments is as follows:

Redistributed N = N + (sum of non-UK practice/non-specific treatments)(N/(sum of UK practice treatments)*

Table 16: Method to derive treatment distribution example (based on untreated immunotherapy patients)

Treatment	N	Redistribution calculation	Redistributed N	Proportion calculation	Proportion
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Treatment	N	Redistribution calculation	Redistributed N	Proportion calculation	Proportion
Total	**68.8**		**68.8**		**100%**

Abbreviations: Durva, durvalumab; IO, immunotherapy; ipi, ipililumab; n, number; nivo, nivolumab.

Subsequent treatments

B12. Priority question. Page 184 of the company submission states that *"treatments were listed in one cell per patient, and it was unclear whether these referred to combination treatments versus monotherapies or multiple doses, as such, assumptions were required to extract the data"*.

a. **Please clarify if this refers to the grouping of subsequent treatments in one cell, or all treatments in one cell.**

The reporting of subsequent treatment was different in each of the real-world datasets.

- The COTA data set reported the dates of treatment, and would allow an understanding of time on treatment for different lines
    - An example from the dataset is "carboplatin_plus_pemetrexed. alimta_pemetrexed. crizotinib_xalkori"
- The 0015 data set simply listed the subsequent treatments received, however it was not clear if these were in combinations, or given as subsequent lines
    - An example from this dataset is "CARBOPLATIN, PEMETREXED"
- The 0035 data set listed each administration, but not the reasons for any differences
    - An example from this dataset is "Carboplatin + Pemetrexed. Carboplatin + Pemetrexed. Crizotinib. Gemcitabine + Pemetrexed. Gemcitabine + Pemetrexed"
- Wong et al. had each treatment type clearly listed, though not necessarily individually identified (aside from crizotinib)

- For example we know patients received immunotherapy or platinum doublet chemotherapy on many occasions, but not the exact agent(s)

b. Please clarify what these assumptions were.

The assumptions used are detailed in Section B.3.5.4 of Document B. For the model, each treatment listed is counted separately. For example, if one patient has docetaxel plus cisplatin for their subsequent treatment then this is counted separately in the model as one having received docetaxel and cisplatin. Repeated subsequent treatments were counted once, e.g., if it is reported a patient had "cisplatin, docetaxel, docetaxel" only one incidence of docetaxel and one incidence of cisplatin were taken for the model.

c. If all treatments regardless of treatment line were listed in one cell, please comment on the implications for the treatment categorisation in the primary ITC.

We believe the answers to part (a) and (b) of this question provide the answer to how data has been handled with the real-world datasets – it should be noted that this relates only to *subsequent* treatments. Given the limitations of the subsequent treatments outlined in response to B12 (a) and lack of data in some data sets, subsequent treatment data was collated separately from the initial treatments within the ITC therefore there is no impact on the indirect comparison of agents compared to tepotinib.

B13. Priority question. Please explain the difference between weighted and unweighted subsequent treatment distributions as per appendix P.1.1 (page 264).

Weighted refers to the subsequent treatment distribution based on the propensity score weighted real-world cohort data. Unweighted refers to the subsequent treatment distribution based on the original real-world cohort data before propensity scoring was applied.

Table 63 in Appendix P1.1 of the company submission presents the weighted subsequent treatment distributions prior to the redistribution of treatments that are not considered UK practice (e.g., durvalumab), or were not specific about the

treatment used (e.g., immunotherapy). The values in this table are not implemented in the economic model and are only presented for completeness.

B14. Priority question. Please explain the difference in the subsequent treatment distributions in Table 57 (page 186) and Table 63 in appendix P.1.1 (page 264). They both appear to be used in the base case economic analysis, but they are different.

Table 58 (based on updated table numbers) in Document B of the company submission presents the treatment distributions and associated costs which are used in the base case of the cost-effectiveness model. In the base case, treatments that are either not used in UK practice (e.g., durvalumab) or were not specified in the data (e.g., "immunotherapy") were categorised as 'other' in Table 63 (Appendix P) and are proportionally redistributed to treatments that are used in UK clinical practice.

Table 63 in Appendix P of the company submission presents all treatments that were received by patients in the real-world data cohort (prior to redistribution). The distributions presented in Table 63 (Appendix P) are not used in the base case analysis and are only provided for completeness.

B15. Priority question. Please explain why the expert-derived distribution of subsequent treatments was not used for both tepotinib and the comparators. The distribution of subsequent treatments for the comparators appears to be the distribution of initial treatments (page 266, appendix P.1.1).

In the base case analysis, the subsequent treatment distributions for all treatments are based on the subsequent treatments received in the studies (VISION for tepotinib and the real-world cohort data for the comparators), redistributed to reflect treatments that would be received in UK practice. This is so the subsequent treatment costs are matched to the efficacy accordingly.

For scenario analysis, expert-derived UK distribution of subsequent treatments are used for both tepotinib and comparators which are based on clinical opinion described in Appendix P1.2.

B16. Priority question. Please explain the choice of alternative subsequent treatments in the sensitivity analyses reported in section B.3.8.2 (pages 196-197).

As stated above, in the base case analysis, the subsequent treatment distributions for all treatments are based on the subsequent treatments received in the studies (VISION for tepotinib and the real-world cohort data for the comparators), redistributed to reflect treatments that would be received in UK practice. To explore variations in UK clinical practice, clinical experts were asked to provide market share estimates for each treatment which was used to create a 'UK specific' subsequent treatment distribution option. Details of how this UK specific distribution is created is presented in Appendix P1.2.

As stated in Section B.3.5.4: *"Experts at the advisory board noted the differences between the distributions from the real-world data compared to what would be used in UK practice, particularly the aggressive treatment patterns (i.e., re-treatment of immunotherapy, or subsequent targeted or MET inhibitors). Therefore, scenarios are presented where UK based subsequent treatment distributions are considered. In this scenario, the distributions of treatments used in clinical practice estimated by clinical experts were used and only subsequent immunotherapies, chemotherapies and platinum-based chemotherapy options are considered.*

- *For immunotherapy, it is assumed that no patients will receive subsequent immunotherapy, therefore all these patients are proportionally re-distributed to the chemotherapy regimens.*

- *For tepotinib it is assumed that the distribution of treatments from first-line and second-line would not be changed (with the exception of immunotherapy in combination with chemotherapy which are only available in untreated patients) therefore both immunotherapies and chemotherapies are included.*

- *For chemotherapy, the distribution of previously treated estimates are used for this scenario.*

It is important to note that the modelled overall survival is based on the initial treatments and subsequent treatment distributions used in the base case, therefore

the scenario considering UK based distributions only impact the costs and not the difference in survival efficacy, and so is an unfair comparison. It is unclear how the differences in these distributions will impact the survival. In addition to exploring UK based distributions, another scenario assuming the same number of treatment lines between tepotinib and comparators are explored."

B17. Priority question. Pemetrexed maintenance is only included as second-line treatment in a scenario economic analysis.

a. **Please clarify the position of pemetrexed maintenance in the treatment recommendations for the decision population in the scope.**

As per the decision problem in the scope, pemetrexed maintenance is a treatment option for previously untreated patients with non-squamous advanced NSCLC, treated with platinum-based chemotherapy. Pemetrexed maintenance is also used in non-squamous patients treated with pembrolizumab and platinum-based chemotherapy. For patients with adenocarcinoma or large cell carcinoma specifically who receive pemetrexed plus a platinum drug, pemetrexed maintenance can be used with cisplatin-containing regimens.

Clinical experts have indicated that 50–60% of patients go onto pemetrexed maintenance following platinum-based chemotherapy with/without pembrolizumab. Clinical experts have also highlighted concerns with pemetrexed maintenance due to renal toxicity, which is particularly a concern in the elderly population of patients with METex14 skipping alterations. Targeted treatments such as tepotinib which could avoid pemetrexed maintenance in the first-line setting will therefore provide an important treatment option for these patients.

b. **Please clarify why it has been excluded from the base case analysis.**

Maintenance therapy with pemetrexed was not clearly reported in the studies used to inform the real-world cohort data set. While pemetrexed maintenance is often used in combination with chemotherapy regimens, it was not clear from the data whether patients administered chemotherapy had received maintenance therapy. For this reason, the assumption in the base case analysis is to exclude pemetrexed maintenance costs as there is uncertainty in whether the efficacy observed incorporates maintenance therapy. If this was included in the model base case, we

would be accounting for the costs of pemetrexed maintenance, without potentially accounting for the efficacy, overestimating comparator costs.

c. **On page 124 the company submission, it states that *"it was unclear if any patients from the real-world cohort data set were on pemetrexed maintenance"*. Please explain why it was unclear.**

See response to B17 (b) above.

B18. NICE guidance for treatment as presented in Figures 3 and 4 (pages 30 to 31) in the company submission recommends different treatment for squamous and non-squamous patients.

Please clarify why comparators and treatment sequences would be the same for both groups as implied by this statement on page 122: "In addition, immunotherapies and chemotherapies are used within both squamous and non-squamous groups, therefore, the overall approach to modelling is unaffected".

Subgroup analysis in the ITC and economic model by histology was not possible due to small patient numbers in histology groups other than adenocarcinoma in VISION ([redacted]% versus [redacted]% for others) and the real-world cohorts.

Squamous and non-squamous patients can receive immunotherapy and/or chemotherapy as standard of care. Although the exact treatment regimens and distributions may differ slightly between subgroups, given the evidence to support similar outcomes between immunotherapies and chemotherapies in advanced NSCLC (see Section B.2.9.3), the overall approach to modelling is not expected to differ. It is expected that the combined treatment distributions for the comparators accounts for the combined histology subgroups and the availability of treatments for each subgroup.

As discussed in Section B.3.5.2.1, METex14 testing is expected to differ between squamous and non-squamous patients with the availability of tepotinib (as squamous patients are currently not tested for driver mutations), and as mentioned there are minor differences in treatment patterns. These cost differences have been accounted for in the base case. Clinical experts expect other modelling costs to be similar between the histology subgroups (i.e., adverse events, disease monitoring).

Furthermore, clinical experts suggested there might be a small difference in outcomes,[7] as squamous patients tend to have slightly worse outcomes compared to non-squamous patients, as they often present with more comorbidities and aggressive disease. However, this difference is already accounted for by combining the data sets between squamous and non-squamous patients in VISION and the real-world cohorts.

Costs

B19. Priority question. Please clarify the relative dose intensity (RDI) values used in the RDI-tepotinib sensitivity analysis, and the basis for using these.

The relative dose intensity (RDI) values are calculated by dividing the sum of the cumulative dose received by the sum of the cumulative planned dose in VISION.

Total cumulative dose received by all patients = [redacted]
Total planned dose for all patients = [redacted]
RDI = [redacted]

For sensitivity analysis, it is assumed that relative dose intensity inputs take a normal distribution which is then used to calculate the 95% confidence intervals.

In the original Document B, the RDI value from VISION was not marked AIC, this has now been marked in the revised documents.

B20. Priority question. According to section B.3.2.1 of the company submission (page 121), *"clinical experts confirmed that although squamous patients tend to not do as well on treatments as adenocarcinoma, the overall costs and outcomes are generalisable between histology groups"*.

Please elaborate and justify this assertion as you would expect costs and outcomes to differ between the histologies.

Please see response to question B18.

B21. Priority question. According to section B.3.5.1.1. of the company submission (page 172), *"the dose reductions allowed in the VISION study differ*

***to the expected use in clinical practice, however given that dose reductions and interruptions can still be considered, the impact is expected to be similar"*.**

Please clarify what is meant by "impact" here, and why the impact is expected to be similar if the dose reductions allowed are expected to be different to clinical practice.

Based on the summary of product characteristics (SmPC), tepotinib can be reduced to 225 mg (equivalent to 250 mg tepotinib hydrochloride) in the case to grade 3 adverse events. In the trial, dose reductions were also included and could be reduced to 300 mg tepotinib hydrochloride for adverse events with further reductions considered in a case by case basis. Although it is not possible to determine how the difference in dose reductions between the trial and SmPC will translate to clinical practice, the impact on tepotinib costs are expected to be similar. The impact of dose intensity is also tested in sensitivity analysis given the associated uncertainty (see Section B.3.8).

B22. Priority question. Please explain why the dose intensity for tepotinib is likely to be significantly lower than the dose intensities for most comparator treatments as per Table 51 of the company submission (page 174).

As highlighted in Table 52 (based on updated table numbers) of Document B of the company submission, the clinical data show that tepotinib has a lower dose intensity compared to the majority of other treatment options in advanced NSCLC. While the exact reason for this is unknown, there are a number of likely reasons why the RDI for tepotinib, calculated from the VISION data, is lower than the majority of comparator treatments:

- Tepotinib is an oral therapy administered daily at home, therefore it is easier to reduce doses for tepotinib than the comparator treatments, where the vast majority of other treatments are infusion based (immunotherapies or chemotherapy), which require infusions in hospital once every week, every 2 weeks or every 3 weeks. This allows treating oncologists the flexibility to easily reduce the daily dose of tepotinib, whereas with infrequent chemotherapy infusions, oncologists may be less likely or reluctant to reduce the dosing. There is also no immunotherapy monotherapy dose flexibility.[33-35]

    - This is similar to dose intensities of other oral treatments for NSCLC; brigatinib had a dose intensity of 88.9% and ceritinib had a dose intensity of 83.6% (TA571 – Section B.3.5.2.1).[36]
- Dose reductions to 225 mg are permitted by the label. As tepotinib is dispensed as 225 mg tablets, no wastage would occur with a reduction from the planned 450 mg dose to 225 mg dose.

In response to this question, we organised a call with two expert oncologists to discuss the RDI of tepotinib compared to comparators (amongst other areas of discussion). They confirmed that oncologists are more comfortable with dose reductions in a more controlled manner for oral treatments. This is not possible with immunotherapies, where dosing can only be paused not stopped. Chemotherapy infusions do sometimes have the dose reduced, although not to the same extent or frequency as oral treatments, as it is not as simple as with oral treatments. This is reflected in the very high RDIs seen for immunotherapy monotherapies in the model (97.7% – 99.2%) and the range of RDIs seen for the different chemotherapy options (78.0% – 98.0%).

Analyses, model results, and model functionality

B23. Priority question. Please report on the probability that tepotinib is cost-effective at cost-effectiveness thresholds £30,000 and £50,000 for fully incremental analysis for the populations: line agnostic, untreated, treated. Furthermore, please provide the executable model with that functionality.

Currently the economic model adopts a pairwise cost-effectiveness analysis approach. As discussed in the clarification questions meeting held via Zoom on 6 August 2021, the response to this question (the probability that tepotinib is cost-effective at the requested thresholds within a fully incremental cost-effectiveness analysis) will follow this response document and will be provided by 27 August 2021. In addition, an updated model with the functionality to perform a fully incremental analysis will also be provided by 27 August 2021.

B24. Priority question. Please clarify how the lower and upper bounds were derived for use in the deterministic sensitivity analyses. Furthermore, please clarify what the upper bound and lower bound represent for the deterministic

sensitivity analyses where a specific treatment is specified as the subsequent treatment, e.g. crizotinib for chemotherapy.

Table 17 presents the key parameters and distributions used to vary the parameters in the probabilistic sensitivity analyses (PSA) and the one-way sensitivity analyses (OWSA). These are also presented for each parameter in Appendix Q.

Table 17: Parameters and their corresponding distributions used to vary values within sensitivity analyses

Parameter	Distribution	Included in PSA	Included in OWSA
Proportion female	Beta	No	No
Patient characteristics (age, BSA, weight)	Normal	Yes	Yes
Proportion untreated	Beta	Yes	Yes
Proportion squamous	Beta	Yes	Yes
Serum creatinine level	Normal	Yes	Yes
HR (PFS vs. ToT, OS IO+chemo vs. chemo, PFS IO+chemo vs. chemo)	Lognormal	Yes	Yes
Costs – Drugs sourced from eMIT	Normal	Yes	Yes
Platinum therapy split	Beta	Yes	Yes
Proportion of patients assigned pemetrexed maintenance	Beta	Yes	Yes
Costs - Administration	Normal	Yes	Yes
RDI	Normal	No	Yes
Baseline utility	Beta	Yes	Yes
Utilities – VISION progression based	Multi-normal	Yes	No
Utilities – Literature progression based	Beta	Yes	Yes
Resource use – Frequencies	Normal	Yes	Yes
Resource use – Proportion of patients	Beta	Yes	Yes
Costs – Resource use	Normal	Yes	Yes
Adverse events – Proportion of patients	Beta	Yes	Yes
Adverse events – Disutility	Beta	Yes	Yes
Adverse events – Duration	Normal	Yes	Yes
Subsequent treatment distribution	Beta	Yes	Yes

Abbreviations: BSA, body surface area; chemo; chemotherapy; eMIT; electronic market information tool; HR, hazard ratio; IO, immunotherapy; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; PSA, probabilistic sensitivity analysis; RDI, relative dose intensity; ToT; time on treatment.

The subsequent treatment inputs have been assigned a beta distribution based on the number of patients who had each treatment in the VISION and real-world data. Given that the actual proportion of patients who have each subsequent treatment is

unknown in clinical practice, the beta distribution was used to estimate the 95% confidence intervals around each percentage and used as the lower and upper bounds in one-way sensitivity analysis. Although it could be argued that subsequent treatment distributions are linked, including each individual subsequent treatment in one-way sensitivity analysis allows the impact of each subsequent treatment to be assessed.

B25. Priority question. For the full incremental analyses and pairwise analyses for the base case analysis and the subgroup analyses, please report the probability that each treatment is cost-effective at a cost-effectiveness threshold of £20,000 per quality-adjusted life years (QALY).

Provide the pairwise analyses probability that tepotinib is cost-effective at the £20,000 threshold for the base case and subpopulations.

Currently the economic model adopts a pairwise cost-effectiveness analysis approach. As discussed on the clarification questions meeting held via Zoom on 6 August 2021, the response to this question (the probability that tepotinib is cost-effective at the £20,000 threshold within a fully incremental cost-effectiveness analysis and with pairwise analysis) will follow this response document and will be provided by 27 August 2021. In addition, an updated model with the functionality to perform a fully incremental analysis will also be provided by 27 August 2021.

B26. Priority question. In section B.2.13.1 of the company submission, the company presents an argument that tepotinib may meet the end-of-life criteria in a group of patients who are contraindicated or unsuitable for immunotherapy, when compared to chemotherapy, but not otherwise. The company submission states on page 34 that chemotherapy is used when immunotherapy is contraindicated or as second-line treatment.

a. **Please clarify if there are any decision problem scenarios including tepotinib for which immunotherapy and chemotherapy are both relevant alternatives, and for which a full incremental cost-effectiveness analysis including all treatments is relevant.**

Clinical expert opinion agreed that the vast majority of patients now receive immunotherapy or immunotherapy in combination with chemotherapy as a first-line

treatment in advanced NSCLC (Appendix P, P.1.2) and only a small proportion receive platinum-based chemotherapy alone at first line (although this is higher for squamous patients), some of whom (although not all) are contraindicated or unsuitable for immunotherapy. This also means that the vast majority of patients also receive some form of chemotherapy at second line, and very few receive immunotherapy.

Therefore, chemotherapy and immunotherapy are both treatment options across lines of therapy, as tepotinib is expected to be. Therefore, full incremental cost-effectiveness analysis including all treatments is relevant.

b. **Please present a summary table of the decision problem populations for which the economic analyses are used to provide evidence of cost-effectiveness for tepotinib, the economic analysis that provides the evidence for that population, and the relevant comparators (chemotherapy, immunotherapy, chemotherapy and immunotherapy combination treatment) for that population. Please make it explicitly clear if the population is dependent or independent of PD-L1 status, squamous status, contraindication/unsuitabilty to other treatment (e.g. immunotherapy), previous treatment. If it is dependent on a factor, please state the relevant status.**

Table 18 describes the decision problem populations which the economic analyses are used to provide evidence of cost-effectiveness for tepotinib. In line with the expected tepotinib label, the population is for patients with advanced NSCLC harbouring METex14 skipping alterations. This is therefore line agnostic, as well as across histology subtypes and independent of PD-L1 expression status. The real-world cohort data allow comparator groupings by type of therapy (as described in Section B.2.9.4 of the submission dossier), so this is how the different decision problem populations are categorised.

Table 18. Decision problem populations which the economic analyses are used to provide evidence of cost-effectiveness for tepotinib

Disease	Patients with advanced NSCLC harbouring METex14 skipping alterations		
Decision problem populations	Patients currently treated with chemotherapy	Patients currently treated with immunotherapy	Patients currently treated with immunotherapy in combination with chemotherapy
Line of therapy	Line agnostic • Previously untreated patients • Previously treated patients	Line agnostic • Previously untreated patients • Previously treated patients	• Previously untreated patients
Comparators	• Pemetrexed, docetaxel, gemcitabine, paclitaxel or vinorelbine + carboplatin or cisplatin • with or without pemetrexed maintenance treatment • Docetaxel, with (for adenocarcinoma histology) or without nintedanib	• Pembrolizumab monotherapy • Atezolizumab monotherapy • Nivolumab monotherapy	• Pembrolizumab + pemetrexed + platinum chemotherapy • Atezolizumab plus bevacizumab, carboplatin and paclitaxel
PD-L1 expression	Independent of PD-L1 expression status • PD-L1 ≥50% • PD-L1 <50%	Both PD-L1 expression groups • PD-L1 ≥50% • PD-L1 <50%	Both PD-L1 expression groups • PD-L1 ≥50% • PD-L1 <50%
Histology subtype	Across histology subtypes • Non-squamous • Squamous	Across histology subtypes • Non-squamous • Squamous	• Non-squamous only
Other factors	• Some patients treated with chemotherapy are contraindicated or unsuitable for immunotherapy		
Source of evidence	Real-world data sources for chemotherapy; indirect treatment comparison	Real-world data sources for immunotherapy; indirect treatment comparison	Real-world data sources for chemotherapy; indirect treatment comparisons, then using hazard ratios from KEYNOTE-189

B27. Priority question. Please provide a table of the net monetary benefit (NMB) values used to create the tornado diagrams in Figures 50 and 51 (page 197) so that these can be checked in the model.

Table 19 and Table 20 present the net monetary benefit (NMB) values used for the tornado diagrams in Figures 50 and 51 of the company submission (Document B) for

comparisons to chemotherapy and immunotherapy respectively. Please note that a minor error was identified post submission for the immunotherapy comparison and has subsequently been corrected (see response to B29 and Appendix 3). Table 20 presents the corrected values (also presented in Appendix 3 Table 27).

Table 19: Top 10 ranked OWSA results on the NMB versus chemotherapy (WTP=£50,000)

Parameter	Lower Bound	Upper Bound
Subsequent treatment - Chemotherapies: Crizotinib	£5,631	£20,541
RDI - Tepotinib	£19,043	£6,574
Subsequent treatment - tepotinib: Crizotinib	£18,201	£6,535
Subsequent treatment - Chemotherapies: Brigatinib	£8,329	£19,378
Subsequent treatment - Chemotherapies: Nivolumab	£10,432	£15,408
Subsequent treatment - tepotinib: Pembrolizumab	£14,582	£10,623
Resource use - prevalence of MET mutation in NSCLC	£9,794	£13,752
Subsequent treatment - tepotinib: Nivolumab	£13,795	£11,424
Subsequent treatment - Chemotherapies: Pembrolizumab	£11,876	£14,226
% squamous	£13,692	£11,704

Abbreviations: MET, mesenchymal-epithelial transition; NMB, net monetary benefit; NSCLC, non-small-cell lung cancer; OWSA, one-way sensitivity analysis; RDI, relative dose intensity; WTP, willingness-to-pay.

Table 20: Top 10 ranked OWSA results on the NMB versus immunotherapy (WTP=£30,000)

Parameter	Lower Bound	Upper Bound
Subsequent treatment - Immunotherapies: Crizotinib	£15,989	£29,310
RDI - Tepotinib	£28,501	£16,032
RDI - Pembrolizumab	£16,043	£28,490
Subsequent treatment - tepotinib: Crizotinib	£27,659	£15,993
Subsequent treatment - Immunotherapies: Brigatinib	£17,718	£28,912
Subsequent treatment - tepotinib: Pembrolizumab	£24,041	£20,082
Resource use - prevalence of MET mutation in NSCLC	£19,252	£23,210
RDI - Nivolumab	£20,557	£23,976
Subsequent treatment - tepotinib: Nivolumab	£23,253	£20,882
Proportion squamous	£23,158	£21,153

Abbreviations: MET, mesenchymal-epithelial transition; NMB, net monetary benefit; NSCLC, non-small-cell lung cancer; OWSA, one-way sensitivity analysis; RDI, relative dose intensity; WTP, willingness-to-pay.

B28. Table 6 in document B indicates that PFS as per investigator assessment was used in the economic model rather than PFS as per independent review committee (IRC).

a. **Please re-run the cost-effectiveness models using PFS as per IRC, not PFS as per investigator assessment.**

Progression-free survival (PFS) by independent review committee (IRC) definition is only available within the data for tepotinib from the VISION trial, and not available from the real-world cohort data for the comparators. PFS by investigator (INV) definition was chosen to inform the cost-effectiveness analyses as the PFS from the comparator real-world cohort data was reported by investigator, as per the nature of real-world data.

Figure 7 provides the Kaplan-Meier (KM) curves of tepotinib PFS by both INV and IRC definitions. No statistically significant difference was found between the curves (p=0.33) with the investigator definition providing lower estimates of survival than the IRC definition at the majority of time points.

Figure 7: Tepotinib PFS by investigator and independent review committee definitions

Abbreviations: p, p-value; INV, investigator; IRC, independent review committee; PFS, progression-free survival.

Table 21 provides the summary statistics for tepotinib PFS by INV and IRC definitions. Median PFS and restricted mean survival time (RMST) were both found to be greater with the IRC definition compared to PFS defined by INV.

Table 21: Summary statistics of tepotinib PFS by investigator and independent review committee definitions

	PFS INV	PFS IRC
All patients	[redacted]	[redacted]
Patients with event, n (%)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
RMST	[redacted]	[redacted]

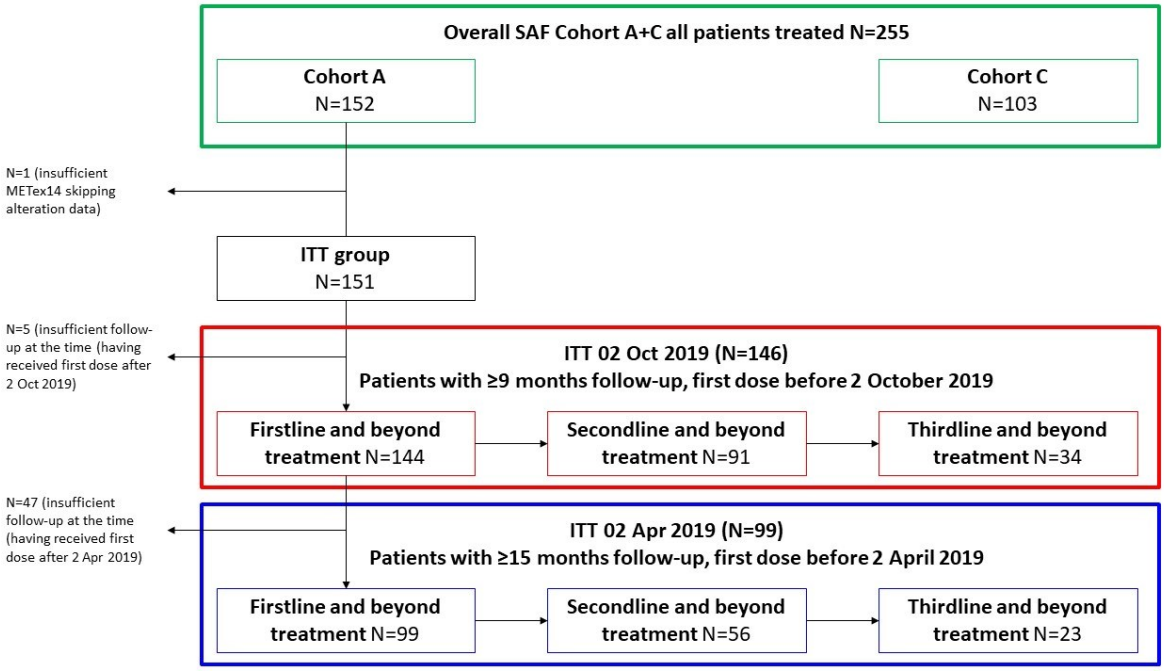
Abbreviations: CI, confidence interval; INV, investigator; IRC, independent review committee; n, number; PFS, progression-free survival; RMST, restricted mean survival time.

As discussed on the clarification questions meeting held via Zoom on 6 August 2021, the results of the cost-effectiveness analysis implementing the IRC definition of tepotinib PFS (as opposed to INV definition in the current analyses) will follow this response document and will be provided by 27 August 2021.

b. Please update Figures 7 and 8 in document B to show the reasons why patients were excluded from each analysis set.

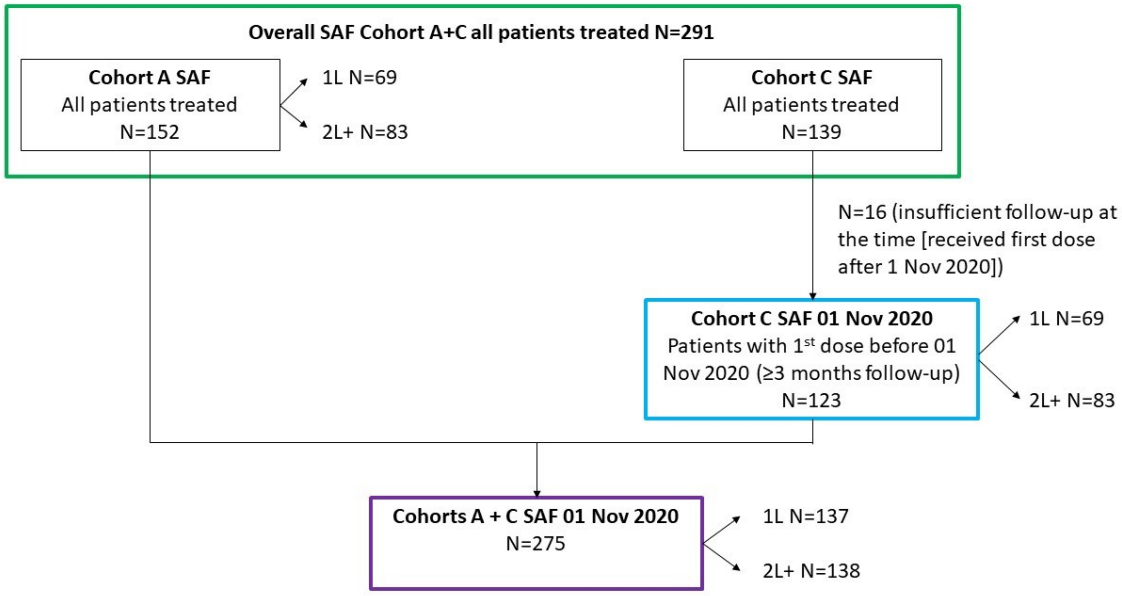
Figure 7 and Figure 8 have been updated and included in the revised Document B (see also below).

Figure 8: VISION analysis sets, at 1 July 2020 data cut-off



Abbreviations: ITT, intention to treat; ITT-02 Apr 2019, Intention-to-Treat analysis set restricted to subjects who received a first dose of tepotinib before 02 April 2019; ITT-02 Oct 2019, Intention-to-Treat analysis set restricted to subjects who received the first dose of tepotinib before 02 October 2019; SAF, safety set

Figure 9. VISION analysis sets, at 1 February 2021 data cut-off



Abbreviations: SAF=safety analysis set

Source: SAF-01 Nov 2020,

Notes: Safety Set analysis set restricted to subjects who received the first dose of tepotinib before 01 October 2020, so with at least 3 months follow; SAF, safety set; 1L, first-line treatment; 2L, second-line treatment

Potential model errors

B29. Priority question. Cells "Treatment costs" P100:P115 sum to 200% as shown in cell "Treatment costs" P116 and cells "Treatment costs" Q100:Q115 sum to 200% as shown in cell "Treatment costs" Q116.

If this is an error, please correct and provide the corrected Excel model. If this is not an error please clarify why the values sum to 200%.

This is an error. Cells P100:Q102 should have values of 0%, giving totals of 100% in cells P116 and Q116. This has been amended in the updated economic model.

As already mentioned, another error was found post submission relating to background mortality for the immunotherapy OS. Details of this error are included within Appendix 3 and have been corrected in the latest model version.

Section C: Textual clarification and additional points

C1. Priority question. Regarding the end of life criteria:

a. **Please check the reported median overall survival (OS) difference between tepotinib and chemotherapy as listed in Table 30. The difference in median OS between tepotinib and chemotherapy is [redacted] months, favouring tepotinib.**

Section B.2.13.1 and Table 31 (based on updated table numbers) in the end-of-life criteria section both report that the median overall survival difference between tepotinib and the real-world cohort group is [redacted] months ([redacted] months for tepotinib and [redacted] months for chemotherapy). This is confirmed in the relevant ITC results section (B.2.9.7) as well as the full ITC report (Appendix L). This has been checked and confirmed.

As discussed in Question B6 of this document and Section B.3.8.7 of the submission dossier, the chemotherapy median OS is likely to be overestimated. Nonetheless the end-of-criteria are still met.

b. **Please check the reference for the bottom row of Table 30. This should reference page 97 instead of page 93.**

The cross reference in the bottom row of Table 31 should refer to Section B.2.9.7.2, p.98 (based on the updated page numbers), this has been updated in Document B.

c. **According to Table 24 of the company submission, the difference between tepotinib and immunotherapy in OS is a median of [redacted] months favouring the former. Please discuss the clinical importance, providing supporting references.**

The real-world cohort data (after propensity score weighing) show a median OS of [redacted] months for patients with METex14 skipping alterations treated with immunotherapy, compared to a median OS of [redacted] months for tepotinib from VISION. As discussed in Section B.3.8.7 of the submission dossier as well as shown in the ITC report (Appendix L), the estimated median OS for immunotherapy is higher than some published studies in the METex14 skipping alterations population (Guisier et al 2020, unweighted OS: 13.4 months; Sabari et al 2018, unweighted

median OS: 18.2 months). This is possibly due to the high numbers of subsequent treatments seen in the real-world cohort data, in particular [redacted]% of patients received a subsequent MET inhibitor after immunotherapy. As also reported in Section B.3.8.7, the real-world cohort data for immunotherapy appears to show a longer OS compared to clinical trials for immunotherapies (pembrolizumab and nivolumab) in previously treated patients, and slightly below the median OS in first-line clinical trials for immunotherapies. This is unsurprising, as the real-world cohort data is a mix of previously untreated and previously treated patients. Although as discussed in Section B.1.3.2, METex14 skipping alterations patients often respond worse to immunotherapy, and so you could expect the real-world cohort OS to be a bit lower, close to the previously treated clinical trials, or the lower estimates from the METex14 skipping alterations population.

Nonetheless, despite the uncertainty for immunotherapy outcomes for the real-world cohort in the METex14 skipping alterations population, and possible overestimation, tepotinib at least demonstrates similar OS to immunotherapy in METex14 skipping alterations patients. This is also supported with the additional MAICs in the METex14 skipping alterations population (Appendix L), where tepotinib either had greater or similar OS to immunotherapy. As shown in the cost-effectiveness section of the dossier, tepotinib remains a cost-effective compared to immunotherapies.

Tepotinib has also demonstrated other advantages to immunotherapies on top of OS. Tepotinib has consistently shown much greater PFS compared to immunotherapy in the METex14 skipping alterations population, across all data sources (even when using the investigator PFS which is lower for tepotinib than the IRC PFS). Tepotinib also provides patients with an oral administration option, whilst meaning patients do not need to go into hospital for lengthy infusions.

C2. Priority question. Regarding the analyses:

a. **Please report the software and package used to conduct the time to event analyses.**

The time to event analyses were conducted in R (version 1.4.1106) using the “survival”, “flexsurv”, “survminer” and “muhaz” packages.

Survival curves (KMs) were created using the “survfit” function from the “survival” package. The “survminer” package was used to plot the KM curves.

Parametric models (both standard and piecewise [following rebasing of the data]) were fit to the data using the “flexsurvreg” function from the “flexsurv” package.

Spline models were fit to the data using the “flexsurvspline” function from the “flexsurv” package.

Smoothed hazard plots were created by obtaining hazard estimates using the “muhaz” function from the “muhaz” package.

b. Please provide the statistical output to all the time to event models fitted to the tepotinib, immunotherapy and chemotherapy data for PFS, OS and ToT.

All survival model parameters, variance-covariance matrices and AIC, BIC goodness of fit statistics can be found in the economic model (Sheets: OS, PFS, ToT. Columns BD:IZ). KM estimates can be found in the “KM” sheet of the economic model.

c. Please report the software and package used to do the linear mixed model (LMM) regression performed to support the interpretation of changes in utility according to progression status (page 162).

The linear mixed model regression was conducted in R (version 1.4.1106) using the “lme4” package.

d. Please provide the statistical output of the model.

Table 22 presents the output of the linear mixed model regression performed to obtain the utility values utilised in the economic model.

Table 22: Linear mixed model output

	Coefficient	Standard Error	p-value
Pre progression	0.71803	0.01676	<0.001
Post progression	-0.08168	0.01432	<0.001
Baseline observation	-0.07808	0.01504	<0.001

Table 23 presents the variance-covariance matrix of the model.

Table 23: Linear mixed model variance-covariance matrix

	Pre progression	Post progression	Baseline observation
Pre progression	0.000281	-0.000048	-0.000056
Post progression	-0.000048	0.000205	-0.000047
Baseline observation	-0.000056	0.000047	0.000226

C3. Priority question. Please provide the clinical study report(s) for all relevant studies.

The clinical study report (CSR) for the VISION study at the 1 July 2020 data cut-off was provided to NICE along with the initial submission. There is not a CSR available for the 1 February 2021 data cut-off.

C4. Are there any additional data cut-off points between February 2021 and the final cut-off of December 2021? Please present data for the most recent cut-off, e.g. for adverse-effects.

There are no planned additional data cuts for global use for VISION between February 2021 and December 2021.

Efficacy data for the most recent 1 February 2021 cut-off is provided in Document B, Appendix E and Appendix R. Summary safety data for the 1 February 2021 data cut-off is available, and is provided in Appendix F.

C5. If possible, please update Figures 10, 11, and 12 due to presenting information from the July 2020 cut-off.

The updated figures have been provided in the updated Document B, provided to NICE.

C6. Is the patient group from Japan an appropriate population given pre-screening did not occur in this group? Please clarify.

VISION was an international clinical trial that was conducted at approximately 120 treatment sites in Austria, Belgium, China, France, Germany, Israel, Italy, Japan, the Netherlands, Poland, South Korea, Spain, Switzerland, Taiwan, and the United States of America (USA). Of these, [redacted]% (N=[redacted]) of patients were from Japan in Cohort A.

As described in Section B.1.3.2 of Document B, patients with METex14 skipping alterations have a number of specific characteristics which differentiate them from other types of NSCLC (wildtype or other genetic driver mutations), including older age and predominantly non-squamous histology, and these characteristics are observed across geographical regions and race, as reported in the SLR report provided. This supports the generalisability of the patient population across geographic regions and race, in line with the specific METex14 skipping alterations population.

Furthermore, although VISION included [redacted]% of patients from Japan, over [redacted]% were from Europe alone (from Cohort A), again supporting the generalisability of VISION to the UK population.

As reported in Appendix E of the company submission, ORR rates are marginally higher for patients enrolled in Japan compared to outside of Japan, although seem similar overall. Furthermore, the confidence intervals cross and the patient numbers are low in the Japan group, supporting the generalisability of the overall results.

The question also notes pre-screening in the Japanese group of VISION. In Japan, patients were allowed to enter the study based on the regular pre-screening using liquid or tissue biopsy, but they could also enrol through screening in the National program LC-SCRUM. In this program, patients with NSCLC send their tissue to be tested centrally for many biomarkers (in the case of METex14 a RT-PCR was used) and then according to what alteration they have, they are then screened for enrolment into an ongoing study (such as VISION). This program was only available in the beginning of VISION. Later on, Merck ended the collaboration with LC-SCRUM and patients were only allowed to enrol through the regular pre-screening/screening using liquid and/or tissue biopsy NGS. The publication on Japanese data for VISION (in the reference pack) describes this methodology. As pre-screening was only related to diagnosis of METex14 skipping alterations, it had no relation to the generalisability of the Japanese group, as all patients needed a METex14 skipping detection regardless of location.[37]

C7. Please specify why no UK real-world cohort was used.

No UK real-world cohort data was available for patients with advanced NSCLC harbouring METex14 skipping alterations treated with immunotherapy, chemotherapy or immunotherapy in combination with chemotherapy. We conducted a literature review to identify all published data in the METex14 skipping alterations population, as well as assessed all sources of patient level data in the METex14 skipping alterations population available to us. Of every study and data source identified, none were available in a UK cohort with sufficient patient numbers or comparators. In fact the only study identified in the UK population for METex14 skipping alterations patients (Benafif et al presented at BTOG 2021)[38] only had seven patients treated with immunotherapy and none treated with chemotherapy. The majority of patients identified with METex14 skipping alterations tend to be treated with MET inhibitors, through clinical trials or early access schemes, and so outcomes for patients with this novel mutation treated with immunotherapy or chemotherapy are very limited.

Despite the limitations of the comparative data and lack of UK data, the ITC was conducted using real-world data in the correct patient population, sufficiently generalisable to the UK population, with a large enough sample size to conduct propensity scoring. This represents one of the largest efficacy datasets in a METex14 skipping alterations population, and one of the first ITCs in this population, where data are currently very limited.

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Appendix 1: clinicaltrial.gov search results

Title	Status	Study Results	Conditions	Interventions	URL	Comment ref PICO
Crizotinb or Standard Chemotherapy in Met Exon 14 Skipping Advanced NSCLC	Recruiting	No Results Available	Non-small Cell Lung Cancer		https://ClinicalTrials.gov/show/NCT04322578	Outcomes - no results posted for relevant outcomes, clinical trial record only
Study of Capmatinib in Chinese Adult Patients With Advanced Non-small Cell Lung Cancer Harboring MET Exon 14 Skipping Mutation	Recruiting	No Results Available	Non-Small Cell Lung Cancer (NSCLC)	Drug: Capmatinib	https://ClinicalTrials.gov/show/NCT04677595	Outcomes - no results posted for relevant outcomes, clinical trial record only
Savolitinib for Treating Locally Advanced or Metastatic Non-small Cell Lung Cancer (NSCLC) Patients	Not yet recruiting	No Results Available	Non-small Cell Lung Cancer Metastatic	Drug: Savolitinib	https://ClinicalTrials.gov/show/NCT04923945	Population not in PICO
Merestinib In Non-Small Cell Lung Cancer And Solid Tumors	Active, not recruiting	No Results Available	Carcinoma, Non-Small-Cell Lung|Solid Tumor	Drug: Merestinib	https://ClinicalTrials.gov/show/NCT02920996	Duplicate - identified in the original searches
Crizotinib in Pretreated Metastatic Non-small-cell Lung Cancer With MET Amplification or ROS1 Translocation (METROS)	Unknown status	No Results Available	Carcinoma, Non-Small-Cell Lung	Drug: Crizotinib	https://ClinicalTrials.gov/show/NCT02499614	Duplicate - identified in the original searches
Special Drug Use-results Surveillance of Tabrecta Tablets	Recruiting	No Results Available	Non-small Cell Lung Cancer	Drug: Tabrecta tablets	https://ClinicalTrials.gov/show/NCT04575025	Study design
Phase II of Neoadjuvant and Adjuvant Capmatinib in NSCLC	Not yet recruiting	No Results Available	Non-small Cell Lung Cancer	Drug: capmatinib	https://ClinicalTrials.gov/show/NCT04926831	Population not in PICO
CABozantinib in Non-Small Cell Lung Cancer (NSCLC) Patients With MET Deregulation	Unknown status	No Results Available	Non-Small Cell Lung Cancer	Drug: Cabozantinib	https://ClinicalTrials.gov/show/NCT03911193	Duplicate - identified in

Title	Status	Study Results	Conditions	Interventions	URL	Comment ref PICO
						the original searches
Tepotinib Phase II in NSCLC Harboring MET Alterations (VISION)	Active, not recruiting	No Results Available	Advanced (Stage IIIB/IV) Non-small Cell Lung Cancer (NSCLC) With MET Exon 14 (METex14) Skipping Alterations or MET Amplification	Drug: Tepotinib	https://ClinicalTrials.gov/show/NCT02864992	Duplicate - identified in the original searches
Assessment of Anti-tumor and Safety in Glumetinib in Patients With c-MET-positive Non-Small Cell Lung Cancer	Recruiting	No Results Available	C-Met Exon 14 Mutation	Drug: Glumetinib	https://ClinicalTrials.gov/show/NCT04270591	Population not in PICO
Study of Capmatinib Efficacy in Comparison With Docetaxel in Previously Treated Participants With Non-small Cell Lung Cancer Harboring MET Exon 14 Skipping Mutation	Recruiting	No Results Available	Carcinoma, Non-Small-Cell Lung	Drug: Capmatinib|Drug: Docetaxel	https://ClinicalTrials.gov/show/NCT04427072	Duplicate - identified in the original searches
Capmatinib in Patients With Non-small Cell Lung Cancer Harboring cMET exon14 Skipping Mutation	Recruiting	No Results Available	Cancer|Lung Cancer Metastatic|MET Gene Mutation	Drug: Capmatinib	https://ClinicalTrials.gov/show/NCT03693339	Duplicate - identified in the original searches
APL-101 Study of Subjects With NSCLC With c-Met EXON 14 Skip Mutations and c-Met Dysregulation Advanced Solid Tumors	Recruiting	No Results Available	Solid Tumor|Advanced Cancer|Renal Cancer|Gastric Cancer|Gastroesophageal Junction Adenocarcinoma|NSCLC|Lung Cancer|Brain Tumor|Glioblastoma Multiforme	Drug: APL-101 Oral Capsules	https://ClinicalTrials.gov/show/NCT03175224	Duplicate - identified in the original searches

Title	Status	Study Results	Conditions	Interventions	URL	Comment ref PICO
Evaluating Crizotinib in the Neoadjuvant Setting in Patients With Non-small Cell Lung Cancer	Completed	No Results Available	Lung Cancer, Nonsmall Cell	Drug: Crizotinib	https://ClinicalTrials.gov/show/NCT03088930	Duplicate - identified in the original searches
A Study of Capmatinib (INC280) in NSCLC Patients With MET Exon 14 Alterations Who Have Received Prior MET Inhibitor	Completed	No Results Available	Malignant Non-small Cell Neoplasm of Lung Stage IV	Drug: Capmatinib (INC280)	https://ClinicalTrials.gov/show/NCT02750215	Duplicate - identified in the original searches
Survival Prolongation by Rationale Innovative Genomics	Active, not recruiting	No Results Available	Non-small Cell Lung Cancer Metastatic|Non-small Cell Lung Cancer Stage III	Drug: Avelumab|Drug: Axitinib|Drug: Palbociclib	https://ClinicalTrials.gov/show/NCT03386929	Study design
A Phase II Study of HMPL-504 in Lung Sarcomatoid Carcinoma and Other Non-small Cell Lung Cancer	Active, not recruiting	No Results Available	Lung Sarcomatoid Carcinoma	Drug: Savolitinib	https://ClinicalTrials.gov/show/NCT02897479	Duplicate - identified in the original searches
Clinical Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-type Advanced Non-small Cell Lung Cancer (Geometry Mono-1)	Active, not recruiting	No Results Available	Carcinoma, Non-Small-Cell Lung	Drug: INC280 (capmatinib)	https://ClinicalTrials.gov/show/NCT02414139	Duplicate - identified in the original searches
Phase 2 Platform Study in Patients With Advanced Non-Small Lung Cancer Who Progressed on First-Line Osimertinib Therapy (ORCHARD)	Recruiting	No Results Available	Non-Small Cell Lung Cancer	Drug: Osimertinib|Drug: Savolitinib|Drug: Gefitinib|Drug: Necitumumab|Drug: Durvalumab|Drug: Carboplatin|Drug: Pemetrexed|Drug: Alectinib|Drug: Selpercatinib	https://ClinicalTrials.gov/show/NCT03944772	Population not in PICO
Nivolumab, Cabozantinib S-Malate, and Ipilimumab in Treating Patients With Recurrent Stage IV Non-small Cell Lung Cancer	Active, not recruiting	No Results Available	Metastatic Lung Non-Squamous Non-Small Cell Carcinoma|Recurrent Lung Non-	Drug: Cabozantinib|Drug: Cabozantinib S-malate|Biological: Ipilimumab|Other: Laboratory Biomarker	https://ClinicalTrials.gov/show/NCT03468985	Duplicate - identified in the original searches

Title	Status	Study Results	Conditions	Interventions	URL	Comment ref PICO
			Squamous Non-Small Cell Carcinoma|Stage IV Lung Non-Small Cell Cancer AJCC v7	Analysis|Biological: Nivolumab|Other: Questionnaire Administration		
A Study Of Oral PF-02341066, A C-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, In Patients With Advanced Cancer	Active, not recruiting	No Results Available	Non-Small Cell Lung Cancer ALK-positive|Non-Small Cell Lung Cancer c-Met Dependent|Non-Small Cell Lung Cancer ROS Marker Positive|Systemic Anaplastic Large-Cell Lymphoma|Advanced Malignancies Except Leukemia	Drug: PF-02341066|Drug: Rifampin|Drug: Itraconazole	https://ClinicalTrials.gov/show/NCT00585195	Duplicate - identified in the original searches
Study of Crizotinib for ROS1 and MET Activated Lung Cancer	Recruiting	No Results Available	Non-squamous Non-small-cell Lung Cancer|Stage IV Non-small Cell Lung Cancer|ROS1 Gene Rearrangement|MET Activating Mutation|MET Amplification	Drug: Crizotinib	https://ClinicalTrials.gov/show/NCT04084717	Duplicate - identified in the original searches
Study of Capmatinib and Spartalizumab/Placebo in Advanced NSCLC Patients With MET Exon 14 Skipping Mutations	Recruiting	No Results Available	Carcinoma, Non-Small-Cell Lung	Drug: Spartalizumab|Drug: Capmatinib|Drug: spartalizumab placebo	https://ClinicalTrials.gov/show/NCT04323436	Duplicate - identified in the original searches

Title	Status	Study Results	Conditions	Interventions	URL	Comment ref PICO
Phase 1 Study of TPX-0022, a MET/CSF1R/SRC Inhibitor, in Patients With Advanced Solid Tumors Harboring Genetic Alterations in MET	Recruiting	No Results Available	Advanced Solid Tumor|Metastatic Solid Tumors|MET Gene Alterations	Drug: TPX-0022	https://ClinicalTrials.gov/show/NCT03993873	Duplicate - identified in the original searches

Appendix 2: Clinical effectiveness review Question A4a

The studies excluded on outcome from the clinical effectiveness review were rescreened in response to clarification question A4a Some adjustments were made to reasons for exclusion (highlighted in orange in the table), but no studies were judged to have been incorrectly excluded from the review.

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
1	Champagnac A, Bringuier PP, Barritault M, Isaac S, Watkin E, Forest F, Maury JM, Girard N, Brevet M. Frequency of MET exon 14 skipping mutations in non-small cell lung cancer according to technical approach in routine diagnosis: results from a real-life cohort of 2,369 patients. J Thorac Dis. 2020 May;12(5):2172-2178. doi: 10.21037/jtd.2020.04.21.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review
2	David S. Hong, Shiraj Sen, Haeseong Park, Rebecca Suk Heist, Shirish M. Gadgeel, Zachary Franklin Zimmerman, Lyudmila Bazhenova. A phase I, open-label, multicenter, first-in-human study of the safety, tolerability, pharmacokinetics, and antitumor activity of TPX-0022, a novel MET/CSF1R/SRC inhibitor, in patients with advanced solid tumors harboring genetic alterations in MET. J Clin Oncol 38: 2020 (suppl; abstr TPS3663)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review, no data reported within the abstract although relevant outcomes are reported
3	Yang J, Lu J, Zhang Q, Fu X, Chen H, Zhao X, Bai, Y, Zhang X. Genomic characterization of circulating tumor DNA from Chinese advanced small-cell lung cancer to reveal potential therapeutic opportunities. 2020.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
4	Ma Y, Du Y, Wang R et al. Analysis of multigene detection in patients with advanced lung adenocarcinoma using cytological specimens. Pathology-Research and Practice 2020; 216: 153036.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review
5	Chen M, Ma H, Yu H et al. Genomic heterogeneity of multifocal NSCLC. Journal of Clinical Oncology 2020; 38: e21595-e21595.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review
6	NCT04323436. Study of Capmatinib and Spartalizumab/Placebo in Advanced NSCLC Patients With MET Exon 14 Skipping Mutations. Available at: https://clinicaltrials.gov/ct2/show/NCT04323436 (last accessed June 2021)	Outcomes not in PICO	Y	Y	N	N	Y	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
7	NCT04427072. Study of Capmatinib Efficacy in Comparison With Docetaxel in Previously Treated Participants With Non-small Cell Lung Cancer Harboring MET Exon 14 Skipping Mutation (GeoMETry-III). Available at: https://clinicaltrials.gov/ct2/show/NCT04427072 (last accessed June 2021)	Outcomes not in PICO	Y	Y	N	Y	Y	Y	No change. Outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
8	Overbeck TR, Cron DA, Schmitz K, Rittmeyer A, Körber W, Hugo S, Schnalke J, Lukat L, Hugo T, Hinterthaner M, Reuter-Jessen K, Rosenthal T, Moecks J, Bleckmann A, Schildhaus HU. Top-level MET gene copy number gain defines a subtype of poorly differentiated pulmonary adenocarcinomas with poor prognosis. Transl Lung Cancer Res. 2020 Jun;9(3):603-616	Outcomes not in PICO	N	N	N	N	N	N	Population not in PICO, MET-Amp
9	Recondo G, Bahcall M, Spurr LF, Che J, Ricciuti B, Leonardi GC, Lo YC, Li YY, Lamberti G,	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
	Nguyen T, Milan MSD, Venkatraman D, Umeton R, Paweletz CP, Albayrak A, Cherniack AD, Price KS, Fairclough SR, Nishino M, Sholl LM, Oxnard GR, Jänne PA, Awad MM. Molecular Mechanisms of Acquired Resistance to MET Tyrosine Kinase Inhibitors in Patients with MET Exon 14-Mutant NSCLC. Clin Cancer Res. 2020 Jun 1;26(11):2615-2625								PICO for clinical review
10	Juergens RA, Ezeife DA, Laskin JJ et al. Demonstrating the value of liquid biopsy for lung cancer in a public health care system. Journal of Clinical Oncology 2020; 38: 3546-3546.	Outcomes not in PICO	N	N	N	Y	N	N	Population, unclear whether METex14 skipping alterations mentioned only molecular profiling of EGFR, ALK +/- ROS1
11	Rotow JK, Gui P, Wu W, Raymond VM, Lanman RB, Kaye FJ, Peled N, Fece de la Cruz F, Nadres B, Corcoran RB, Yeh I, Bastian BC, Starostik P, Newsom K, Olivas VR, Wolff AM, Fraser JS, Collisson EA, McCoach CE, Camidge DR, Pacheco J, Bazhenova L, Li T, Bivona TG, Blakely CM. Co-occurring Alterations in the RAS-MAPK Pathway Limit Response to MET Inhibitor Treatment in MET Exon 14 Skipping Mutation-Positive Lung Cancer. Clin Cancer Res. 2020 Jan 15;26(2):439-449	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review
12	Ren S, Zhang J, Zhao Y et al. A multi-center phase II study of toripalimab with chemotherapy in patients with EGFR mutant advanced NSCLC patients resistant to EGFR TKIs: Efficacy and biomarker analysis. Journal of Clinical Oncology 2020; 38: e21618-e21618.	Outcomes not in PICO	N	Y	N	Y	Y	N	Population, EGFR mutant advanced NSCLC patients, who developed resistance to 1st/2nd generation of EGFR TKIs and

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
									without T790M mutation
13	Shimokawa, M., Nosaki, K., Seto, T. et al. Phase II, open-label, multicenter trial of crizotinib in Japanese patients with advanced non-small cell lung cancer harboring a MET gene alteration: Co-MET study. Trials 21, 298 (2020). https://doi.org/10.1186/s13063-020-4221-7	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes, no extractable data for outcomes in PICO, report of study protocol
14	Song Z, Xu C, He Y, Li F, Wang W, Zhu Y, Gao Y, Ji M, Chen M, Lai J, Cheng W, Benes CH, Chen L. Simultaneous Detection of Gene Fusions and Base Mutations in Cancer Tissue Biopsies by Sequencing Dual Nucleic Acid Templates in Unified Reaction. Clin Chem. 2020 Jan 1;66(1):178-187	Outcomes not in PICO	N	N	N	N	N	N	Intervention: Did not evaluate clinical effectiveness of pharmacotherapeutic interventions, evaluation of assay for variant detection
15	Rowlands T, Boyapati A, Li S, Daly C, Seebach FA, Lowry I, Rietschel P. A phase I/II study of REGN5093, a MET x MET bispecific antibody, in patients with MET-altered advanced non-small cell lung cancer (NSCLC). Journal of Clinical Oncology 2020; 38: TPS9628-TPS9628.	Outcomes not in PICO	N	N	N	N	N	N	Population, MET-altered disease (includes METex14 gene mutation, METamp, elevated MET protein expression)
16	Xu Z, Li H, Dong Y, Cheng P, Luo F, Fu S, Gao M, Kong L, Che N. Incidence and PD-L1 Expression of MET 14 Skipping in Chinese Population: A Non-Selective NSCLC Cohort Study Using RNA-Based Sequencing. Onco Targets Ther. 2020;13:6245-6253 https://doi.org/10.2147/OTT.S241231	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (prevalence of METex14 skipping alteration)
17	Awad MM, Oxnard GR, Jackman DM, Savukoski DO, Hall D, Shivdasani P, Heng JC, Dahlberg SE, Jänne PA, Verma S, Christensen J, Hammerman	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
	PS, Sholl LM. MET Exon 14 Mutations in Non-Small-Cell Lung Cancer Are Associated With Advanced Age and Stage-Dependent MET Genomic Amplification and c-Met Overexpression. J Clin Oncol. 2016 Mar 1;34(7):721-30								review (clinical characteristics of METex14 mutated NSCLC)
18	Baldacci S, Figeac M, Antoine M et al. High MET Overexpression Does Not Predict the presence of MET exon 14 Splice Mutations in NSCLC: Results From the IFCT PREDICT.amm study. Journal of Thoracic Oncology 2020; 15: 120-124.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (prevalence of METex14 mutation in people with NSCLC and high MET overexpression)
19	Baltschukat S, Engstler BS, Huang A, Hao HX, Tam A, Wang HQ, Liang J, DiMare MT, Bhang HC, Wang Y, Furet P, Sellers WR, Hofmann F, Schoepfer J, Tiedt R. Capmatinib (INC280) Is Active Against Models of Non-Small Cell Lung Cancer and Other Cancer Types with Defined Mechanisms of MET Activation. Clin Cancer Res. 2019 May 15;25(10):3164-3175	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (commentary on capmatinib preclinical data and clinical biomarker strategy)
20	Benayed R, Offin M, Mullaney K et al. High Yield of RNA Sequencing for Targetable Kinase Fusions in Lung Adenocarcinomas with No Mitogenic Driver Alteration Detected by DNA Sequencing and Low Tumor Mutation Burden. Clinical Cancer Research 2019; 25: 4712-4722.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (evaluation of DNA sequencing)
21	Bubendorf L, Dafni U, Schöbel M, Finn SP, Tischler V, Sejda A, Marchetti A, Thunnissen E, Verbeken EK, Warth A, Sansano I, Cheney R, Speel EJM, Nonaka D, Monkhorst K, Hager H, Martorell M, Savic S, Kerr KM, Tan Q, Tsourti Z,	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (epidemiological

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
	Geiger TR, Kammler R, Schulze K, Das-Gupta A, Shames D, Peters S, Stahel RA; Lungscape Consortium. Prevalence and clinical association of MET gene overexpression and amplification in patients with NSCLC: Results from the European Thoracic Oncology Platform (ETOP) Lungscape project. Lung Cancer. 2017 Sep;111:143-149.								study - prevalence including of METex14 skipping alteration in a cohort with NSCLC)
22	Buyuksimsek M, Togun M, Oguz KI, Bisgin A, Boga I, Tohumcuoglu M, Ogul A, Evren YA, Sahin B, Erdem SH, Mirili C. Results of Liquid Biopsy Studies by Next Generation Sequencing in Patients with Advanced Stage Non-small Cell Lung Cancer: Single Center Experience from Turkey. Balkan J Med Genet. 2019 Dec 21;22(2):17-24	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (NGS using liquid biopsy in patients with NSCLC)
23	Byeon S, Lee B, Park W-Y et al. Benefit of Targeted DNA Sequencing in Advanced Non–Small-Cell Lung Cancer Patients Without EGFR and ALK Alterations on Conventional Tests. Clinical lung cancer 2020; 21: e182-e190.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (targeted DNA sequencing in patients with NSCLC without EGFR and ALK alterations on conventional tests)
24	Davies KD, Lomboy A, Lawrence CA et al. DNA-Based versus RNA-Based Detection of MET Exon 14 Skipping Events in Lung Cancer. Journal of Thoracic Oncology 2019; 14: 737-741.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (RNA-based assay vs DNA-based assay)
25	Descarpentries C, Leprêtre F, Escande F, Kherrouche Z, Figeac M, Sebda S, Baldacci S, Grégoire V, Jamme P, Copin MC, Tulasne D,	Outcomes not in PICO	N	N	N	N	N	N	Intervention: Did not evaluate clinical

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
	Cortot AB. Optimization of Routine Testing for MET Exon 14 Splice Site Mutations in NSCLC Patients. J Thorac Oncol. 2018 Dec;13(12):1873-1883								effectiveness of pharmacotherapeutic interventions, compared RNA-based assay vs DNA-based assay
26	Digumarthy SR, Mendoza DP, Zhang EW, Lennerz JK, Heist RS. Clinicopathologic and Imaging Features of Non-Small-Cell Lung Cancer with MET Exon 14 Skipping Mutations. Cancers (Basel). 2019 Dec 17;11(12):2033	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (clinicopathologic characteristics)
27	Engstrom LD, Aranda R, Lee M, Tovar EA, Essenburg CJ, Madaj Z, Chiang H, Briere D, Hallin J, Lopez-Casas PP, Baños N, Menendez C, Hidalgo M, Tassell V, Chao R, Chudova DI, Lanman RB, Olson P, Bazhenova L, Patel SP, Graveel C, Nishino M, Shapiro GI, Peled N, Awad MM, Jänne PA, Christensen JG. Glesatinib Exhibits Antitumor Activity in Lung Cancer Models and Patients Harboring MET Exon 14 Mutations and Overcomes Mutation-mediated Resistance to Type I MET Inhibitors in Nonclinical Models. Clin Cancer Res. 2017 Nov 1;23(21):6661-6672	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review
28	Frampton GM, Ali SM, Rosenzweig M, Chmielecki J, Lu X, Bauer TM, Akimov M, Bufill JA, Lee C, Jentz D, Hoover R, Ou SH, Salgia R, Brennan T, Chalmers ZR, Jaeger S, Huang A, Elvin JA, Erlich R, Fichtenholtz A, Gowen KA, Greenbowe J, Johnson A, Khaira D, McMahon C, Sanford EM, Roels S, White J, Greshock J, Schlegel R, Lipson D, Yelensky R, Morosini D, Ross JS, Collisson E, Peters M, Stephens PJ, Miller VA. Activation of MET via diverse exon 14 splicing alterations	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (prevalence of METex14 skipping alterations)

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
	occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. Cancer Discov. 2015 Aug;5(8):850-9								
29	Guo R, Berry LD, Aisner DL, Sheren J, Boyle T, Bunn PA Jr, Johnson BE, Kwiatkowski DJ, Drilon A, Sholl LM, Kris MG. MET IHC Is a Poor Screen for MET Amplification or MET Exon 14 Mutations in Lung Adenocarcinomas: Data from a Tri-Institutional Cohort of the Lung Cancer Mutation Consortium. J Thorac Oncol. 2019 Sep;14(9):1666-1671	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (association of MET IHC with METex14 and METamp))
30	Heist, R. S., Shim, H. S., Gingipally, S., Mino-Kenudson, M., Le, L., Gainor, J. F., Zheng, Z., Aryee, M., Xia, J., Jia, P., Jin, H., Zhao, Z., Pao, W., Engelman, J. A., & Iafrate, A. J. (2016). MET Exon 14 Skipping in Non-Small Cell Lung Cancer. The oncologist, 21(4), 481–486	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review
31	Kim EK, Kim KA, Lee CY, Kim S, Chang S, Cho BC, Shim HS. Molecular Diagnostic Assays and Clinicopathologic Implications of MET Exon 14 Skipping Mutation in Non-small-cell Lung Cancer. Clin Lung Cancer. 2019 Jan;20(1):e123-e132	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (DNA and RNA NGS and clinic pathologic implications of each in METex14 population)
32	Lambros L, Uguen A. MET Immunohistochemistry Should Be Avoided in Selecting Non-small-cell Lung Cancers Requiring MET Exon 14 Skipping Mutation Analysis. Clin Lung Cancer. 2019 May;20(3):e418-e420	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review
33	Lambros L, Uguen A. MET Immunohistochemistry Should Be Avoided in Selecting Non-small-cell	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
	Lung Cancers Requiring MET Exon 14 Skipping Mutation Analysis. Clin Lung Cancer. 2019 May;20(3):e418-e420								PICO for clinical review
34	Lee GD, Lee SE, Oh DY, Yu DB, Jeong HM, Kim J, Hong S, Jung HS, Oh E, Song JY, Lee MS, Kim M, Jung K, Kim J, Shin YK, Choi YL, Kim HR. MET Exon 14 Skipping Mutations in Lung Adenocarcinoma: Clinicopathologic Implications and Prognostic Values. J Thorac Oncol. 2017 Aug;12(8):1233-1246	Outcomes not in PICO	Y	N	N	N	N	N	Intervention: Surgical procedure
35	Li S, Choi Y-L, Gong Z et al. Comprehensive Characterization of Oncogenic Drivers in Asian Lung Adenocarcinoma. Journal of Thoracic Oncology 2016; 11: 2129-2140.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (incidence data)
36	Li Y, Gao L, Ma D, Qiu T, Li W, Li W, Guo L, Xing P, Liu B, Deng L, Fu J, Li J, Yu Y, Ying J. Identification of MET exon14 skipping by targeted DNA- and RNA-based next-generation sequencing in pulmonary sarcomatoid carcinomas. Lung Cancer. 2018 Aug;122:113-119	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (RNA-based assay vs DNA-based assay)
37	Liang, X., Li, Q., Xu, B. et al. Mutation landscape and tumor mutation burden analysis of Chinese patients with pulmonary sarcomatoid carcinomas. Int J Clin Oncol 24, 1061–1068 (2019).	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (assessed NGS in patients with PSC including MET exon 14 skipping)
38	Liu SY, Gou LY, Li AN, Lou NN, Gao HF, Su J, Yang JJ, Zhang XC, Shao Y, Dong ZY, Zhou Q, Zhong WZ, Wu YL. The Unique Characteristics of	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (assessed

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
	MET Exon 14 Mutation in Chinese Patients with NSCLC. J Thorac Oncol. 2016 Sep;11(9):1503-10.								NGS on DNA and Danger sequencing on complementary DNA)
39	Liu X, Jia Y, Stoopler MB et al. Next-Generation Sequencing of Pulmonary Sarcomatoid Carcinoma Reveals High Frequency of Actionable MET Gene Mutations. Journal of Clinical Oncology 2016; 34: 794-802.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (assessed NGS in patients with PSC including MET exon 14 skipping)
40	Lu X, Peled N, Greer J, Wu W, Choi P, Berger AH, Wong S, Jen KY, Seo Y, Hann B, Brooks A, Meyerson M, Collisson EA. MET Exon 14 Mutation Encodes an Actionable Therapeutic Target in Lung Adenocarcinoma. Cancer Res. 2017 Aug 15;77(16):4498-450	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (estimate rate of MET exon skipping)
41	Lung J, Hung MS, Lin YC, Lee KF, Jiang YY, Huang SL, Fang YH, Lu MS, Lin CK, Yang TM, Lin PY, Hsieh MJ, Tsai YH. MET exon 14 skipping mutations and gene amplification in a Taiwanese lung cancer population. PLoS One. 2019 Aug 1;14(8):e0220670	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (clinicopathologic characteristics)
42	Mignard X, Ruppert AM, Antoine M, Vasseur J, Girard N, Mazières J, Moro-Sibilot D, Fallet V, Rabbe N, Thivolet-Bejui F, Rouquette I, Lantuejoul S, Cortot A, Saffroy R, Cadranel J, Lemoine A, Wislez M. c-MET Overexpression as a Poor Predictor of MET Amplifications or Exon 14 Mutations in Lung Sarcomatoid Carcinomas. J Thorac Oncol. 2018 Dec;13(12):1962-1967	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (immunohistochemistry on patients with LSC)

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
43	NCT00585195. A Study Of Oral PF-02341066, A C-Met/Hepatocyte Growth Factor Tyrosine Kinase Inhibitor, In Patients With Advanced Cancer (PROFILE 1001)/ Available at: https://clinicaltrials.gov/ct2/show/NCT00585195 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
44	NCT02414139. Clinical Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-type Advanced Non-small Cell Lung Cancer (Geometry Mono-1). Available at: https://clinicaltrials.gov/ct2/show/NCT02414139 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
45	NCT02499614. Crizotinib in Pretreated Metastatic Non-small-cell Lung Cancer With MET Amplification or ROS1 Translocation (METROS) (METROS). Available at: https://clinicaltrials.gov/ct2/show/NCT02499614 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
46	NCT02750215. A Study of Capmatinib (INC280) in NSCLC Patients With MET Exon 14 Alterations Who Have Received Prior MET Inhibitor Available at: https://clinicaltrials.gov/ct2/show/NCT02750215 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
47	NCT02864992. Tepotinib Phase II in NSCLC Harboring MET Alterations (VISION). Available at: https://clinicaltrials.gov/ct2/show/NCT02864992 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO,

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
									clinical trial record only
48	NCT02897479. A Phase II Study of HMPL-504 in Lung Sarcomatoid Carcinoma and Other Non-small Cell Lung Cancer. Available at: https://clinicaltrials.gov/ct2/show/NCT02897479 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
49	NCT02920996. Merestinib In Non-Small Cell Lung Cancer And Solid Tumors. Available at: https://clinicaltrials.gov/ct2/show/NCT02920996 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
50	NCT03088930. Evaluating Crizotinib in the Neoadjuvant Setting in Patients With Non-small Cell Lung Cancer. Available at: https://clinicaltrials.gov/ct2/show/NCT03088930 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
51	NCT03175224. APL-101 Study of Subjects With NSCLC With c-Met EXON 14 Skip Mutations and c-Met Dysregulation Advanced Solid Tumors (SPARTA). Available at: https://clinicaltrials.gov/ct2/show/NCT03175224 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
52	NCT03468985. Nivolumab, Cabozantinib S-Malate, and Ipilimumab in Treating Patients With Recurrent Stage IV Non-small Cell Lung Cancer.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
	https://ClinicalTrials.gov/show/NCT03468985 (last accessed June 2021)								extractable data for outcomes in PICO, clinical trial record only
53	NCT03693339. Capmatinib in Patients With Non-small Cell Lung Cancer Harboring cMET exon14 Skipping Mutation. Available at: https://clinicaltrials.gov/ct2/show/NCT03693339 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
54	NCT03911193. CABozantinib in Non-Small Cell Lung Cancer (NSCLC) Patients With MET Deregulation (CABinMET). Available at: https://clinicaltrials.gov/ct2/show/NCT03911193 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
55	NCT03993873. Phase 1 Study of TPX-0022, a MET/CSF1R/SRC Inhibitor, in Patients With Advanced Solid Tumors Harboring Genetic Alterations in MET. Available at: https://clinicaltrials.gov/ct2/show/NCT03993873 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only
56	NCT04084717. Study of Crizotinib for ROS1 and MET Activated Lung Cancer. https://ClinicalTrials.gov/show/NCT04084717 (last accessed June 2021)	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes – results not posted. No extractable data for outcomes in PICO, clinical trial record only

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
57	Poirot B, Doucet L, Benhenda S, Champ J, Meignin V, Lehmann-Che J. MET Exon 14 Alterations and New Resistance Mutations to Tyrosine Kinase Inhibitors: Risk of Inadequate Detection with Current Amplicon-Based NGS Panels. J Thorac Oncol. 2017 Oct;12(10):1582-1587	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (diagnostic data for NGS detecting METex14)
58	Qiu T, Li W, Zhang T, Xing P, Huang W, Wang B, Chu L, Guo L, Liu X, Li Y, Ying J, Li J. Distinct MET Protein Localization Associated With MET Exon 14 Mutation Types in Patients With Non-small-cell Lung Cancer. Clin Lung Cancer. 2018 Jul;19(4):e391-e398	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (immunohistochemistry on patients with NSCLC)
59	Reis H, Metzenmacher M, Goetz M et al. MET Expression in Advanced Non–Small-Cell Lung Cancer: Effect on Clinical Outcomes of Chemotherapy, Targeted Therapy, and Immunotherapy. Clinical lung cancer 2018; 19: e441-e463.	Outcomes not in PICO	Y	N	Y	N	N	N	Change to intervention, no intervention (clinical outcomes compared based on MET expression)
60	Rotow JK, Gui P, Wu W, Raymond VM, Lanman RB, Kaye FJ, Peled N, Fece de la Cruz F, Nadres B, Corcoran RB, Yeh I, Bastian BC, Starostik P, Newsom K, Olivas VR, Wolff AM, Fraser JS, Collisson EA, McCoach CE, Camidge DR, Pacheco J, Bazhenova L, Li T, Bivona TG, Blakely CM. Co-occurring Alterations in the RAS-MAPK Pathway Limit Response to MET Inhibitor Treatment in MET Exon 14 Skipping Mutation-Positive Lung Cancer. Clin Cancer Res. 2020 Jan 15;26(2):439-449	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (sequencing analysis on patients with advanced stage METex14 NSCLC)
61	Saffroy R, Fallet V, Girard N, Mazieres J, Sibilot DM, Lantuejoul S, Rouquette I, Thivolet-Bejui F,	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
	Vieira T, Antoine M, Cadranel J, Lemoine A, Wislez M. MET exon 14 mutations as targets in routine molecular analysis of primary sarcomatoid carcinoma of the lung. Oncotarget. 2017 Jun 27;8(26):42428-4243								PICO for clinical review (screening mutations affecting MET exon 14 splice sites in Sarcomatoid Carcinoma)
62	Saigi M, McLeer-Florin A, Pros E, Nadal E, Brambilla E, Sanchez-Cespedes M. Genetic screening and molecular characterization of MET alterations in non-small cell lung cancer. Clin Transl Oncol. 2018 Jul;20(7):881-888	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (characterize MET alterations in a cohort of NSCLC patients treated with surgery)
63	Sands JM, Nguyen T, Shivdasani P et al. Next-generation sequencing informs diagnosis and identifies unexpected therapeutic targets in lung squamous cell carcinomas. Lung Cancer 2020; 140: 35-41.	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (NGS results in patients with lung squamous cell carcinomas – subpop had METex14)
64	Schrock AB, Frampton GM, Suh J, Chalmers ZR, Rosenzweig M, Erlich RL, Halmos B, Goldman J, Forde P, Leuenberger K, Peled N, Kalemkerian GP, Ross JS, Stephens PJ, Miller VA, Ali SM, Ou SH. Characterization of 298 Patients with Lung Cancer Harboring MET Exon 14 Skipping Alterations. J Thorac Oncol. 2016 Sep;11(9):1493-502	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (genomic profiling of patients with lung cancer and METex14

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
									skipping alterations)
665	Schrock AB, Li SD, Frampton GM, Suh J, Braun E, Mehra R, Buck SC, Bufill JA, Peled N, Karim NA, Hsieh KC, Doria M, Knost J, Chen R, Ou SI, Ross JS, Stephens PJ, Fishkin P, Miller VA, Ali SM, Halmos B, Liu JJ. Pulmonary Sarcomatoid Carcinomas Commonly Harbor Either Potentially Targetable Genomic Alterations or High Tumor Mutational Burden as Observed by Comprehensive Genomic Profiling. J Thorac Oncol. 2017 Jun;12(6):932-942	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (genomic profiling was performed on DNA of patients with PSC)
66	Suzawa K, Offin M, Lu D, Kurzatkowski C, Vojnic M, Smith RS, Sabari JK, Tai H, Mattar M, Khodos I, de Stanchina E, Rudin CM, Kris MG, Arcila ME, Lockwood WW, Drilon A, Ladanyi M, Somwar R. Activation of KRAS Mediates Resistance to Targeted Therapy in MET Exon 14-mutant Non-small Cell Lung Cancer. Clin Cancer Res. 2019 Feb 15;25(4):1248-1260	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (analysis of KRAS mutations in METex14 NSCLC patients)
67	Tong JH, Yeung SF, Chan AW, Chung LY, Chau SL, Lung RW, Tong CY, Chow C, Tin EK, Yu YH, Li H, Pan Y, Chak WP, Ng CS, Mok TS, To KF. MET Amplification and Exon 14 Splice Site Mutation Define Unique Molecular Subgroups of Non-Small Cell Lung Carcinoma with Poor Prognosis. Clin Cancer Res. 2016 Jun 15;22(12):3048-56	Outcomes not in PICO	N	N	N	N	N	N	No change, outcomes not in PICO for clinical review (incidence of METex14 in NSCLC)
68	Wang SXY, Zhang BM, Wakelee HA, Koontz MZ, Pan M, Diehn M, Kunder CA, Neal JW. Case series of MET exon 14 skipping mutation-positive non-small-cell lung cancers with response to crizotinib and cabozantinib. Anticancer Drugs. 2019 Jun;30(5):537-541	Outcomes not in PICO	N	N	N	Y	N	N	Study design, case series <10 participants

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
69	Zheng D, Wang R, Ye T, Yu S, Hu H, Shen X, Li Y, Ji H, Sun Y, Chen H. MET exon 14 skipping defines a unique molecular class of non-small cell lung cancer. Oncotarget. 2016 Jul 5;7(27):41691-41702	Outcomes not in PICO	N	N	N	Y	N	N	No change, outcomes not in PICO for clinical review (clinical and pathological characteristics for METex14 skipping patients from a cohort of NSCLC)
70	Mayenga M, Assie J-B, Monnet I et al. Durable responses to immunotherapy of non-small cell lung cancers harboring MET exon-14-skipping mutation: A series of 6 cases. Lung cancer (Amsterdam, Netherlands) 2020; 150: 21-25.	Outcomes not in PICO: 6 cases in whom clinical characteristics after response to immunotherapy were assessed	N	N	N	N	N	N	Outcomes not in PICO: 6 cases in whom clinical characteristics after response to immunotherapy were assessed
71	Wong S, Alex D, Bosdet I et al. P85.05 MET Exon 14 Skipping Mutation Positive Non-Small Cell Lung Cancer: A Population-Based Cohort. Journal of Thoracic Oncology 2021; 16: S670-S671.	Outcomes not in PICO: population characteristics eg demographics, prior treatments	N	N	N	N	N	N	Outcomes not in PICO: population characteristics eg demographics, prior treatments
72	Mazieres J, Veillon R, Felip E et al. P85.01 Activity of Tepotinib in Brain Metastases (BM): Preclinical and Clinical Data in MET Exon 14 (METex14) Skipping NSCLC. Journal of Thoracic Oncology 2021; 16: S668-S669.	Outcomes not in PICO: preclinical and clinical but METex14 NSCLC + brain metastasis	N	N	N	N	N	N	Outcomes not in PICO: preclinical and clinical but METex14 NSCLC + brain metastasis
73	Viteri S, Mazieres J, Veillon R et al. MO01.46 Tepotinib Activity in Brain Metastases (BM): Preclinical Models and Clinical Data from MET Exon 14 (METex14) Skipping NSCLC. Journal of Thoracic Oncology 2021; 16: S35-S36.	Outcomes not in PICO: preclinical and clinical but METex14 NSCLC + brain metastasis (and overlap with Mazieres 2021)	N	N	N	N	N	N	Outcomes not in PICO: preclinical and clinical but METex14 NSCLC + brain metastasis (and overlap with Mazieres 2021)

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
74	Cai B, Zhou Z, Xue W et al. Budget impact of capmatinib in adult patients with metastatic non-small cell lung cancer whose tumors have a mutation that leads to MET exon 14 skipping in the United States. Journal of Managed Care and Specialty Pharmacy 2020; 26: S22-S23.	Outcomes not in scope of clinical review – budget impact	N	N	N	N	N	N	Outcomes not in scope of clinical review – budget impact
75	Stargardter M. Financial impact of tepotinib for the treatment of adult patients with metastatic non-small cell lung cancer bearing METex14 skipping in the United States. ASCO Annual Meeting, 2021	Outcomes not in scope of clinical review – budget impact	N	N	N	N	N	N	Outcomes not in scope of clinical review – budget impact
76	Shimokawa M, Nosaki K, Seto T et al. Phase II, open-label, multicenter trial of crizotinib in Japanese patients with advanced non-small cell lung cancer harboring a MET gene alteration: Co-MET study. Trials 2020; 21: 298.	Outcomes: publication reported protocol detail only, no results posted	N	N	N	N	N	N	Outcomes: publication reported protocol detail only, no results posted
77	Euctr DE. Study of efficacy of capmatinib in comparison with standard of care docetaxel as a second or third line therapy in participants with non-small cell lung cancers harboring MET exon 14 skipping mutation. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2020-001578-31-DE 2020.	Outcomes: results not posted	N	N	N	N	N	N	Outcomes: results not posted
78	Nct. Study of Capmatinib Efficacy in Comparison With Docetaxel in Previously Treated Participants With Non-small Cell Lung Cancer Harboring MET Exon 14 Skipping Mutation. https://clinicaltrialsgov/show/NCT04427072 2020.	Outcomes: results not posted	N	N	N	N	N	N	Outcomes: results not posted
79	Heist RS, Garon EB, Tan DSW et al. Accurate Detection of METex14 Mutations in Non-Small Cell Lung Cancer (NSCLC) with Comprehensive Genomic Sequencing: Results from the	Outcomes: study evaluated diagnostic technique	N	N	N	N	N	N	Outcomes: study evaluated diagnostic technique

			Outcomes (bold in NICE scope)						
	Citation	**Reason for Exclusion**	**OS**	**PFS**	TTP	**RR**	**Safety**	**HRQL**	**Comment**
	GEOMETRY Mono-1 Study. Journal of Thoracic Oncology 2020; 15: S30-S31.								

Appendix 3: Model corrections

As part of the post submission process, we have noticed an error associated with the OS for immunotherapy. Within the 'OS' sheet cells AH63:AH1628, the formula was using the incorrect cell to incorporate background mortality. This has now been corrected within these cells. An example of the change from AH63 is shown below:

Previous formula: *=IF(ISERROR(MATCH($AG$61,Lists!$N$97:$N$115,0)),NA(),AH62*(1-MAX(**$AZ64**,IFERROR(1-(AG63/AG62),1))))*

Corrected formula: *=IF(ISERROR(MATCH($AG$61,Lists!$N$97:$N$115,0)),NA(),AH62*(1-MAX(**$AZ63**,IFERROR(1-(AG63/AG62),1))))*

This has marginal impact on the results previously presented versus immunotherapy which have now been corrected and presented below:

All patients

Base case results

Table 24: Base-case pairwise results – all patients (vs immunotherapy)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NMB [a]
Tepotinib	[redacted]	2.85	[redacted]					
Immunotherapy	[redacted]	2.84	[redacted]	[redacted]	0.00	[redacted]	Dominant	£22,267

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years
Notes: a Willingness-to-pay threshold is £30,000 versus immunotherapy

Table 25: Base-case fully incremental analysis – all patients

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)	Incremental ICER (extended dominance)
Chemotherapies	[redacted]	[redacted]				
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£19,512	£19,512
Immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Strictly dominated

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

Probabilistic sensitivity analysis

Table 26: Mean results of PSA (1,000 runs) and comparison with deterministic results – all patients

Technology	Total costs		Total QALYs		ICER (£)		NMB [a]	
	Det.	PSA	Det.	PSA	Det.	PSA	Det.	PSA
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]				
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant	£22,267	£21,687

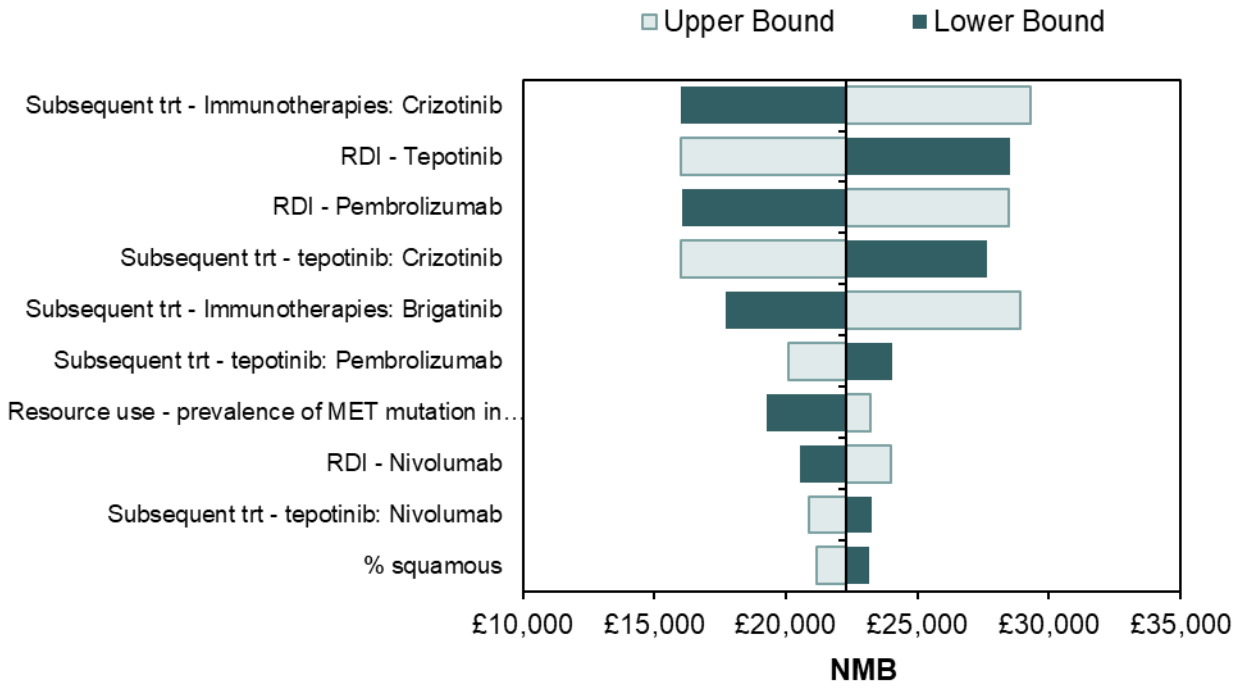
Abbreviations: DET, deterministic; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Notes:
a Willingness-to-pay threshold is £30,000 versus immunotherapy

Figure 10: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus immunotherapy – all patients

Abbreviations: QALYs, quality-adjusted life years

One-way sensitivity analysis

Figure 11: Tornado diagram showing OWSA results on the NMB versus immunotherapy (WTP=£30,000) – all patients



Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis; RDI, relative dose intensity

Table 27: Top 10 ranked OWSA results on the NMB versus immunotherapy (WTP=£30,000) – immunotherapy – all patients

Parameter	Lower Bound	Upper Bound
Subsequent treatment - Immunotherapies: Crizotinib	£15,989	£29,310
RDI - Tepotinib	£28,501	£16,032
RDI - Pembrolizumab	£16,043	£28,490
Subsequent treatment - tepotinib: Crizotinib	£27,659	£15,993
Subsequent treatment - Immunotherapies: Brigatinib	£17,718	£28,912
Subsequent treatment - tepotinib: Pembrolizumab	£24,041	£20,082
Resource use - prevalence of MET mutation in NSCLC	£19,252	£23,210
RDI - Nivolumab	£20,557	£23,976
Subsequent treatment - tepotinib: Nivolumab	£23,253	£20,882
Proportion squamous	£23,158	£21,153

Abbreviations: MET, mesenchymal-epithelial transition; NMB, net monetary benefit; NSCLC, non-small-cell lung cancer; OWSA, one-way sensitivity analysis; RDI, relative dose intensity; WTP, willingness-to-pay.

Scenario analysis

Table 28: Results of scenario analysis versus immunotherapy – all patients

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB [a]
Time horizon	30 years	10 years	[redacted]	[redacted]	[redacted]	Dominant	£22,430
		20 years	[redacted]	[redacted]	[redacted]	Dominant	£22,243
Discount rates	3.5%	0.0%	[redacted]	[redacted]	[redacted]	Dominant	£21,596
		6.0%	[redacted]	[redacted]	[redacted]	Dominant	£22,656
Weight data source	All patients	European patients	[redacted]	[redacted]	[redacted]	Dominant	£22,283
Drug wastage	Include	Exclude	[redacted]	[redacted]	[redacted]	Dominant	£23,016
Dose intensity	Include	Exclude	[redacted]	[redacted]	[redacted]	Dominant	£15,402
Pemetrexed maintenance	Exclude	Include	[redacted]	[redacted]	[redacted]	Dominant	£22,267
AE disutility	Include	Exclude	[redacted]	[redacted]	[redacted]	Dominant	£22,194
MET mutation testing	Include	Exclude	[redacted]	[redacted]	[redacted]	Dominant	£24,314
Subsequent treatment	VISION/real-world data	UK based distribution	[redacted]	[redacted]	[redacted]	Dominant	£7,402
		UK based distribution matching number of subsequent lines	[redacted]	[redacted]	[redacted]	Dominant	£7,159
Utility source	VISION	Nafees et al, 2008[39]	[redacted]	[redacted]	[redacted]	Dominant	£23,576
		Chouaid et al, 2013 - 1L[40]	[redacted]	[redacted]	[redacted]	Dominant	£21,781
		Chouaid et al, 2013 - 2L[40]	[redacted]	[redacted]	[redacted]	Dominant	£23,071
		Chouaid et al, 2013 - 3L/4L[40]	[redacted]	[redacted]	[redacted]	Dominant	£23,082
		TA428 – Pembrolizumab[41]	[redacted]	[redacted]	[redacted]	Dominant	£22,381
		TA484 – Nivolumab[42]	[redacted]	[redacted]	[redacted]	Dominant	£21,932
		TA484 - Nivolumab (committee preference)[42]	[redacted]	[redacted]	[redacted]	Dominant	£22,978

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB [a]
		TA584 - Atezolizumab in combination[43]	[redacted]	[redacted]	[redacted]	Dominant	£21,551
		TA531 – Pembrolizumab[16]	[redacted]	[redacted]	[redacted]	Dominant	£22,696
		TA655 – Nivolumab[44]	[redacted]	[redacted]	[redacted]	Dominant	£23,171
		TA655 - Nivolumab (committee preference)[44]	[redacted]	[redacted]	[redacted]	Dominant	£23,421
Tepotinib OS parametric curve	Log-logistic	Log-normal	[redacted]	[redacted]	[redacted]	Dominant	£22,736
Tepotinib PFS parametric curve	Log-normal	Gen Gamma	[redacted]	[redacted]	[redacted]	Dominant	£22,540
		Gompertz	[redacted]	[redacted]	[redacted]	Dominant	£22,682
		Log-logistic	[redacted]	[redacted]	[redacted]	Dominant	£22,611
Tepotinib ToT parametric curve	Gen Gamma	Exponential	[redacted]	[redacted]	[redacted]	Dominant	£23,214
		Gompertz	[redacted]	[redacted]	[redacted]	Dominant	£21,216
		Log-logistic	[redacted]	[redacted]	[redacted]	Dominant	£15,270
		Log-normal	[redacted]	[redacted]	[redacted]	Dominant	£17,038
		Weibull	[redacted]	[redacted]	[redacted]	Dominant	£23,334
Immunotherapy OS parametric curve	Spline - 1 knot normal	Exponential	[redacted]	[redacted]	[redacted]	Dominant	£29,560
		Gompertz	[redacted]	[redacted]	[redacted]	Dominant	£28,873
		Weibull	[redacted]	[redacted]	[redacted]	Dominant	£26,643
		Spline - 2 knot odds	[redacted]	[redacted]	[redacted]	Dominant	£27,612
		Spline - 3 knot odds	[redacted]	[redacted]	[redacted]	Dominant	£28,218
		Spline - 1 knot hazard	[redacted]	[redacted]	[redacted]	Dominant	£28,586
		Spline - 2 knot normal	[redacted]	[redacted]	[redacted]	Dominant	£29,305
		Spline - 3 knot normal	[redacted]	[redacted]	[redacted]	Dominant	£29,946
		Gen Gamma	[redacted]	[redacted]	[redacted]	Dominant	£18,791

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB [a]
Immunotherapy PFS parametric curve	Piecewise - Log-logistic	Piecewise - Exponential	[redacted]	[redacted]	[redacted]	Dominant	£24,104
		Piecewise - Gen Gamma	[redacted]	[redacted]	[redacted]	Dominant	£22,689
		Piecewise - Log-logistic	[redacted]	[redacted]	[redacted]	Dominant	£22,267
		Piecewise - Log-normal	[redacted]	[redacted]	[redacted]	Dominant	£22,506
		Piecewise – Weibull	[redacted]	[redacted]	[redacted]	Dominant	£23,759
Immunotherapy ToT	Literature (capped at PFS)	Same as PFS	[redacted]	[redacted]	[redacted]	Dominant	£34,763
		Using HR (PFS vs ToT)	[redacted]	[redacted]	[redacted]	Dominant	£22,944

Abbreviations: AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-years; ToT, time on treatment
Notes:
a Willingness-to-pay threshold is £30,000 versus immunotherapy

Untreated population

Base case results

Table 29: Base-case pairwise results – untreated population (vs immunotherapy)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NMB [a]
Tepotinib	[redacted]	[redacted]	[redacted]					
Immunotherapy	[redacted]	[redacted]	[redacted]	-£58,747	-0.25	-0.14	£418,802	£54,539

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years
Notes: a Willingness-to-pay threshold is £30,000 versus immunotherapy

Table 30: Base-case fully incremental analysis – untreated population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)	Incremental ICER (extended dominance)
Chemotherapies	[redacted]	[redacted]	-	-		
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£23,354	£23,354
Immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	£418,802	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,345	£186,293

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

Probabilistic sensitivity analysis

Table 31: Mean results of PSA (1,000 runs) and comparison with deterministic results – untreated population

Technology	Total costs		Total QALYs		ICER (£)		NMB [a]	
	Det.	PSA	Det.	PSA	Det.	PSA	Det.	PSA
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]				
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£418,802	£270,915	£54,539	£50,808

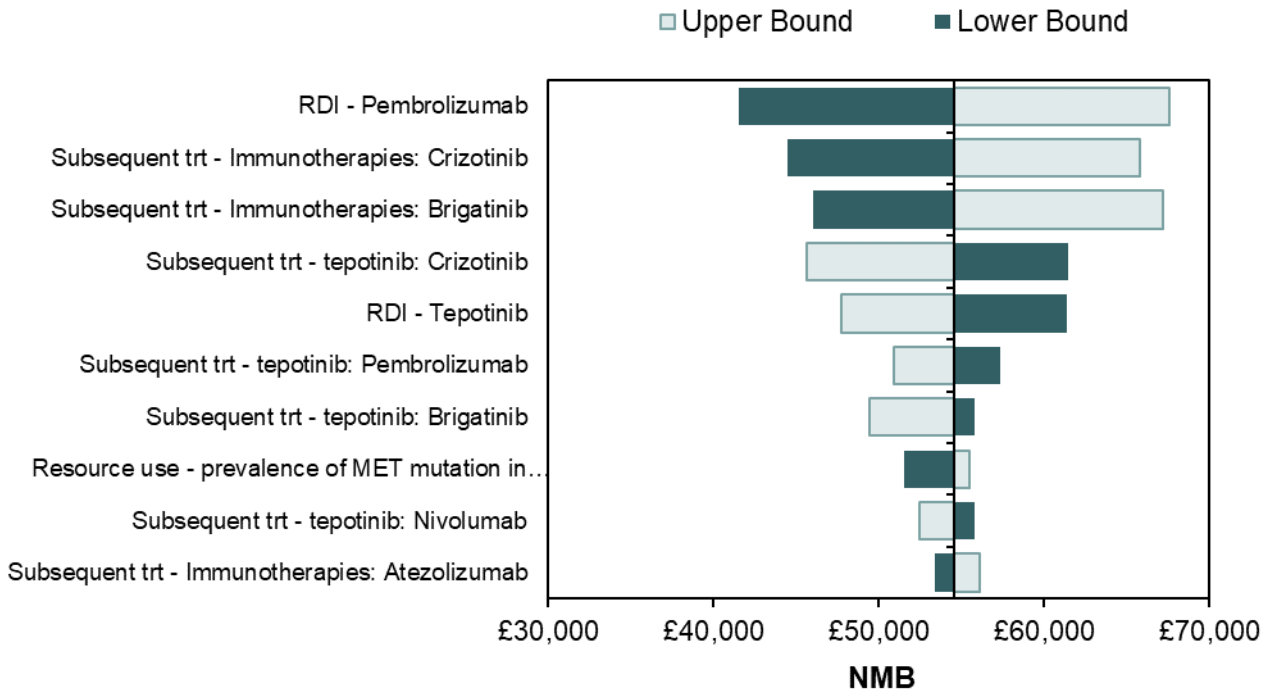
Abbreviations: DET, deterministic; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Notes:
a Willingness-to-pay threshold is £30,000 versus immunotherapy

Figure 12: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus immunotherapy – untreated population

Abbreviations: QALYs, quality-adjusted life years

One-way sensitivity analysis

Figure 13: Tornado diagram showing OWSA results on the NMB versus immunotherapy (WTP=£30,000) – untreated population



Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis; RDI, relative dose intensity

Table 32: Top 10 ranked OWSA results on the NMB versus immunotherapy (WTP=£30,000) – immunotherapy – untreated population

Parameter	Lower Bound	Upper Bound
RDI - Pembrolizumab	£41,536	£67,541
Subsequent treatment - Immunotherapies: Crizotinib	£44,514	£65,783
Subsequent treatment - Immunotherapies: Brigatinib	£46,037	£67,205
Subsequent treatment - tepotinib: Crizotinib	£61,435	£45,618
RDI - Tepotinib	£61,340	£47,737
Subsequent treatment - tepotinib: Pembrolizumab	£57,351	£50,908
Subsequent treatment - tepotinib: Brigatinib	£55,823	£49,414
Resource use - prevalence of MET mutation in NSCLC	£51,524	£55,482
Subsequent treatment - tepotinib: Nivolumab	£55,756	£52,467
Subsequent treatment - Immunotherapies: Atezolizumab	£53,386	£56,107

Abbreviations: MET, mesenchymal-epithelial transition; NMB, net monetary benefit; NSCLC, non-small-cell lung cancer; OWSA, one-way sensitivity analysis; RDI, relative dose intensity; WTP, willingness-to-pay.

Scenario analysis

Table 33: Results of scenario analysis versus immunotherapy – untreated population

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB
Time horizon	30 years	10 years	[redacted]	[redacted]	[redacted]	£395,329	£54,173
		20 years	[redacted]	[redacted]	[redacted]	£414,222	£54,529
Discount rates	3.5%	0.0%	[redacted]	[redacted]	[redacted]	£391,718	£55,589
		6.0%	[redacted]	[redacted]	[redacted]	£442,054	£53,878
Weight data source	All patients	European patients	[redacted]	[redacted]	[redacted]	£418,907	£54,554
Drug wastage	Include	Exclude	[redacted]	[redacted]	[redacted]	£424,157	£55,290
Dose intensity	Include	Exclude	[redacted]	[redacted]	[redacted]	£366,652	£47,223
AE disutility	Include	Exclude	[redacted]	[redacted]	[redacted]	£412,420	£54,474
MET mutation testing	Include	Exclude	[redacted]	[redacted]	[redacted]	£433,395	£56,586
Subsequent treatment	VISION/real-world data	UK based distribution	[redacted]	[redacted]	[redacted]	£226,661	£27,586
		UK based distribution matching number of subsequent lines	[redacted]	[redacted]	[redacted]	£206,659	£24,781
Utility source	VISION	Nafees et al, 2008	[redacted]	[redacted]	[redacted]	£679,773	£56,154
		Chouaid et al, 2013 - 1L	[redacted]	[redacted]	[redacted]	£381,073	£54,122
		Chouaid et al, 2013 - 2L	[redacted]	[redacted]	[redacted]	£491,974	£55,165
		Chouaid et al, 2013 - 3L/4L	[redacted]	[redacted]	[redacted]	£654,673	£56,055
		TA428 - Pembrolizumab	[redacted]	[redacted]	[redacted]	£404,914	£54,394
		TA484 - Nivolumab	[redacted]	[redacted]	[redacted]	£375,850	£54,058
		TA484 - Nivolumab (committee preference)	[redacted]	[redacted]	[redacted]	£507,200	£55,272
		TA584 - Atezolizumab in combination	[redacted]	[redacted]	[redacted]	£363,401	£53,897
		TA531 - Pembrolizumab	[redacted]	[redacted]	[redacted]	£370,031	£53,984

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB
		TA655 - Nivolumab	[redacted]	[redacted]	[redacted]	£495,452	£55,190
		TA655 - Nivolumab (committee preference)	[redacted]	[redacted]	[redacted]	£608,708	£55,852
Tepotinib OS parametric curve	Log-normal	Exponential	[redacted]	[redacted]	[redacted]	£111,916	£45,948
		Gen Gamma	[redacted]	[redacted]	[redacted]	£137,464	£48,438
		Gompertz	[redacted]	[redacted]	[redacted]	£113,469	£46,137
		Log-logistic	[redacted]	[redacted]	[redacted]	£284,248	£53,186
		Weibull	[redacted]	[redacted]	[redacted]	£102,424	£44,670
Tepotinib PFS parametric curve	Log-normal	Gen Gamma	[redacted]	[redacted]	[redacted]	£426,763	£54,712
		Gompertz	[redacted]	[redacted]	[redacted]	£537,245	£56,634
		Log-logistic	[redacted]	[redacted]	[redacted]	£421,028	£54,602
Tepotinib ToT parametric curve	Gen Gamma	Exponential	[redacted]	[redacted]	[redacted]	£432,302	£56,432
		Gompertz	[redacted]	[redacted]	[redacted]	£338,290	£43,245
		Log-logistic	[redacted]	[redacted]	[redacted]	£352,187	£45,195
		Log-normal	[redacted]	[redacted]	[redacted]	£348,390	£44,662
		Weibull	[redacted]	[redacted]	[redacted]	£428,717	£55,930
Immunotherapy OS parametric curve	Spline - 2 knot normal	Exponential	[redacted]	[redacted]	[redacted]	Dominant	£61,015
		Gen Gamma	[redacted]	[redacted]	[redacted]	Dominant	£60,839
		Spline - 2 knot odds	[redacted]	[redacted]	[redacted]	£307,321	£53,539
		Spline - 3 knot odds	[redacted]	[redacted]	[redacted]	Dominant	£57,946
		Spline - 1 knot hazard	[redacted]	[redacted]	[redacted]	£157,140	£49,688
		Spline - 2 knot hazard	[redacted]	[redacted]	[redacted]	Dominant	£60,690
		Spline - 3 knot hazard	[redacted]	[redacted]	[redacted]	Dominant	£62,894
		Spline - 3 knot normal	[redacted]	[redacted]	[redacted]	Dominant	£59,533

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB
Immunotherapy PFS parametric curve	Piecewise – Weibull	Exponential	[redacted]	[redacted]	[redacted]	£598,441	£64,073
		Spline - 1 knot hazard	[redacted]	[redacted]	[redacted]	£287,532	£49,224
		Spline - 2 knot normal	[redacted]	[redacted]	[redacted]	£298,100	£50,466
		Piecewise - Exponential	[redacted]	[redacted]	[redacted]	£441,304	£55,344
		Piecewise - Log-logistic	[redacted]	[redacted]	[redacted]	£349,107	£52,525
		Piecewise - Log-normal	[redacted]	[redacted]	[redacted]	£357,311	£53,205
Immunotherapy ToT	Literature (capped at PFS)	Same as PFS	[redacted]	[redacted]	[redacted]	£539,616	£71,486
		Using HR (PFS vs ToT)	[redacted]	[redacted]	[redacted]	£439,321	£57,417

Abbreviations: AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-years; ToT, time on treatment
Notes: a Willingness-to-pay threshold is £30,000 versus immunotherapy

Previously treated population

Base case results

Table 34: Base-case pairwise results – previously treated population (vs immunotherapy)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NMB [a]
Tepotinib	[redacted]	2.61	[redacted]					
Immunotherapy	[redacted]	1.87	[redacted]	[redacted]	0.74	[redacted]	£24,824	£2,119

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years
Notes: a Willingness-to-pay threshold is £50,000 versus immunotherapy

Table 35: Base-case fully incremental analysis – previously treated population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)	Incremental ICER (extended dominance)
Immunotherapies	[redacted]	[redacted]				
Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	£44,475	Extendedly dominated
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£18,176	£24,824

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

Probabilistic sensitivity analysis

Table 36: Mean results of PSA (1,000 runs) and comparison with deterministic results – previously treated population

Technology	Total costs		Total QALYs		ICER (£)		NMB [a]	
	Det.	PSA	Det.	PSA	Det.	PSA	Det.	PSA
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]				
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£24,824	£30,654	£10,307	£7,669

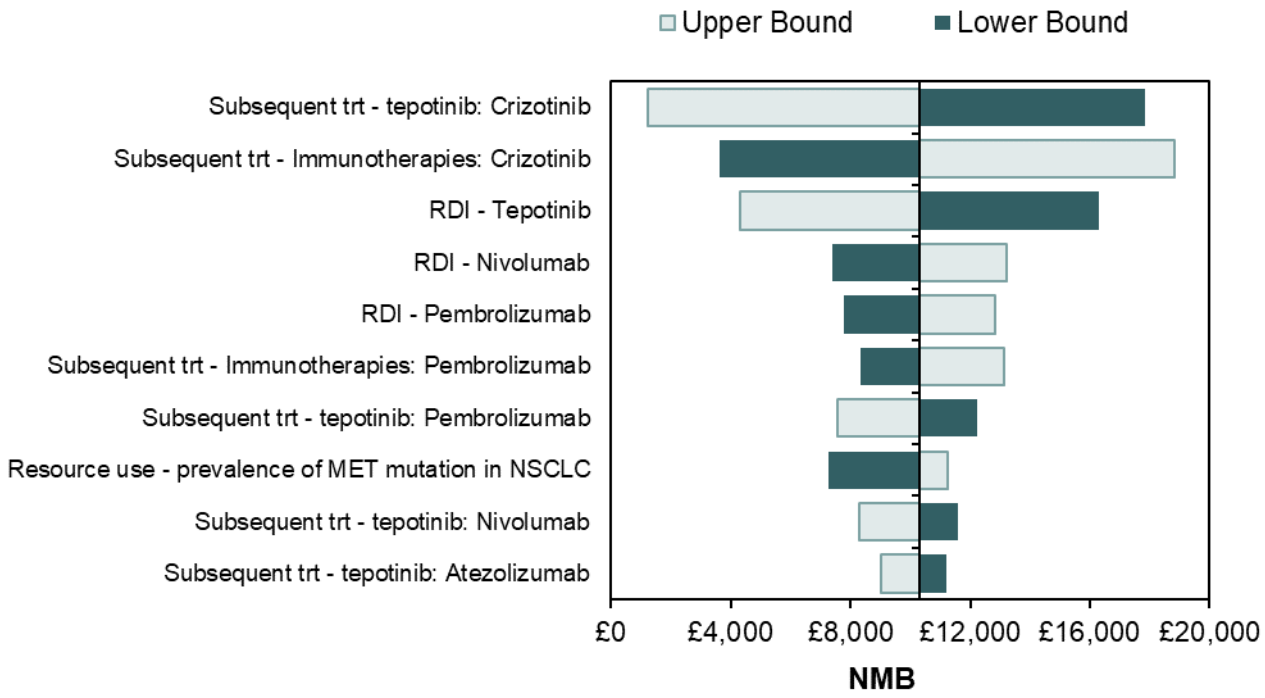
Abbreviations: DET, deterministic; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Notes:
a Willingness-to-pay threshold is £50,000 versus immunotherapy

Figure 11: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus immunotherapy – previously treated population

Abbreviations: QALYs, quality-adjusted life years

One-way sensitivity analysis

Figure 14: Tornado diagram showing OWSA results on the NMB versus immunotherapy (WTP=£50,000) – previously treated population



Abbreviations: NMB, net monetary benefit; OWSA, one-way sensitivity analysis; RDI, relative dose intensity

Table 37: Top 10 ranked OWSA results on the NMB versus immunotherapy (WTP=£50,000) – immunotherapy – previously treated

Parameter	Lower Bound	Upper Bound
Subsequent treatment - tepotinib: Crizotinib	£17,849	£1,223
Subsequent treatment - Immunotherapies: Crizotinib	£3,628	£18,808
RDI - Tepotinib	£16,306	£4,308
RDI - Nivolumab	£7,402	£13,213
RDI - Pembrolizumab	£7,797	£12,817
Subsequent treatment - Immunotherapies: Pembrolizumab	£8,331	£13,128
Subsequent treatment - tepotinib: Pembrolizumab	£12,242	£7,564
Resource use - prevalence of MET mutation in NSCLC	£7,293	£11,251
Subsequent treatment - tepotinib: Nivolumab	£11,590	£8,296
Subsequent treatment - tepotinib: Atezolizumab	£11,210	£9,027

Abbreviations: MET, mesenchymal-epithelial transition; NMB, net monetary benefit; NSCLC, non-small-cell lung cancer; OWSA, one-way sensitivity analysis; RDI, relative dose intensity; WTP, willingness-to-pay.

Scenario analysis

Table 38: Results of scenario analysis versus immunotherapy – previously treated population

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB
Time horizon	30 years	10 years	[redacted]	[redacted]	[redacted]	£26,503	£8,418
		20 years	[redacted]	[redacted]	[redacted]	£24,994	£10,088
Discount rates	3.5%	0.0%	[redacted]	[redacted]	[redacted]	£24,948	£12,287
		6.0%	[redacted]	[redacted]	[redacted]	£24,434	£9,375
Weight data source	All patients	European patients	[redacted]	[redacted]	[redacted]	£24,792	£10,320

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB
Drug wastage	Include	Exclude	[redacted]	[redacted]	[redacted]	£22,725	£11,166
Dose intensity	Include	Exclude	[redacted]	[redacted]	[redacted]	£41,183	£3,610
AE disutility	Include	Exclude	[redacted]	[redacted]	[redacted]	£24,011	£11,000
MET mutation testing	Include	Exclude	[redacted]	[redacted]	[redacted]	£19,823	£12,354
Subsequent treatment	VISION/real-world data	UK based distribution	[redacted]	[redacted]	[redacted]	£24,662	£10,374
		UK based distribution matching number of subsequent lines	[redacted]	[redacted]	[redacted]	£18,841	£12,756
Utility source	VISION	Nafees et al, 2008	[redacted]	[redacted]	[redacted]	£26,371	£9,106
		Chouaid et al, 2013 - 1L	[redacted]	[redacted]	[redacted]	£25,173	£10,023
		Chouaid et al, 2013 - 2L	[redacted]	[redacted]	[redacted]	£23,975	£11,032
		Chouaid et al, 2013 - 3L/4L	[redacted]	[redacted]	[redacted]	£28,739	£7,519
		TA428 - Pembrolizumab	[redacted]	[redacted]	[redacted]	£23,628	£11,343
		TA484 - Nivolumab	[redacted]	[redacted]	[redacted]	£24,139	£10,888
		TA484 - Nivolumab (committee preference)	[redacted]	[redacted]	[redacted]	£24,916	£10,232
		TA584 - Atezolizumab in combination	[redacted]	[redacted]	[redacted]	£25,202	£10,000
		TA531 - Pembrolizumab	[redacted]	[redacted]	[redacted]	£20,819	£14,244
		TA655 - Nivolumab	[redacted]	[redacted]	[redacted]	£23,637	£11,334
		TA655 - Nivolumab (committee preference)	[redacted]	[redacted]	[redacted]	£25,595	£9,690
Tepotinib OS parametric curve	Log-normal	Exponential	[redacted]	[redacted]	[redacted]	£34,961	£3,702
		Log-logistic	[redacted]	[redacted]	[redacted]	£23,831	£11,494
Tepotinib PFS parametric curve	Log-normal	Exponential	[redacted]	[redacted]	[redacted]	£26,071	£9,597
		Gen Gamma	[redacted]	[redacted]	[redacted]	£23,873	£10,867
		Gompertz	[redacted]	[redacted]	[redacted]	£25,388	£9,982
		Log-logistic	[redacted]	[redacted]	[redacted]	£23,767	£10,929

Parameter	Base case	Scenario	Tepotinib versus immunotherapy				
			Inc. costs	Inc. LYs	Inc. QALYs	ICER	NMB
Tepotinib ToT parametric curve	Gen Gamma	Exponential	[redacted]	[redacted]	[redacted]	£22,240	£11,365
		Gompertz	[redacted]	[redacted]	[redacted]	£22,779	£11,144
		Log-logistic	[redacted]	[redacted]	[redacted]	£37,624	£5,067
		Log-normal	[redacted]	[redacted]	[redacted]	£29,068	£8,569
		Weibull	[redacted]	[redacted]	[redacted]	£21,601	£11,627
Immunotherapy OS parametric curve	Spline - 1 knot normal	Exponential	[redacted]	[redacted]	[redacted]	£22,260	£13,819
		Gompertz	[redacted]	[redacted]	[redacted]	£20,829	£16,327
		Weibull	[redacted]	[redacted]	[redacted]	£22,206	£13,908
		Spline - 1 knot odds	[redacted]	[redacted]	[redacted]	£30,036	£5,970
		Spline - 2 knot odds	[redacted]	[redacted]	[redacted]	£22,953	£12,732
		Spline - 3 knot odds	[redacted]	[redacted]	[redacted]	£23,193	£12,378
		Spline - 1 knot hazard	[redacted]	[redacted]	[redacted]	£21,425	£15,250
		Spline - 2 knot hazard	[redacted]	[redacted]	[redacted]	£20,757	£16,483
		Spline - 3 knot hazard	[redacted]	[redacted]	[redacted]	£20,918	£16,182
		Spline - 2 knot normal	[redacted]	[redacted]	[redacted]	£21,587	£15,013
		Spline - 3 knot normal	[redacted]	[redacted]	[redacted]	£21,778	£14,675
Immunotherapy PFS parametric curve	Spline 1 knot hazard	Exponential	[redacted]	[redacted]	[redacted]	£5,767	£18,390
		Gen Gamma	[redacted]	[redacted]	[redacted]	£26,955	£9,708
		Gompertz	[redacted]	[redacted]	[redacted]	£15,505	£14,200
Immunotherapy ToT	Literature (capped at PFS)	Same as PFS	[redacted]	[redacted]	[redacted]	£11,342	£15,826
		Using HR (PFS vs ToT)	[redacted]	[redacted]	[redacted]	£33,551	£6,734

Abbreviations: AE, adverse event; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-years; ToT, time on treatment

Notes: a Willingness-to-pay threshold is £50,000 versus immunotherapy

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

August 2021

File name	Version	Contains confidential information	Date
ID3761 tepotinib company response to ERG clarification letter – additional responses 27Aug21 ACIC	**1**	**No**	**27 August 2021**

Analyses, model results, and model functionality

B23. Priority question. Please report on the probability that tepotinib is cost-effective at cost-effectiveness thresholds £30,000 and £50,000 for fully incremental analysis for the populations: line agnostic, untreated, treated. Furthermore, please provide the executable model with that functionality.

The economic model has been adapted to include the functionality to run probabilistic sensitivity analysis for all treatments simultaneously and hence provide fully incremental analysis probabilities. The probability that tepotinib is cost-effective at the £20,000, £30,000 and £50,000 thresholds for each population is presented in Table 1. Detailed results of the probabilistic sensitivity analysis informing the probabilities are presented in Appendix 1.

Table 1: Probability of cost-effectiveness using fully incremental analysis

Population	Tepotinib	Immunotherapy	Chemotherapy	Immunotherapy plus chemotherapy
Line agnostic				
£20,000 threshold	47.9%	0.0%	52.1%	NA
£30,000 threshold	66.6%	0.2%	33.2%	NA
£50,000 threshold	84.6%	1.9%	18.4%	NA
Untreated				
£20,000 threshold	38.3%	0.0%	61.7%	0.0%
£30,000 threshold	52.4%	0.0%	47.6%	0.0%
£50,000 threshold	67.1%	2.5%	29.9%	0.5%
Previously treated				
£20,000 threshold	23.8%	45.8%	30.4%	NA
£30,000 threshold	39.6%	33.7%	26.7%	NA
£50,000 threshold	56.7%	20.9%	22.4%	NA

B25. Priority question. For the full incremental analyses and pairwise analyses for the base case analysis and the subgroup analyses, please report the probability that each treatment is cost-effective at a cost-effectiveness threshold of £20,000 per quality-adjusted life years (QALY).

Provide the pairwise analyses probability that tepotinib is cost-effective at the £20,000 threshold for the base case and subpopulations.

Please see response to B23 (Table 1) which presents the probability of tepotinib being cost-effective for the full incremental analysis at the threshold of £20,000 per

QALY gained. The probability that tepotinib is cost-effective at £20,000, £30,000 and £50,000 thresholds for each population using pairwise analysis is presented in Table 2. Detailed results of the probabilistic sensitivity analysis informing the probabilities are presented in Appendix 2.

Table 2: Probability of cost-effectiveness for the pair-wise analyses

Population	Tepotinib vs immunotherapy	Tepotinib versus chemotherapy	Tepotinib versus immunotherapy plus chemotherapy
Line agnostic			
£20,000 threshold	99.3%	68.4%	NA
£30,000 threshold	97.8%	79.0%	NA
£50,000 threshold	91.1%	90.1%	NA
Untreated			
£20,000 threshold	99.8%	49.9%	99.9%
£30,000 threshold	98.8%	57.9%	99.1%
£50,000 threshold	92.7%	66.7%	91.1%
Previously treated			
£20,000 threshold	48.9%	56.3%	NA
£30,000 threshold	61.5%	65.7%	NA
£50,000 threshold	73.4%	75.5%	NA

B28. Table 6 in document B indicates that PFS as per investigator assessment was used in the economic model rather than PFS as per independent review committee (IRC).

a. Please re-run the cost-effectiveness models using PFS as per IRC, not PFS as per investigator assessment.

Progression-free survival (PFS) by independent review committee (IRC) definition is only available within the data for tepotinib from the VISION trial, and not available from the real-world cohort data for the comparators. PFS by investigator (INV) definition was chosen to inform the cost-effectiveness analyses as the PFS from the comparator real-world cohort data was reported by investigator, as per the nature of real-world data.

Figure 1 provides the Kaplan-Meier (KM) curves of tepotinib PFS by both INV and IRC definitions. No statistically significant difference was found between the curves

(p=0.33) with the investigator definition providing lower estimates of survival than the IRC definition at the majority of time points.

Figure 1: Tepotinib PFS by investigator and independent review committee definitions

Abbreviations: p, p-value; INV, investigator; IRC, independent review committee; PFS, progression-free survival.

Table 3 provides the summary statistics for tepotinib PFS by INV and IRC definitions. Median PFS and restricted mean survival time (RMST) were both found to be greater with the IRC definition compared to PFS defined by INV.

Table 3: Summary statistics of tepotinib PFS by investigator and independent review committee definitions

	PFS INV	PFS IRC
All patients	[redacted]	[redacted]
Patients with event, n (%)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
RMST	[redacted]	[redacted]

Abbreviations: CI, confidence interval; INV, investigator; IRC, independent review committee; n, number; PFS, progression-free survival; RMST, restricted mean survival time.

The IRC definition of tepotinib PFS has been fitted with parametric survival models (PSMs) and included within the economic model. Details of the overall population are presented below with the subgroups presented in Appendix 3.

Diagnostic plots were produced to assess the suitability of the PSMs to model the tepotinib PFS data. The plots are presented in Figure 2 and discussed in turn below.

Figure 2: Diagnostic plots – VISION PFS (ITT) - IRC – overall population

Abbreviations: ITT, intention to treat; IRC, independent review committee; PFS, progression free survival; S(t), survivor function; t, time; Tep, tepotinib

Notes:

Plot A: An approximately straight line indicates that the survivor function is Weibull. If the gradient is approximately equal to 1, the survivor function is exponential.

Plot B: An approximately straight line indicates the survivor function is log-logistic.

Plot C: An approximately straight line indicates the survivor function is log-normal.

Plot D: Turning points indicate the need for parametric survival models that are able to reflect non-monotonic hazard functions. A maximum time point of 42 months was selected to calculate the smoothed hazard estimation within the R muhaz package.

A log-cumulative hazard plot (LCHP) was produced to assess the appropriateness of fitting exponential and Weibull PSMs that assume proportional hazards (Figure 2: A). The gradient of the curve in the LCHP appears to be relatively constant over time, indicating that an exponential or Weibull PSM may provide a reasonable fit to the data.

To assess the suitability of a log-logistic PSM, Figure 2: B presents the logit survival plot for the VISION PFS data. A relatively straight line is seen for the PFS data indicating that the log-logistic PSM may provide a reasonable fit to the data, however, a small bump is seen in the initial portion of the curve.

To assess the suitability of a log-normal PSM, Figure 2: C presents the inverse normal survival plot. An approximately straight line is observed for the VISION PFS data for the latter portion of the curve; however a slight deviation is observed in the initial section. This indicates that the log-normal PSM may provide a reasonable fit to the data.

The final assessment of the PFS data undertaken was the inspection of the smoothed hazard plot. A maximum time of 42 months was set when producing the smoothed hazard plot as hazard estimates are subject to substantial uncertainty and become unstable when the number of patients at risk is small. The smoothed hazard plot (Figure 2: D) demonstrated that the hazard of death does not appear to be constant over time for tepotinib PFS, suggesting an exponential model is unlikely to provide a good fit to the data. The curve appears to be monotonically decreasing (with slight deviations in gradient), providing evidence to suggest that the Weibull and Gompertz models may provide a reasonable fit to the data.

Based on the diagnostic plots, it is unlikely that the exponential model will provide a good fit to the tepotinib PFS data, however, for completeness, no specific parameterisations were ruled out of the economic model. Consequently, a total of six PFS extrapolations were available for use in the PFS tepotinib arm within the economic model.

The statistical goodness-of-fit of all fitted PSMs to the tepotinib PFS data is provided in Table 4. Based on the AIC and BIC scores, the log-normal model provided the best statistical fit to the tepotinib PFS data, with the log-logistic and generalised

gamma providing reasonably similar fits (within five points). Given the log-normal distribution was selected for the investigator PFS and has the best statistical fit, this has also been selected for the IRC PFS base case for the overall population (Figure 3).

Table 4: Statistical goodness-of-fit scores - VISION PFS (ITT) - IRC – overall population

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Exponential	678.45	681.47	5	4
Weibull	680.45	686.48	6	6
Gompertz	677.25	683.29	4	5
Log-logistic	672.14	678.17	3	2
Log-normal	669.53	675.56	1	1
Generalised-gamma	670.88	679.93	2	3

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression free survival; IRC, independent review committee

Figure 3: Parametric curve fits – VISION PFS (ITT) - IRC – overall population

Time (years)	0	1	2	3	4	5	6	7	8	9	10
Numbers at risk	151	44	10	1	1	0	0	0	0	0	0

Abbreviations: KM, Kaplan-Meier; ITT, intention to treat; PFS, progression-free survival; IRC, independent review committee

Deterministic pairwise and incremental analysis results using tepotinib PFS IRC scenario are presented in Table 5 and Table 6, respectively.

Table 5: Pairwise results – IRC PFS scenario – overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NMB [a]
Tepotinib	[redacted]	2.85	[redacted]					
Chemotherapy	[redacted]	1.99	[redacted]	[redacted]	0.86	[redacted]	£16,135	£15,122
Immunotherapy	[redacted]	2.84	[redacted]	[redacted]	0.00	[redacted]	Dominant	£24,052

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years
Notes:
a Willingness-to-pay threshold is £30,000 versus immunotherapy and £50,000 versus chemotherapy

Table 6: Fully incremental analysis – IRC PFS scenario – overall population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)	Incremental ICER (extended dominance)
Chemotherapies	[redacted]	[redacted]				
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£16,135	£16,135
Immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Strictly dominated

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

Appendix 1: Fully incremental analysis probabilistic sensitivity analysis

Overall

Table 7: Mean results of PSA (1,000 runs) and comparison with deterministic results – overall population

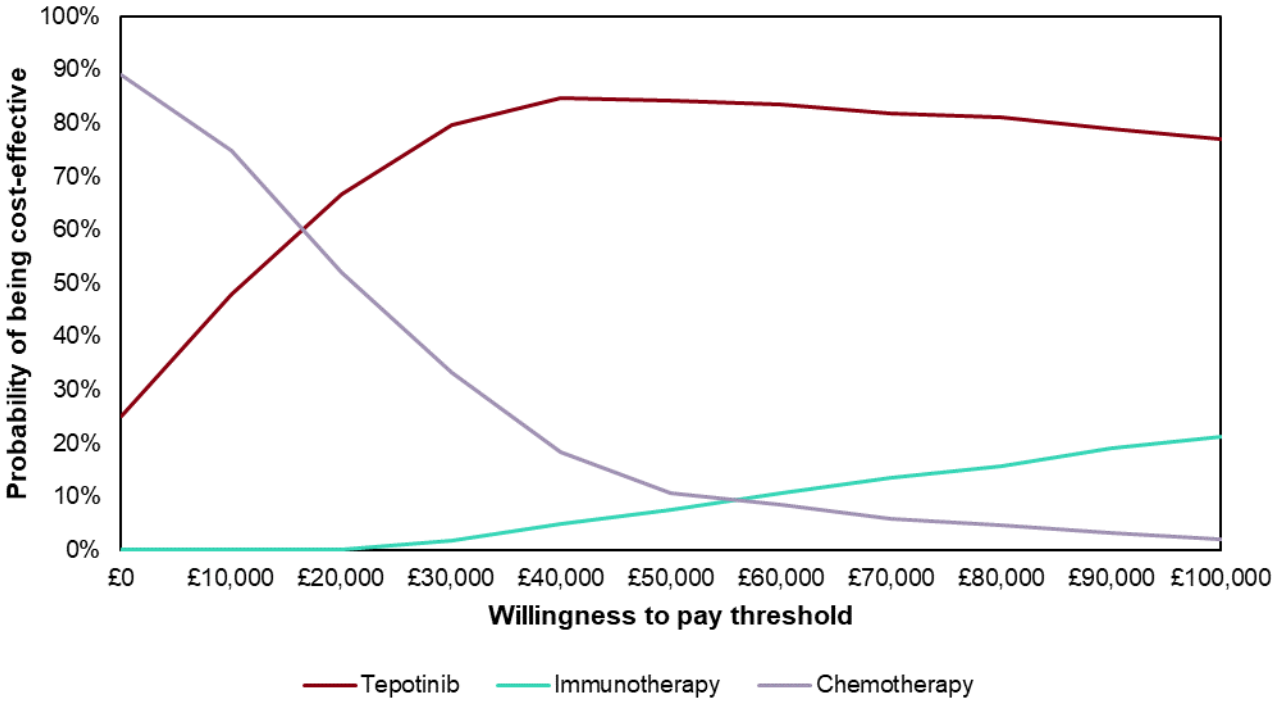
Technology	Total costs		Total QALYs		Pairwise ICER (£)	
	Det.	PSA	Det.	PSA	Det.	PSA
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]		
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£19,512	£21,010

Abbreviations: DET, deterministic; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Figure 4: Cost-effectiveness plane (1,000 PSA runs) – overall population

Abbreviations: QALYs, quality-adjusted life years

Figure 5: Cost-effectiveness acceptability curve – tepotinib versus chemotherapy



Untreated

Table 8: Mean results of PSA (1,000 runs) and comparison with deterministic results – untreated population

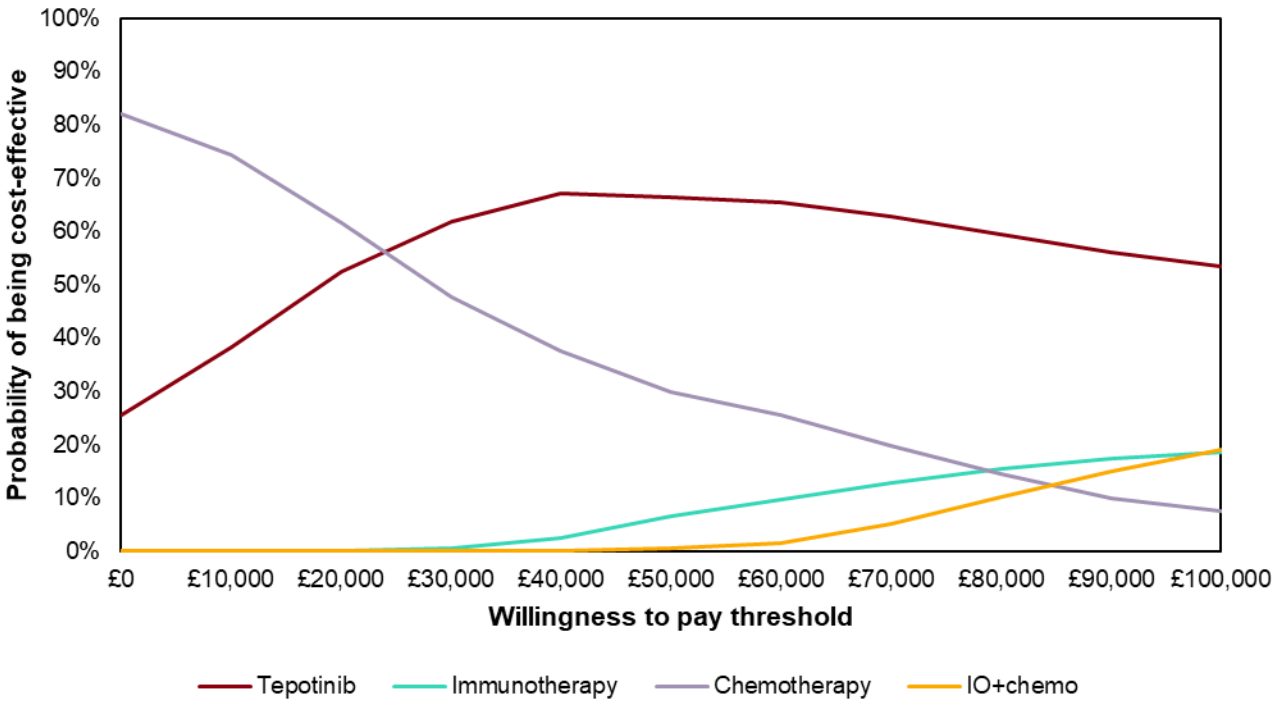
Technology	Total costs		Total QALYs		Pairwise ICER (£)	
	Det.	PSA	Det.	PSA	Det.	PSA
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]		
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£418,802 (SW)	£279,650 (SW)
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£23,354	£28,463
IO + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£186,293 (SW)	£175,861 (SW)

Abbreviations: DET, deterministic; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SW, South-West

Figure 6: Cost-effectiveness plane (1,000 PSA runs) – untreated population

Abbreviations: QALYs, quality-adjusted life years

Figure 7: Cost-effectiveness acceptability curve – tepotinib versus chemotherapy



Previously treated

Table 9: Mean results of PSA (1,000 runs) and comparison with deterministic results – overall population

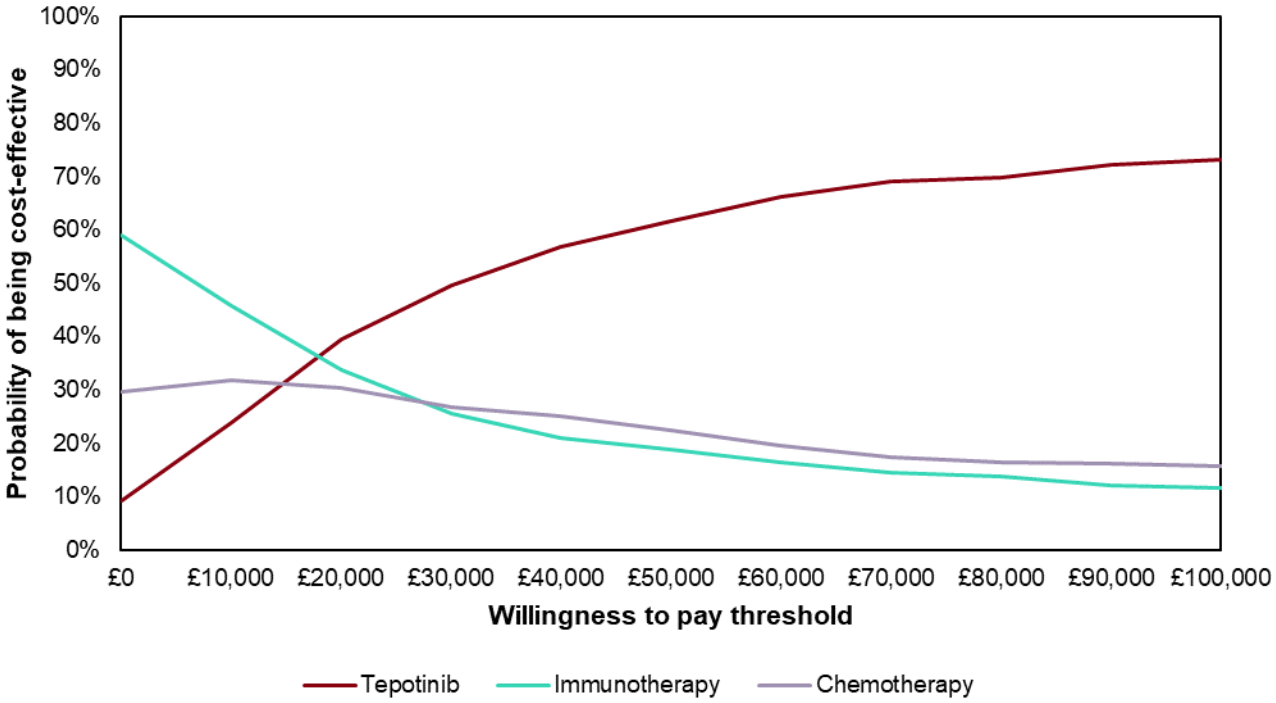
Technology	Total costs		Total QALYs		Pairwise ICER (£)	
	Det.	PSA	Det.	PSA	Det.	PSA
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]		
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£24,824	£30,643
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£18,176	£24,994

Abbreviations: DET, deterministic; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Figure 8: Cost-effectiveness plane (1,000 PSA runs) – overall population

Abbreviations: QALYs, quality-adjusted life years

Figure 9: Cost-effectiveness acceptability curve – tepotinib versus chemotherapy



Appendix 2: Pairwise probabilistic sensitivity analysis

Overall

Table 10: Mean results of PSA (1,000 runs) and comparison with deterministic results – overall population

Technology	Total costs		Total QALYs		ICER (£)	
	Det.	PSA	Det.	PSA	Det.	PSA
Versus chemotherapy						
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]		
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£19,512	£21,369
Versus immunotherapy						
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]		
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	Dominant

Abbreviations: DET, deterministic; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Figure 10: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus chemotherapy – overall population

Abbreviations: QALYs, quality-adjusted life years

Figure 11: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus immunotherapy – overall population

Abbreviations: QALYs, quality-adjusted life years

Figure 12: Cost-effectiveness acceptability curve – tepotinib versus chemotherapy – overall population

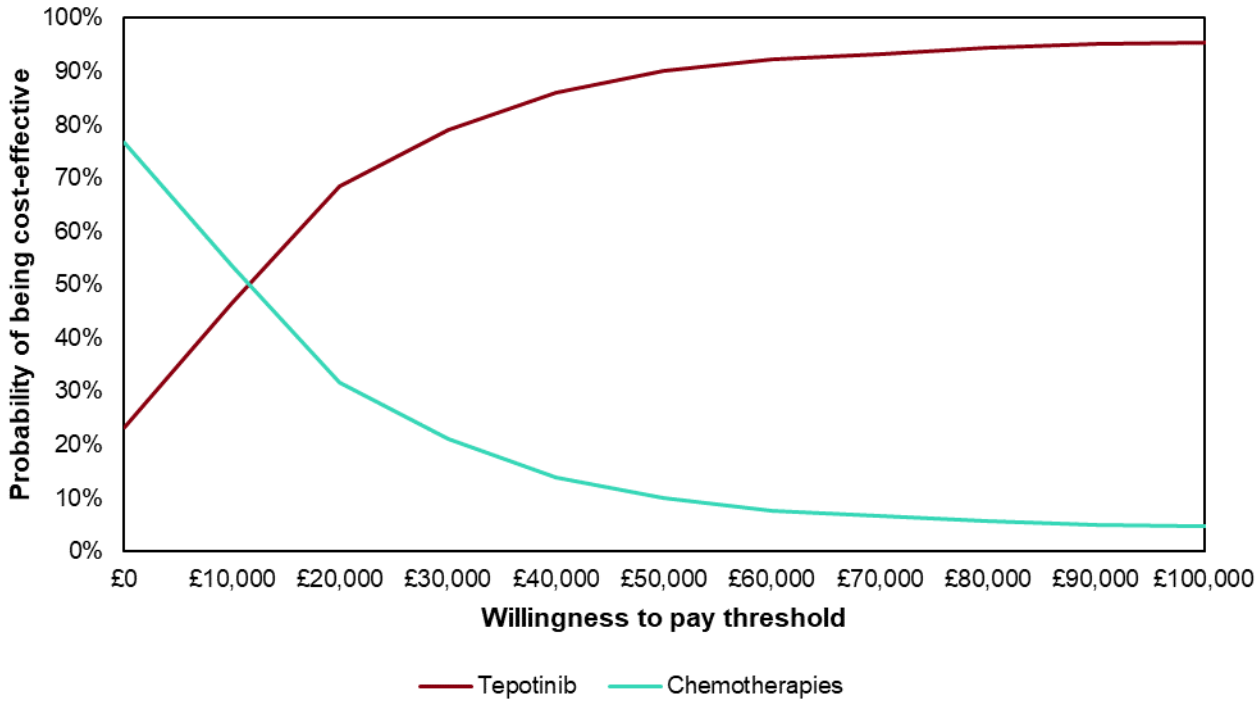
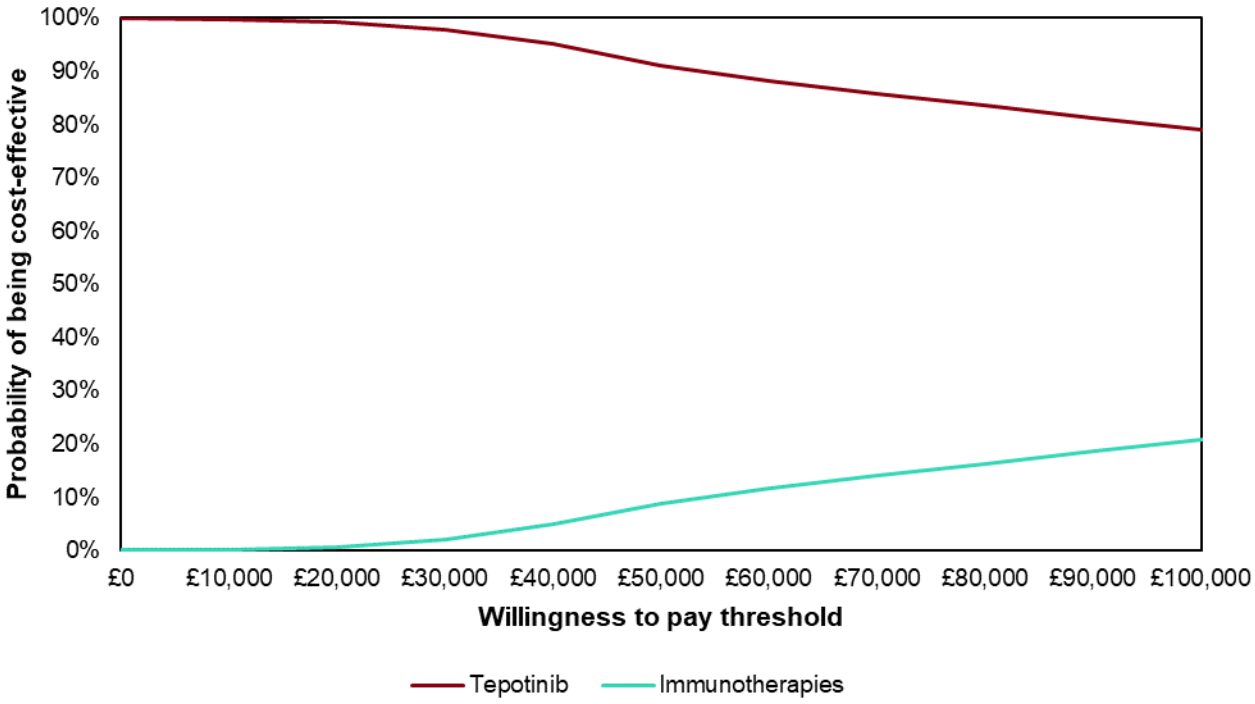


Figure 13: Cost-effectiveness acceptability curve – tepotinib versus immunotherapy – overall population



Untreated

Table 11: Mean results of PSA (1,000 runs) and comparison with deterministic results – untreated population

Technology	Total costs		Total QALYs		ICER (£)	
	Det.	PSA	Det.	PSA	Det.	PSA
Versus chemotherapy						
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]		
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£23,354	£30,794
Versus immunotherapy						
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]		
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£418,802 (SW)	£272,628 (SW)
Versus immunotherapy plus chemotherapy						
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]		
Immunotherapy + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£186,293 (SW)	£173,259 (SW)

Abbreviations: DET, deterministic; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; SW, South West

Figure 14: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus chemotherapy – untreated population

Abbreviations: QALYs, quality-adjusted life years

Figure 15: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus immunotherapy – untreated population

Abbreviations: QALYs, quality-adjusted life years

Figure 16: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus immunotherapy plus chemotherapy – untreated population

Abbreviations: QALYs, quality-adjusted life years

Figure 17: Cost-effectiveness acceptability curve – tepotinib versus chemotherapy – untreated population

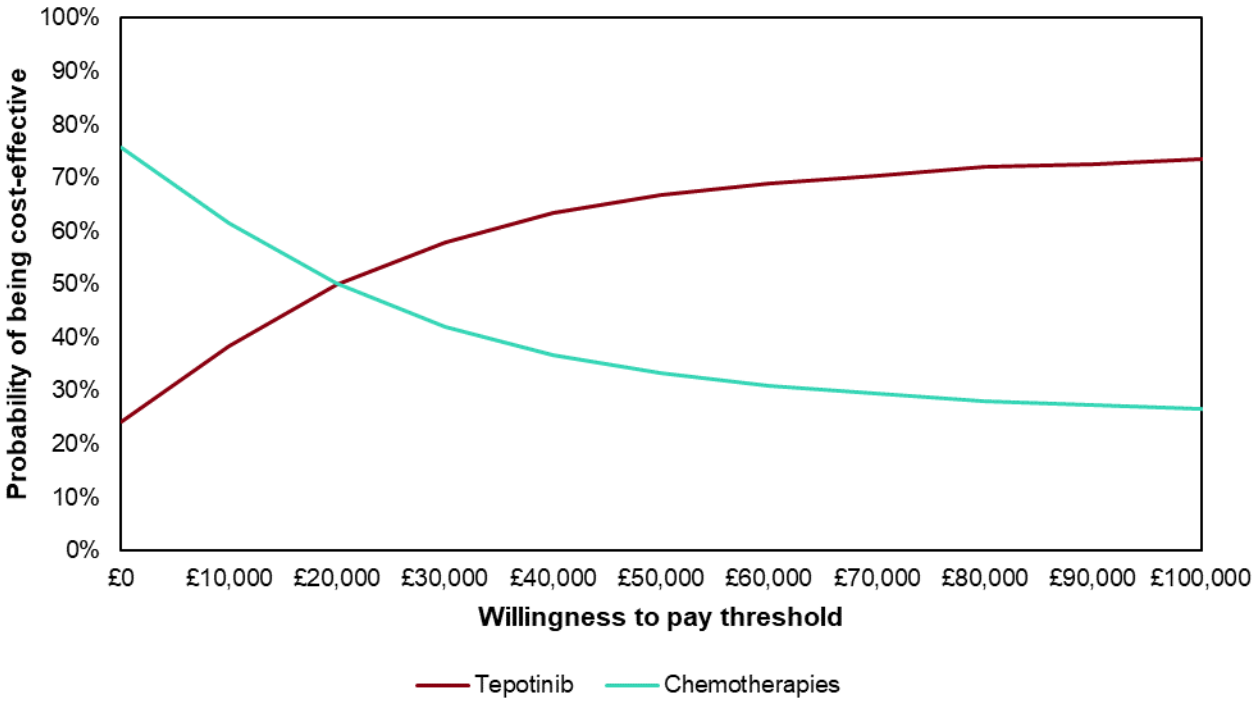


Figure 18: Cost-effectiveness acceptability curve – tepotinib versus immunotherapy – untreated population

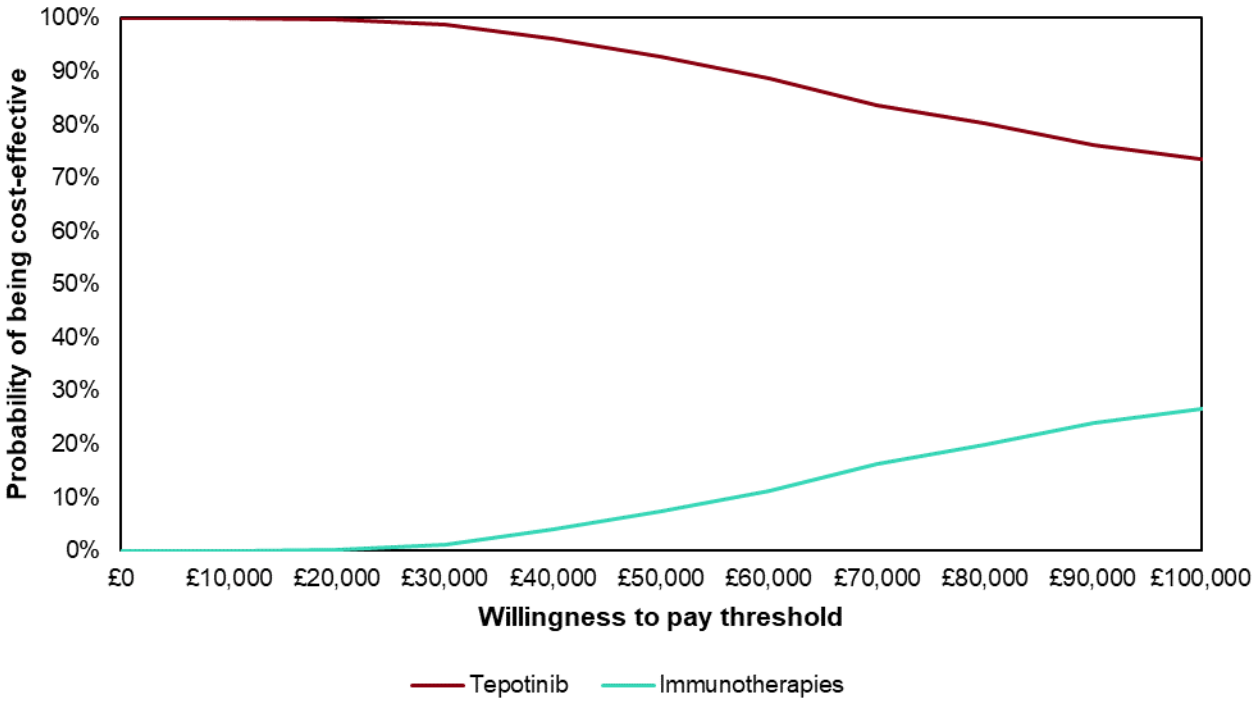
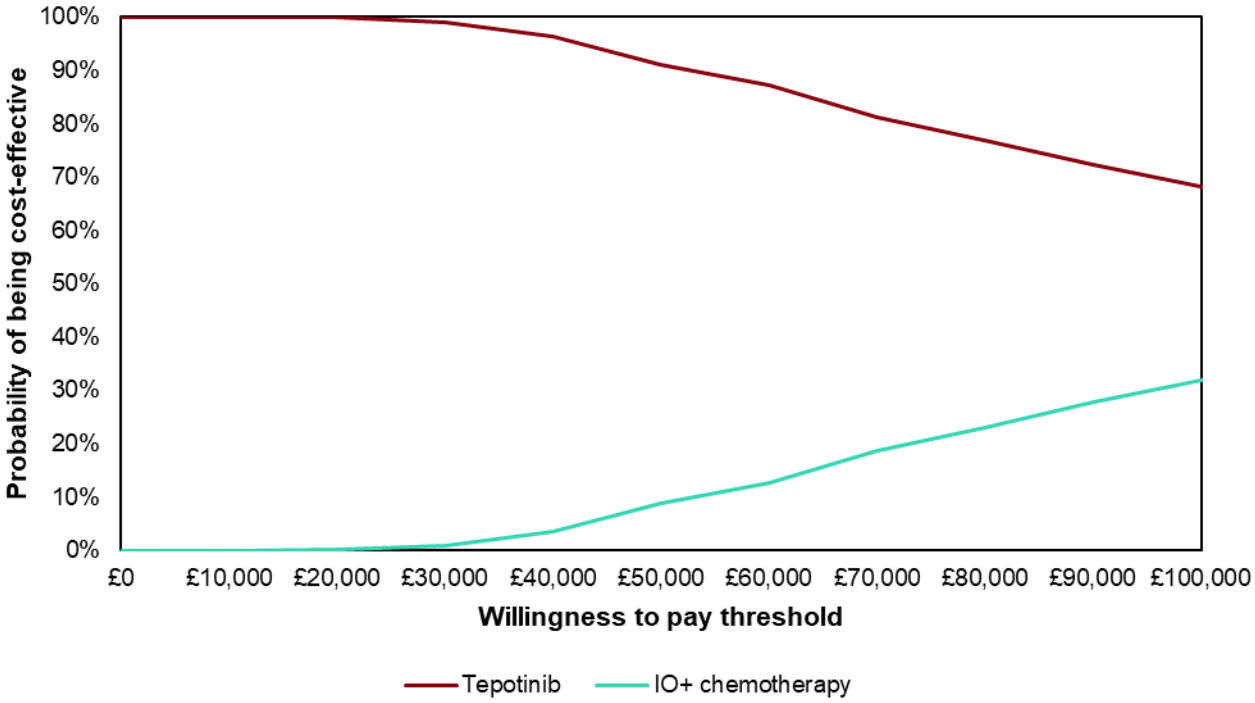


Figure 19: Cost-effectiveness acceptability curve – tepotinib versus immunotherapy plus chemotherapy – untreated population



Previously treated

Table 12: Mean results of PSA (1,000 runs) and comparison with deterministic results – previously treated population

Technology	Total costs		Total QALYs		ICER (£)	
	Det.	PSA	Det.	PSA	Det.	PSA
Versus chemotherapy						
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]		
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£18,176	£23,201
Versus immunotherapy						
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]		
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£24,824	£32,086

Abbreviations: DET, deterministic; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Figure 20: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus chemotherapy – previously treated population

Abbreviations: QALYs, quality-adjusted life years

Figure 21: Cost-effectiveness plane (1,000 PSA runs) – tepotinib versus immunotherapy – previously treated population

Abbreviations: QALYs, quality-adjusted life years

Figure 22: Cost-effectiveness acceptability curve – tepotinib versus chemotherapy – previously treated population

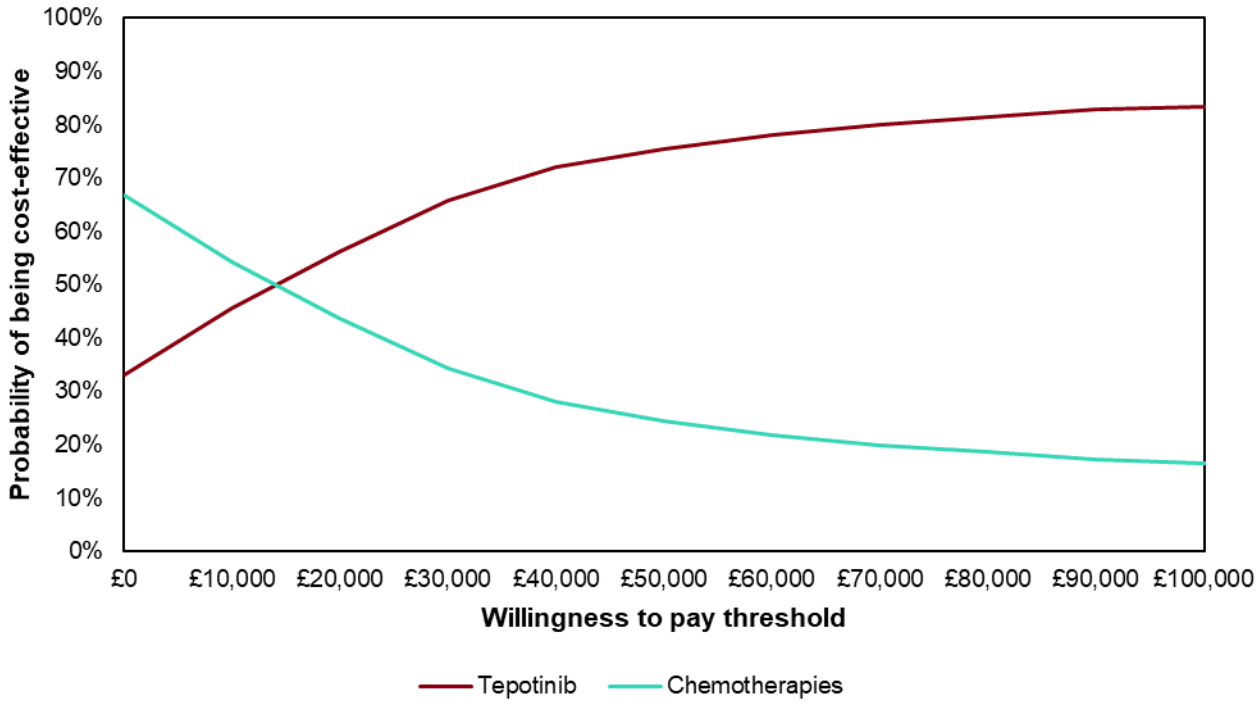
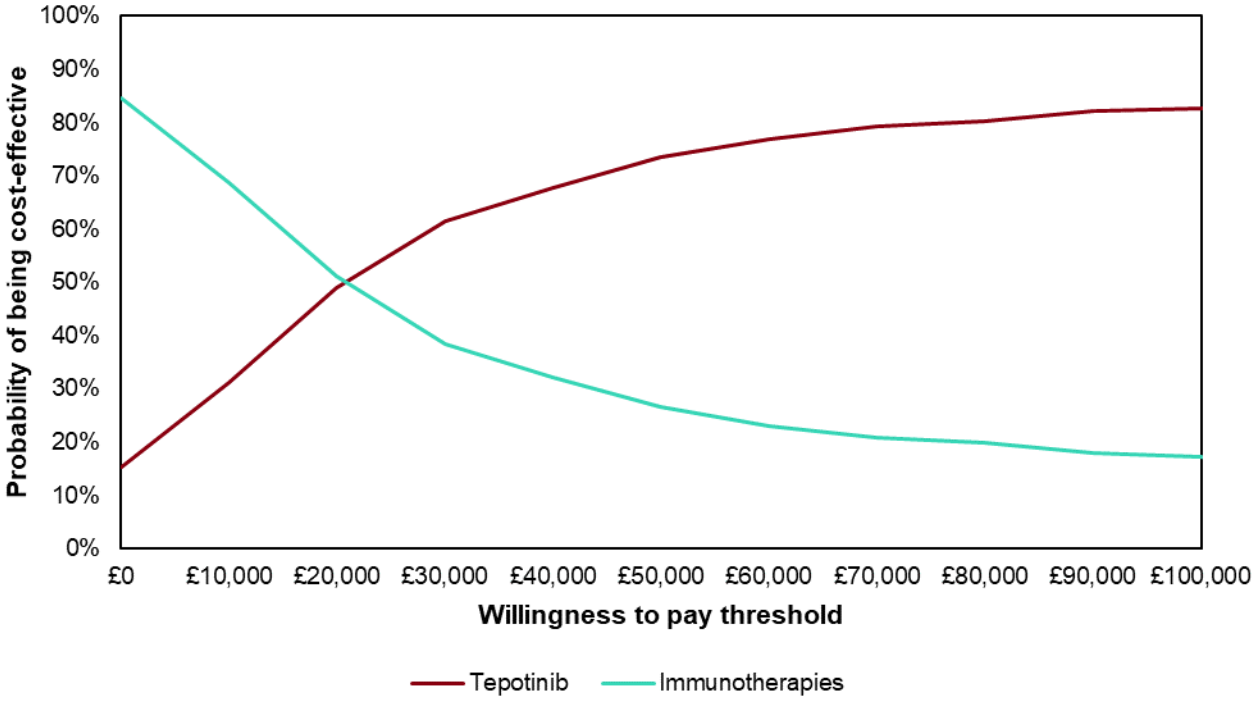


Figure 23: Cost-effectiveness acceptability curve – tepotinib versus immunotherapy – previously treated population



Appendix 3: PFS IRC scenario for subgroups

Untreated

Diagnostic plots were produced to assess the suitability of the PSMs to model the tepotinib PFS data. The plots are presented in Figure 24 and discussed in turn below.

Figure 24: Diagnostic plots – VISION PFS (ITT) - IRC – untreated population

Abbreviations: ITT, intention to treat; IRC, independent review committee; PFS, progression free survival; S(t), survivor function; t, time; Tep, tepotinib

Notes:

Plot A: An approximately straight line indicates that the survivor function is Weibull. If the gradient is approximately equal to 1, the survivor function is exponential.

Plot B: An approximately straight line indicates the survivor function is log-logistic.

Plot C: An approximately straight line indicates the survivor function is log-normal.

Plot D: Turning points indicate the need for parametric survival models that are able to reflect non-monotonic hazard functions. A maximum time point of 21 months was selected to calculate the smoothed hazard estimation within the R muhaz package.

A LCHP was produced to assess the appropriateness of fitting exponential and Weibull PSMs that assume proportional hazards (Figure 24: A). The gradient of the curve in the LCHP does not appear to be relatively constant over time, indicating that an exponential or Weibull PSM may not provide a reasonable fit to the data.

To assess the suitability of a log-logistic PSM, Figure 24: B presents the logit survival plot for the VISION PFS data. The line does not appear relatively straight for the PFS IRC data indicating that the log-logistic PSM may not provide a reasonable fit to the data.

To assess the suitability of a log-normal PSM, Figure 24: C presents the inverse normal survival plot. An approximately straight line is observed for the middle section of VISION PFS IRC data with plateaus observed in the tails. This indicates that the log-normal PSM may provide a reasonable fit to the majority of the data but is unlikely to capture the extremes.

The final assessment of the PFS data undertaken was the inspection of the smoothed hazard plot. A maximum time of 21 months was set when producing the smoothed hazard plot as hazard estimates are subject to substantial uncertainty and become unstable when the number of patients at risk is small. The smoothed hazard plot (Figure 24: D) demonstrated that the hazard of death does not appear to be constant overtime for tepotinib PFS, suggesting an exponential model is unlikely to provide a good fit to the data. The curve shows a turning point at approximately 6 months providing evidence to suggest that the Weibull and Gompertz models may not provide reasonable fits to the data.

Based on the diagnostic plots, it is unlikely that the exponential, Weibull and Gompertz models will provide a good fit to the tepotinib PFS data, however, for completeness, no specific parameterisations were ruled out of the economic model. Consequently, a total of six PFS extrapolations were available for use in the PFS tepotinib arm within the economic model.

The statistical goodness-of-fit of all fitted PSMs to the tepotinib PFS data is provided in Table 13. Based on the AIC and BIC scores, the log-normal model provided the best statistical fit to the tepotinib PFS data, with the log-logistic providing a

reasonably similar fit (within five points), and so were visually compared in order to select the base-case extrapolation (shown in Figure 25). The parametric curves appear to fit the data reasonably well, until around 18 months when it struggles to fit the tail of the Kaplan-Meier. Given the similar visual and statistical fit to the data and selection for the INV PFS, the log-normal was selected for the base case.

Table 13: Statistical goodness-of-fit scores - VISION PFS (ITT) - IRC – untreated population

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Exponential	299.0	301.2	5	2
Weibull	300.3	304.8	6	6
Gompertz	297.7	302.1	4	4
Log-logistic	296.9	301.4	2	3
Log-normal	295.7	300.2	1	1
Generalised-gamma	297.3	304.0	3	5

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression free survival; IRC, independent review committee

Figure 25: Parametric curve fits – VISION PFS (ITT) - IRC – untreated population

Time (years)	0	1	2	3	4	5	6	7	8	9	10
Numbers at risk	69	21	7	0	0	0	0	0	0	0	0

Abbreviations: KM, Kaplan-Meier; ITT, intention to treat; PFS, progression-free survival; IRC, independent review committee

Deterministic pairwise and incremental analysis results using tepotinib PFS IRC scenario are presented in Table 14 and Table 15, respectively.

Table 14: Pairwise results – IRC PFS scenario – untreated population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NMB [a]
Tepotinib	[redacted]	3.20	[redacted]					
Chemotherapy	[redacted]	2.42	[redacted]	[redacted]	0.78	[redacted]	£17,681	£5,063
Immunotherapy	[redacted]	3.45	[redacted]	[redacted]	-0.25	[redacted]	£575,628 (SW)	£57,107
Immunotherapy plus chemotherapy	[redacted]	3.79	[redacted]	[redacted]	-0.60	[redacted]	£211,541 (SW)	£58,487

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years; SW, South-West
Notes:
a Willingness-to-pay threshold is £30,000

Table 15: Fully incremental analysis – IRC PFS scenario – untreated population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)	Incremental ICER (extended dominance)
Chemotherapies	[redacted]	[redacted]				
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£17,681	£17,681
Immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	£575,628	Extendedly dominated
Immunotherapy plus chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,345	£211,541

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

Previously treated

Diagnostic plots were produced to assess the suitability of the PSMs to model the tepotinib PFS data. The plots are presented in Figure 26 and discussed in turn below.

Figure 26: Diagnostic plots – VISION PFS (ITT) - IRC – previously treated population

Abbreviations: ITT, intention to treat; IRC, independent review committee; PFS, progression free survival; S(t), survivor function; t, time; Tep, tepotinib

Notes:

Plot A: An approximately straight line indicates that the survivor function is Weibull. If the gradient is approximately equal to 1, the survivor function is exponential.

Plot B: An approximately straight line indicates the survivor function is log-logistic.

Plot C: An approximately straight line indicates the survivor function is log-normal.

Plot D: Turning points indicate the need for parametric survival models that are able to reflect non-monotonic hazard functions. A maximum time point of 33 months was selected to calculate the smoothed hazard estimation within the R muhaz package.

A LCHP was produced to assess the appropriateness of fitting exponential and Weibull PSMs that assume proportional hazards (Figure 26: A). The gradient of the curve in the LCHP appears to be relatively constant over time however, with large steps over log time, indicating that an exponential or Weibull PSM may provide a reasonable fit to the data.

To assess the suitability of a log-logistic PSM, Figure 26: B presents the logit survival plot for the VISION PFS data. Similar to the LCHP, a relatively straight line is seen for the PFS data with large steps, indicating that the log-logistic PSM may be able to provide a reasonable fit to the data.

To assess the suitability of a log-normal PSM, Figure 26: C presents the inverse normal survival plot. The line does not appear relatively straight over log time for the VISION PFS IRC data. This indicates that the log-normal PSM may not provide a good fit to the data.

The final assessment of the PFS data undertaken was the inspection of the smoothed hazard plot. A maximum time of 33 months was set when producing the smoothed hazard plot as hazard estimates are subject to substantial uncertainty and become unstable when the number of patients at risk is small. The smoothed hazard plot (Figure 26: D) demonstrated that the hazard of death does not appear to be constant overtime for tepotinib PFS, suggesting an exponential model is unlikely to provide a good fit to the data. A turning point is observed in the curve at approximately 12 months, providing evidence to suggest that the Weibull and Gompertz models are unlikely to provide reasonable fits to the data.

Based on the diagnostic plots, it is unlikely that the exponential, Weibull and Gompertz models will provide a good fit to the tepotinib PFS IRC data, however, for completeness, no specific parameterisations were ruled out of the economic model. Consequently, a total of six PFS extrapolations were available for use in the PFS tepotinib arm within the economic model.

The statistical goodness-of-fit of all fitted PSMs to the tepotinib PFS data is provided in Table 16. Based on the AIC and BIC scores, the log-normal model provided the best statistical fit to the tepotinib PFS data, with the log-logistic and generalised gamma providing reasonably similar fits (within five points), and so were visually

compared in order to select the base-case extrapolation (shown in Figure 27). The parametric curves appear to fit the data reasonably well, until around 18 months when it struggles to fit the tail of the Kaplan-Meier. Given the similar visual and statistical fit to the data and selection for the INV PFS, the log-normal was selected for the base case.

Table 16: Statistical goodness-of-fit scores - VISION PFS (ITT) - IRC – previously treated population

Parameterisation	Statistical goodness of fit		Rank	
	AIC	BIC	AIC	BIC
Exponential	380.6	383.0	4	3
Weibull	382.1	386.9	6	6
Gompertz	382.1	386.9	5	5
Log-logistic	377.2	382.1	3	2
Log-normal	375.2	380.0	1	1
Generalised-gamma	376.5	383.7	2	4

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression free survival; IRC, independent review committee

Figure 27: Parametric curve fits – VISION PFS (ITT) - IRC – previously treated population

Time (years)	0	1	2	3	4	5	6	7	8	9	10
Numbers at risk	82	23	3	1	1	0	0	0	0	0	0

Abbreviations: KM, Kaplan-Meier; ITT, intention to treat; PFS, progression-free survival; IRC, independent review committee

Deterministic pairwise and incremental analysis results using tepotinib PFS IRC scenario are presented in Table 14 and Table 15, respectively.

Table 17: Pairwise results – IRC PFS scenario – previously treated population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NMB [a]
Tepotinib	[redacted]	2.61	[redacted]					
Chemotherapy	[redacted]	2.00	[redacted]	[redacted]	0.60	[redacted]	£15,103	£11,339
Immunotherapy	[redacted]	1.87	[redacted]	[redacted]	0.74	[redacted]	£22,198	£11,911

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years
Notes:
a Willingness-to-pay threshold is £50,000

Table 18: Fully incremental analysis – IRC PFS scenario – previously treated population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)	Incremental ICER (extended dominance)
Immunotherapies	[redacted]	[redacted]				
Chemotherapies	[redacted]	[redacted]	[redacted]	[redacted]	£44,475	Extendedly dominated
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£15,103	£22,198

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

NICE National Institute for Health and Care Excellence

Patient organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	Roy Castle Lung Cancer Foundation
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Roy Castle Lung Cancer Foundation is a UK wide lung cancer charity. We fund lung cancer research and work in lung cancer patient care (information, support and advocacy activity). Our funding base is a broad mixture including community, retail, corporate, legacies and charitable trusts. Clearly, our patient group members and contacts are a self-selected group, who have taken the step to seek out information or have accessed specialist support services. As most lung cancer sufferers tend to be older, from lower social class groups and with the five year survival being around 15%, less physically well, we acknowledge that our patients are perhaps not representative of the vast majority of lung cancer patients, who are not so well informed. It is, however, important that the opinions expressed to us, be passed on to NICE, as it considers the place of this product in the management of lung cancer
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

5. How did you gather information about the experiences of patients and carers to include in your submission?	As a result of the COVID pandemic, our contact with patients and carers has become virtual. The Foundation has contact with patients/carers through its UK wide network of Lung Cancer Patient Support Groups, patient/carer panel, online forums, Keep in Touch' service and its nurse-led Lung Cancer Information Helpline.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	According to the National Lung Cancer Audit, the one year survival for lung cancer is 37%. Thus, this group of lung cancer patients have a particularly poor outlook. with an obvious impact on family and carers. Symptoms such as breathlessness, cough and weight loss are difficult to treat, without active anti-cancer therapy. Furthermore, these are symptoms which can be distressing for loved ones to observe. The following is our understanding of MET. Mesenchymal-epithelial transition (MET) activation is an oncogenic driver in lung cancer. Alterations in the MET pathway are most commonly Exon 14 skipping and amplification. MET alterations are more likely to be found in patients with advanced disease and are associated with poor prognosis. Loss of MET exon 14, by exon skipping leads to increased MET stability and so sustained oncogenic activity. Tumours with this alteration generally do not have other known oncogenic drivers. METex14 skipping is found in 3% to 4% of patients with nsclc. Increases in the copy number of the MET gene, or MET amplification, results in increased production of MET compared with normal cells. It is typically found with other oncogenic drivers (eg EGFR) and is found in 1% to 5% of patients with nsclc. Patients with MET amplification are more commonly male and current or former smokers. Those with METex14 skipping tend to be older and more likely female and non-smokers.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	In recent years, we have seen new targeted therapy options for some patients with nsclc. This has, so far, not been the case for those with MET alterations. There are currently no NICE recommended treatments, specifically for MET ex14 skipping mutations or MET amplification. Current systemic treatment (first and second line treatment) would be with standard NSCLC treatment – a combination of chemotherapy and immunotherapy.
8. Is there an unmet need for patients with this condition?	Yes
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As above, this would be the first NICE approved therapy available specifically targeted at MET alterations. We refer to the VISION Study – a multicentre, non randomised, open label, multicohort study. Cohorts A and C in this study refer to patients with test confirmed METex14 skipping mutations and Cohort B, MET amplification. METex14 skipping mutations - Amongst the 69 treatment naïve patients, the ORR was 43%, with a median response duration of 10.8 months. Amongst the 83 previously treated patients, the ORR was 43%, with a median response duration 11.1 months. So, virtually no difference between use in the first or the second line setting, with partial response in around half of patients. MET amplification – we understand that the results of Cohort B of the VISION Study have not yet been published. We note studies ongoing. Tepotinib is a once a day, oral treatment (tablet), with the obvious advantages of home/ease of administration, reduction in patient time at hospital (important in this new COVID world) etc..

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The side effects associated with the therapy. Peripheral oedema was the most commonly reported serious side effect. Other commonly reported were fatigue, diarrhoea, musculoskeletal pain, dyspnoea and nausea.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when	

considering this condition and the technology?	
Other issues	
13. Are there any other issues that you would like the committee to consider?	We understand that further clinical trials studies with Tepotinib are ongoing. As data matures and as new data emerges, this is perhaps a therapy, at this time, which could be made available through the Cancer Drugs Fund.
Key messages	

14. In up to 5 bullet points, please summarise the key messages of your submission:

- First targeted therapy being assessed specifically for MET alterations – published data for METex14 skipping mutations.
- Oral treatment
- Consider availability through the Cancer Drugs Fund, reassessing after data matures, new data and new indications emerge.
-

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Thoracic Oncology Group (BTOG)**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The British Thoracic Oncology Group (BTOG) is the multi-disciplinary group for healthcare professionals involved with thoracic malignancies throughout the UK.** **BTOG's mission is to support and educate thoracic oncology healthcare professionals, creating a professional community to exchange ideas, information and innovation and to foster the development of research.** **The overall aim is to represent the needs of people with thoracic malignancies in the UK and ensure they have equitable access to optimal care.** **BTOG does not receive any funding from the NHS but is supported through sponsorship and education grants from industry and registration fees.**
5b. Has the organisation received any funding from the manufacturer(s) of the	**No**

technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	**Treatment is palliative: to reduce and/or control extent of disease, improve quality of life and prolong survival.** **It is used in patients with advanced stage (metastatic) lung cancer.**

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	**Reduction in size of existing extent of disease by 20% or more.** **And/Or** **Statistically significant improvement in Quality of Life, as measured by recognised (Lung) Cancer specific Quality of Life scores.**
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	**Yes.** **There are no licensed agents in the UK specific for lung cancer harbouring an MET Exon 14 (MET Ex14) Skipping mutation.** **Patients with MET Exon 14 Skipping mutations are characterised by being older, and having aggressive disease with a worse prognosis. For example median overall survival is 6.7 months for those with MET Ex14, compared to 11.2 months for those without (Gow et al., Lung Cancer. 2017; 103:82-89).** **Consequently, finding treatments specific for this mutation is especially important.**
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	**Patient are most likely managed as per standard NICE guidelines for non-small cell lung cancer (NSCLC), depending on PD-L1 levels and histology sub-type (albeit MET Ex14 is rarer in squamous cell carcinoma).** **If PD-L1 >50%, non-squamous NSCLC:** **1st line: Single agent Pembrolizumab** **2nd line: Pemetrexed and Platinum, followed by Maintenance Pemetrexed** **3rd Line: Docetaxel +/- Nintedanib** **If PD-L1 >50%,squamous NSCLC:** **1st line: Single agent Pembrolizumab** **2nd line: Platinum-doublet chemotherapy (e.g. Gemcitabine and Carboplatin)** **3rd Line: Docetaxel** **If PD-L1 <50%, non-squamous NSCLC:** **1st Line: Pembrolizumab, Pemetrexed and Platinun, followed by Pemetrexed and Pembrolizumab maintenance** **2nd Line: Docetaxel +/- Nintedanib** **If PD-L1 <50%, squamous NSCLC:** **1st Line: Pembrolizumab, Paclitaxel and Platinun, followed by Pembrolizumab maintenance** **2nd Line: Docetaxel**
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	**There are no MET Ex14 Specific guidelines, reflecting that no agents are yet licensed by EMA or MHRA.**

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	**There is no defined pathway specific for MET Ex14, reflecting that there are no agents licensed and routinely commissioned in the UK.** **Current pathways would therefore be the NICE NSCLC standards, as summarised above.**
• What impact would the technology have on the current pathway of care?	**Tepotinib would become a fundamental part of the treatment paradigm of patients with MET Ex14 NSCLC.** **Reflecting data from the VISION clinical trial, which included both treatment naïve and previously treated disease, and in keeping with the current FDA approval of Tepotinib, it would seem likely that the UK license would be for any patient with MET Ex14 NSCLC, regardless of line of therapy.** **Consequently, if Tepotinib were to become available, it would be ideally used as a first line therapy, in place of the agents mentioned in previous sections. Should 1st line treatment with Tepotinib not be possible, it would likely be seen as the preferable 2nd line treatment.**
10. Will the technology be used (or is it already used) in	**(See below)**

the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	**Tepotinib would be used in thoracic oncology clinics, but being an oral therapy it would not require chemotherapy day-unit attendance. This would reduce workload for chemotherapy units compared to current standard of care. In addition, being oral, it will reduce workload for oncology pharmacy units which prepare individual chemotherapy doses for patients.** **It seems that Tepotinib would be given in 4-weekly cycles. This would reduce the number of attendance in oncology clinic, compared to chemotherapy or chemo-immnotherapy (which are given 3-weekly).** **There would be no difference in pathology blood tests required per cycle, compared to chemotherapy or chemo-immunotherapy. Nor would there be a difference in frequency or type of re-staging investigations.**
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	**Secondary care, delivered in thoracic oncology clinic as an outpatient.**

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	**None.** **The technology would fit into existing infrastructure for delivery of oral therapies in lung cancer.**
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	**The VISION trial (Paik et al., N Engl J Med 2020;383:931-43) demonstrated a response rate of 48-50% (independent review) which is greater than what which we would expect with current standards of care for patients with MET Ex14 NSCLC. Patients with oncogene driven lung cancers tend to have a lower response rate to immunotherapy, as well.** **Median duration of response was 11.1 months, which is more than that which we would expect from current standards of care, especially given that patients with MET Ex14 tend to be older and have more aggressive disease. Intra-cranial disease activity (response rate = 55%) was notable, and is again higher than that which we would expect from current standard of care.** **Based on higher response rate, duration of response and intra-cranial activity, I would expect there to be a clinically meaningful improvement in benefit with Tepotinib, compared to current standard of care.**

• Do you expect the technology to increase length of life more than current care?	**Yes.** **As mentioned above, the response rate and median duration of response are more than we expect from current standards of care. This, combined with the typically aggressive course of MET Ex14 NSCLC and comparative lack of activity of existing options, would suggest that length of life will be prolonged with Tepotinib.** **There is no mature Overall Survival data available yet.**
• Do you expect the technology to increase health-related quality of life more than current care?	**Quality of Life (QoL) data was reported in the Supplementary Data of the VISION trial (Paik et al., N Engl J Med 2020;383:931-43). Mean changes from baseline in cough indicated a reduction in symptoms, whilst symptoms of dyspnoea and chest pain showed stability. Scores for global functioning showed stability.** **Given the favourable side effect profile of Tepotinib compared to chemo/immunotherapy, and the probable greater efficacy, it would seem probable that Tepotinib will be associated with a better quality of life compared to existing therapy options.**

	There is no direct, head-to-head QoL data of Tepotinib vs. current standard of care.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	**It would only be appropriate for lung cancer patients with a proven MET Ex14 Skipping mutation.** **It would not be licensed, nor effective, for those without this.**
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	**It is likely that Tepotinib will be easier for patients to take. Firstly, it is oral and is given monthly, as opposed to chemo/immunotherapy which is intra-venous and usually 3-weekly. Secondly, the side effect profile is generally favourable (see section 17), compared to chemotherapy-based alternatives.** **Oral anti-cancer therapies are well established in lung oncology clinics (for example EGFR, ALK and ROS1 inhibitors) and their convenience and efficiency for oncology services are well known.** **Not additional clinical equipment or services are needed, specific to Tepotinib.**

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	**It would only be appropriate for lung cancer patients with a proven MET Ex14 Skipping mutation. It should be noted that this is a rare subtype of lung cancer, and so the potential patient 'pool' for use of this drug is small.** **It would not be licensed, nor effective, for those without this.** **Multi-target Next Generation Sequencing for MET Copy Number Variants (which would detect MET Ex 14 Skipping Mutations) is already included in the NHS England National Genomic Test Directory for NSCLC.** **Treatment would continue as long as it was clinically effective, and tolerated.**
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	**No.**

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	**The Quality of Life data mentioned in Section 11, combined with the clinical activity data mentioned in section 11, and the Side Effect data mentioned in Section 17, suggest that Tepotinib will have positive impacts on health-related benefits.** **This will be an improvement from current therapies because these are probably less effective, have more side effects, and struggle to good clinical benefit in this aggressive sub-type of cancer affecting older patients.**
• Is the technology a 'step-change' in the management of the condition?	**Yes, because to date there remains no agents specifically targeting MET Ex14.** **MET Ex14 NSCLC is aggressive, with a typically poor response to current treatments such as chemotherapy and/or immunotherapy. As such, having a drug directed against MET Ex14 itself is a step-change.**
• Does the use of the technology address any	

particular unmet need of the patient population?	**Yes. There is no agents specifically targeting MET Ex14. This patient group tends to be older and have aggressive disease. There is a unmet need to find treatments that are effective, and tolerable, in patients with MET Ex14.**
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	**Tepotinib was generally well tolerated.** **Grade 4 Adverse Events were rare (2%).** **Grade 3 Adverse Events were comparatively low (25%), when compared to current standards of care such as chemotherapy or chemo-immunotherapy. The commonest Grade 3 event is peripheral oedema (accounting for half of these cases), whilst others are often 'paper toxicities' such as elevated amylase and lipase from which patients are usually asymptomatic, and no treatment is needed.** **Tepotinib is associated with common Grade 1 and 2 side effects, for example nausea, vomiting, diarrhoea, fatigue, reduced appetite. But being lower grade, and being associated with a drug with meaningful clinical activity, it is likely that these will allow Quality of Life to be maintained, as opposed to impacted.** **33% of patients required a dose reduction, and overall treatment discontinuation rate was 11%. These were principally due to oedema, and that is certainly the most problematic side effect of this**

	agent. But the discontinuation rate is not high, suggesting that side effects are not affecting management of the condition in the great majority (90%) of patients.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	**The VISION trial is a phase 2 study, and like all trials, does not fully represent real-world clinical situations, especially in that only performance status 0-1 patient were included. However the patient age, race, and smoking history are consistent with UK practice.** **This was a single arm study, and so there was no comparison arm in which to reflect current UK practive.** **MET Ex14 Skipping mutations are now being routinely investigated as part of the NHS England Genomics test Directory, although not all areas of England yet have the same quality of service, and testing in the Devolved Nations is also different.**
• If not, how could the results be extrapolated to the UK setting?	**It is reasonable to assume that the clinical activity seen here is, within the confines of the representativeness of all clinical trial data in medicine, similar to that which we would expect to see in the UK. I do not identify reasons why the UK population should differ in any particular fashion.**

• What, in your view, are the most important outcomes, and were they measured in the trials?	1. **Overall Survival: not measured. This was a phase 2 single arm study, survival data not mature.** 2. **Progression Free Survival: Overall Survival: not measured. This was a phase 2 single arm study, survival data not mature.** 3. **Response Rate: Measured (independent, and investigator assessed)** 4. **Duration of Response: Measured** 5. **Safety / Adverse Events: Measured** 6. **Quality of Life: Measured**
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	**Duration of Response (DoR) can be seen as surrogate end-point for Progression Free Survival, and DoR of 11.1 months is good. However this does not accurately predict long-term outcomes, especially with the comparatively immature data available.**
• Are there any adverse effects that were not apparent in clinical trials	

but have come to light subsequently?	**Not that I am aware of.**
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	**No.**
20. How do data on real-world experience compare with the trial data?	**This is not known, and no data has been published on this. But as with all clinical trial data in oncology, it is likely that in the real-world patient will be older and will have a less good performance status, than those in clinical trials. Whether this translates into poor outcome is not yet known.**
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	**No**

21b. Consider whether these issues are different from issues with current care and why.	**No**

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- **MET Exon14 NSCLC is a rare, aggressive, sub-type of lung cancer, affecting older patients, in which existing treatments are comparatively ineffective and prognosis is poor.**
- **There are no other licensed drugs for targeting MET Ex14 NSCLC. Tepotinib would ideally be a first line therapy.**
- **Tepotinib shows good clinical activity, with a response rate of 50% and Duration of Response of 11.1 months, better than what we would typically expect of current standards of care.**
- **Tepotinib is well tolerated, with low grade 3-4 adverse events, and Quality of Life is maintained.**
- **Clinical data is limited to a main Phase 2 trial (VISION). Survival data, and head-to-head data, is not yet available.**

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in collaboration with:

Newcastle University

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

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

Authors
Nigel Armstrong, Health Economics Manager, KSR Ltd
Stephen Rice, Senior Research Associate, Newcastle University
Hosein Shabaninejad, Research Associate, Newcastle University
Pawel Posadzki, Systematic Reviewer, KSR Ltd
Steve Ryder, Health Economist, KSR Ltd
Lisa Stirk, Information Specialist, KSR Ltd
Robert Wolf, Managing Director, KSR Ltd
Jos Kleijnen, Director, KSR Ltd

Correspondence to
Nigel Armstrong, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, United Kingdom
YO19 6FD

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Declared competing interests of the authors

None.

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[redacted]

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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1. EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. If possible, it also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 presents the key model outcomes. Section 1.3 discusses the decision problem, Section 1.4 issues relates to the clinical effectiveness, and Section 1.5 issues related to the cost effectiveness. Other key issues are discussed in Section 1.6 while a summary in presented in Section 1.7.

Background information on the condition, technology and evidence and information on key as well as non-key issues are in the main ERG report, see Sections 2 (decision problem), 3 (clinical effectiveness) and 4 (cost effectiveness) for more details.

All issues identified represent the ERG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the ERG's key issues

Table 1.1: Summary of key issues

ID1457	Summary of issue	Report sections
1	Lack of clarity in the population	Section 2.1
2	Lack of subgroup (line of therapy, histological status, PD-L1 status) analysis according to scope	Section 2.3 and 3.4
3	Selection of analysis data set from VISION (cohort A instead of cohort A+C, and depending on length of follow-up)	Section 3.2.3
4	Selection of studies to obtain data for the ITC	Section 3.3
5	Source of AE frequencies not justified	Section 3.3
6	Selection of method of adjustment for confounding in the ITC	Section 3.4
7	Lack of justification for partitioned survival model vis-à-vis a state transition model	Section 4.2.2 & 4.2.6
8	No analyses are considered for the subgroups stated in the decision problem	Section 4.2.3 (Table 14 & Table 15)
9	No analyses were considered using the individual treatment comparators for which there was enough evidence.	Section 4.2.4
10	Potential bias from clinicians' selection of survival curves for the comparators, and lack of alternative scenario.	Section 4.2.6
11	Representativeness of AE utility values for the UK population	Section 4.2.8
12	It is possible there is a better fitting model for ToT for tepotinib which was not fitted to the data by the company	
13	Uncertainty in the cost estimates for immunotherapy and chemotherapy	
14	Uncertainty in the cost estimates for subsequent treatments	
15	Insufficient reporting and clarity of reporting of the cost-effectiveness results	Section 5.1

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Difference in progression-free survival
- Difference in overall survival
- Difference in the distribution of serious adverse events.

Overall, the technology is modelled to affect costs by:

- Different unit costs per period of time (e.g. per 3 weeks)
- Different stopping rules (no stopping rule for tepotinib; 6 month stopping rule for chemotherapy and 2 year stopping rule for immunotherapy)
- Different treatment stopping rates due to adverse events
- Different diagnostic costs (it is assumed that the population only needs to be identified using a diagnostic test as the decision population when tepotinib is prescribed, but not chemotherapy or immunotherapy)
- Different dose intensities (lower for tepotinib given the tablet rather than infusion mode of delivery)
- Different distributions of subsequent treatments
- Different time periods in progression-free and progressed states, which are associated with different monitoring costs.

The modelling assumptions that have the greatest effect on the ICER are:

- The survival model selections for progression-free survival (PFS) and overall survival (OS) for chemotherapy and immunotherapy for the overall, treated and untreated populations
- The time-to-event model selection for time on treatment (ToT) for tepotinib
- The percentage of patients receiving each subsequent treatment following the initial tepotinib, chemotherapy or immunotherapy treatment.

1.3 The decision problem: summary of the ERG's key issues

The decision problem addressed in the company submission (CS) is broadly in line with the final scope issued by NICE. However, there is a lack of evidence on adult patients (Table 1.2) as well as on certain comparators (Table 1.3).

Table 1.2: Key issue 1: Lack of clarity in the population

Report section	**2.1**
Description of issue and why the ERG has identified it as important	It needs to be made clear that the population in the decision problem appears to be more specific than advanced disease: it is stage IIIB-IV excluding anaplastic lymphoma kinase (ALK)+ and epidermal growth factor receptor (EGFR)+ patients.
What alternative approach has the ERG suggested?	Because this is not explicitly stated in the decision problem table, this can be resolved by clarification by the company.
What is the expected effect on the cost effectiveness estimates?	Unknown

Report section	2.1
What additional evidence or analyses might help to resolve this key issue?	Because this is not explicitly stated in the decision problem table, this can be resolved by clarification by the company.

Table 1.3: Key issue 2: Lack of subgroup (line of therapy, histological status, PD-L1 status) analysis according to scope

Report section	2.3, 3.4
Description of issue and why the ERG has identified it as important	Not differentiating according to subgroup in the scope in terms of programmed death ligand 1 (PD-L1) status and histology might disguise a variation in treatment effect and cost effectiveness between these subgroups. The treatment effect and cost effectiveness relative to the mixture of either immunotherapies or chemotherapies might also be biased if the proportion of each of the individual treatments within the mixture is not as would be observed in UK clinical practice. Therefore, lack of analysis by appropriate subgroup including comparators appropriate to that subgroup is potentially a serious limitation.
What alternative approach has the ERG suggested?	Given that the comparators in the scope and as recommended by NICE are according to line of therapy, despite smaller patient numbers, the ERG would argue that the results by treatment experience are the most relevant.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Analysis by appropriate subgroup including comparators appropriate to that subgroup including PD-L1 status and histology is recommended. This is notwithstanding any current lack of subgroup data, particularly in terms of PD-L1 status in the VISION study.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Table 1.4: Key issue 3: Selection of analysis data set from VISION (cohort A instead of cohort A+C, and depending on length of follow-up)

Report section	3.2.3
Description of issue and why the ERG has identified it as important	It is unclear how why Cohort A was preferred over combined Cohorts A+C for the efficacy analysis and why not all patients in Cohorts A+C were preferred for the safety analysis. There appears to be little difference in all outcomes between Cohort A and Cohorts A+C.
What alternative approach has the ERG suggested?	It would seem reasonable to use Cohorts A+C for the indirect treatment comparison (ITC).
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	It would seem reasonable to use Cohorts A+C for the ITC.

Table 1.5: Key issue 4: Selection of studies to obtain data for the ITC

Report section	3.3
Description of issue and why the ERG has identified it as important	The choice of the patient level data (PLD) employed for the indirect treatment comparison (ITC) using propensity scoring was not justified by the company: it is likely that it was driven at least to some extent by availability, at least in the case of those studies conducted by the company. There was also a similar lack of justification for the trials used in the ITC to compare VISION with immunotherapy chemotherapy combination.
What alternative approach has the ERG suggested?	The provision of more justification for the inclusion of these studies and ideally, based on the systematic review, either the demonstration that there were no other studies or the inclusion of any other suitable studies.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	The provision of more justification for the inclusion of these studies and ideally, based on the systematic review, either the demonstration that there were no other studies or the inclusion of any other suitable studies.

Table 1.6: Key issue 5: Source of AE frequencies not justified

Report section	3.2.3
Description of issue and why the ERG has identified it as important	It is unclear how the sources of comparator adverse event (AE) data that were used in the economic model were obtained. It appears that mostly NICE technology appraisals (TAs) were used for the immunotherapies, which makes sense as these are likely to be a comprehensive source. Similarly, for the chemotherapies prescribing information was used several times.
What alternative approach has the ERG suggested?	The lack of rationale is a source of uncertainty, which might be reduced by greater consistency in source of AE frequency estimates.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	The ERG would recommend a more systematic approach to obtaining AE frequencies, ideally a systematic literature review.

Table 1.7: Key issue 6: Selection of method of adjustment for confounding in the ITC

Report section	3.4.1
Description of issue and why the ERG has identified it as important	Using propensity score weighting is a method of PLD analysis that is recommended in technical support document (TSD) 17. However, it is not clear why standardised mortality rates (SMRs) were chosen instead of inverse probability of treatment, only the latter being recommended in TSD 17. Also, the former is limited to estimating the treatment effect only in the population that would receive the intervention i.e. the average treatment effect of the treated (ATT), in this case tepotinib, as opposed to the whole eligible population i.e. the average treatment effect (ATE).

Report section	3.4.1
	However, although not entirely clear, it does appear that estimating the ATT and by doing so not adjusting the tepotinib data enables separate analysis versus chemotherapy or immunotherapy. This implies that the estimates of treatment effect vs. either treatment group can also be compared to each other as if from the same population, which is those who received tepotinib in VISION. This then facilitates the full incremental analysis in the cost effectiveness analysis. It is also not clear why regression adjustment (RA) or doubly robust methods of combining RA with inverse probability weighting (IPW) were not considered.
What alternative approach has the ERG suggested?	Further explanation and analyses are required.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Further explanation and analyses are required.
What additional evidence or analyses might help to resolve this key issue?	The lack of rationale is a source of uncertainty, which might be reduced by greater consistency in source of AE frequency estimates.

1.5 The cost effectiveness evidence: summary of the ERG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 6, the ERG's summary and detailed critique in Section 5, and the ERG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in Tables 1.8 to 1.16.

Table 1.8: Key issue 7: Lack of justification for partitioned survival model vis-à-vis a state transition model

Report section	4.2.2, 4.2.6
Description of issue and why the ERG has identified it as important	The company used a partitioned survival model (PSM) which is a common approach to economic modelling in an oncology setting. The approach independently models PFS and OS, which is a limitation of the approach. By contrast, a state-transition model includes both the probability of death during the progression-free state and during the progressed state. OS depends on disease progression and the likelihood of dying in each state. Given sufficient evidence, a state-transition model may produce more accurate cost effectiveness results.
What alternative approach has the ERG suggested?	The potential alternative to a PSM is a state-transition model.
What is the expected effect on the cost effectiveness estimates?	Unknown.

Report section	4.2.2, 4.2.6
What additional evidence or analyses might help to resolve this key issue?	The company could provide a justification for why PSM is a better modelling approach than a state-transition model for this cost-effectiveness analysis.

Table 1.9: Key issue 8: No analyses are considered for the subgroups stated in the decision problem

Report section	4.2.3
Description of issue and why the ERG has identified it as important	The NICE scope listed the relevant individual immunotherapy and chemotherapy treatments as comparators to tepotinib according to subgroup. The company addressed five decision questions. These included immunotherapy, chemotherapy and combined therapy comparators. Combined therapy was only a relevant comparator in the untreated population. The company did not report the cost effectiveness for tepotinib for each subgroup.
What alternative approach has the ERG suggested?	The cost effectiveness of tepotinib could be reported for each subgroup according to the class of therapy of the specific treatment listed. For example, if only immunotherapy treatments and combined immunotherapy and chemotherapy treatments are listed for a subgroup then the relevant comparators for that subgroup are immunotherapy and combined immunotherapy and chemotherapy.
What is the expected effect on the cost effectiveness estimates?	For the subgroups for which chemotherapy is not a relevant comparator, tepotinib is expected to be cost-effective. The cost effectiveness of tepotinib is expected to be uncertain if chemotherapy is a relevant comparator.
What additional evidence or analyses might help to resolve this key issue?	The ERG has presented the cost effectiveness results for tepotinib using both the company model assumption and the ERG model assumptions in Section 6.

Table 1.10: Key issue 9: No analyses were considered using the individual treatment comparators for which there was enough evidence

Report section	4.2.4
Description of issue and why the ERG has identified it as important	The comparators included in the CS were immunotherapy, chemotherapy, and combined immunotherapy and chemotherapy treatment. The justification for this approach was the limited data available for specific treatments. In order to cost the immuno-therapy and chemotherapy treatment classes, assumptions had to be made regarding the individual treatment distributions within each class. There is uncertainty associated with the cost estimates for each class because of this approach; and it may be that when compared to a specific treatment, tepotinib becomes more or less cost effective.
What alternative approach has the ERG suggested?	The cost effectiveness of tepotinib could have been conducted with carboplatin and pemetrexed (20 patients in the data set) and pembrolizumab (22 patients in the data set) as comparators. These were the treatments with the greatest frequency for chemotherapy and immunotherapy. There would be more

Report section	4.2.4
	uncertainty in the effectiveness estimates, but more certainty in the cost estimates.
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Survival models could be fitted to the subsets of data, the cost of carboplatin and pemetrexed and pembrolizumab directly included in the analysis. The same economic model would be used.

Table 1.11: Key issue 10: Potential bias from clinicians' selection of survival curves for the comparators, and lack of alternative scenario

Report section	4.2.6
Description of issue and why the ERG has identified it as important	The company elicited clinical expert opinion to help select survival models for OS and PFS. The clinical experts selected survival models for immunotherapy and chemotherapy that did not have the best fit due to what they considered to be poor predictions of survival at, for example, five years in the future. If the clinical expert assessment of the reasons for the poor predictions are correct, the company survival model selections may be appropriate. But there is uncertainty around the reasons for the poor predictions according to the clinical experts. If the reason were related to the generalisability of the VISION population to the overall UK population with the condition as stated in the NICE scope, then it is possible that the clinical expert survival model selections may introduce bias into the relative effectiveness of tepotinib compared to chemotherapy and immunotherapy.
What alternative approach has the ERG suggested?	While the company conducted scenario analyses around individual survival models one at a time, alternative sets of survival models selected according to the Akaike Information Criterion (AIC) and Bayesian information criterion (BIC) statistics, while deselecting survival curves where the OS and PFS curves cross within a short time frame, e.g. seven years or less, could be defined. This presents an alternative scenario analysis. The difference in the cost-effectiveness results between the company survival model assumptions and the alternative survival model assumptions would be an indication of the uncertainty associated with the clinical evidence and process of deriving the relative effectiveness of tepotinib compared to each comparator.
What is the expected effect on the cost effectiveness estimates?	Considering best fit models as a base-case, the ERG notes there is no ICER difference between ERG base-case and company base-case to change the decision.
What additional evidence or analyses might help to resolve this key issue?	The ERG has made an alternative selection of survival models and produced the cost effectiveness results as a scenario analysis.

Table 1.12: Key issue 11: Representativeness of AE utility values for the UK population

Report section	4.2.8
Description of issue and why the ERG has identified it as important	Several utility estimates for adverse events were either not estimated using the European Quality of Life-5 Dimensions (EQ-5D) instrument or were not obtained from a UK population.
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Conducting sensitivity analyses using alternative sources might be informative.

Table 1.13: Key issue 12: It is possible there is a better fitting model for ToT for tepotinib which was not fitted to the data by the company

Report section	4.2.9
Description of issue and why the ERG has identified it as important	The time-to-event model selected for time on treatment (ToT) by the company for tepotinib was the generalised gamma distribution. This was based on clinical expert opinion. The cost effectiveness results are quite sensitive to the choice of time-to-event model. The ICER for tepotinib is significantly greater when one of the best-fitting models, the log-logistic model, is used in the economic analysis.
What alternative approach has the ERG suggested?	The ERG considers the log-logistic distribution possibly over-fits the tail-end of the data, but only parametric models were fit to the data. The company could have tried to fit more flexible models to the data as they did for OS and PFS, piece-wise parametric or spline models.
What is the expected effect on the cost effectiveness estimates?	Unknown. It is possible that a more flexible model would predict a smaller number on treatment in the short term, but a greater number on treatment in the long-term.
What additional evidence or analyses might help to resolve this key issue?	The company could have tried to fit more flexible models to the ToT data.

Table 1.14: Key issue 13: Uncertainty in the cost estimates for immunotherapy and chemotherapy

Report section	4.2.9
Description of issue and why the ERG has identified it as important	There is significant uncertainty in the cost estimates for immunotherapy and chemotherapy for two reasons: (1) the company sometimes classified single treatment as a combined treatment and cost the combined treatment, and (2) it was not clear how the treatment distribution within immunotherapy or within chemotherapy was derived. The ERG could not reproduce the percentages.
What alternative approach has the ERG suggested?	A clear explanation could be provided for how the treatment distributions were derived.

Report section	4.2.9
	A clear justification for why carboplatin and pemetrexed was costed the same as pemetrexed.
What is the expected effect on the cost effectiveness estimates?	N/A
What additional evidence or analyses might help to resolve this key issue?	Explanations and justifications required.

Table 1.15: Key issue 14: Uncertainty in the cost estimates for subsequent treatments

Report section	4.2.9
Description of issue and why the ERG has identified it as important	The cost effectiveness results were quite sensitive to the proportion of patients receiving subsequent treatment. Subsequent treatment is also likely to be influenced by the countries included in the clinical studies. This will affect both the cost and effectiveness results.
What alternative approach has the ERG suggested?	A randomised controlled trial in the UK with a sufficient sample size and follow-up would provide adequate evidence on subsequent treatment.
What is the expected effect on the cost effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	A randomised controlled trial in the UK with a sufficient sample size and follow-up.

Table 1.16: Key issue 15: Insufficient reporting and clarity of reporting of the cost effectiveness results

Report section	5.1
Description of issue and why the ERG has identified it as important	The decision models produced by the company were based on three populations: Overall, Untreated and Treated. In the main section of the results in the CS, the company focused on drawing conclusions for populations contra-indicated to chemotherapy and a pair-wise analysis with immunotherapy. This was also true in the end-of-life section. In the interpretation and conclusions section of the CS, conclusions appeared to be drawn for the overall population. The CS could have been much clearer regarding the different populations for which it was drawing conclusions.
What alternative approach has the ERG suggested?	The ERG has constructed a table of decision questions it believes are addressed in the CS based on the CS and company clarifications.
What is the expected effect on the cost effectiveness estimates?	A clear description of the decision questions which may be informed by the cost-effectiveness evidence would inform the NICE Committee of populations in which tepotinib may be cost effective.
What additional evidence or analyses might help to resolve this key issue?	The ERG has constructed a table of decision questions it believes are addressed in the CS. The Company may wish to review this and confirm if it is correct.

1.6 Other key issues: summary of the ERG's view

None.

1.7 Summary of the ERG's view

The ERG produced an alternative base-case which was considered equally plausible to the company base-case. The difference reflects uncertainty in the relative effectiveness of tepotinib compared to immunotherapy and compared to chemotherapy. Both the company and ERG base case results for the overall population and by treatment experience are summarised in Tables 1.17, 1.18 and 1.19.

The cost effectiveness of tepotinib for the ERG and company base-case analyses for each of the subgroups according to the decision problem is summarised in Table 1.20.

Table 1.17: ERG base-case full incremental results for Overall population and the company base-case ICER

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company base-case ICER (£/QALY)
Chemotherapy	[redacted]		2.45		[redacted]			
Tepotinib	[redacted]	[redacted]	2.85	0.40	[redacted]	[redacted]	32,753	19,512
Immunotherapy	[redacted]	[redacted]	2.02	-0.83	[redacted]	[redacted]	Dominated	Dominated
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 1.18: ERG base-case full incremental results for Untreated population and the Company ICER

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company ICER (£/QALY)
Chemotherapy	[redacted]		3.18		[redacted]			
Tepotinib	[redacted]	[redacted]	3.06	-0.13	[redacted]	[redacted]	Dominated	23,354
Immunotherapy	[redacted]	[redacted]	3.45	0.39	[redacted]	[redacted]	Extendedly dominated	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	1.98	[redacted]	[redacted]	63,768	186,293
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 1.19: ERG base-case full incremental results for Treated population and the Company ICER

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company ICER (£/QALY)
Immunotherapy	[redacted]		1.67		[redacted]			
Chemotherapy	[redacted]	[redacted]	2.58	0.92	[redacted]	[redacted]	17,363	Extendedly dominated
Tepotinib	[redacted]	[redacted]	2.61	0.02	[redacted]	[redacted]	55,879	£24,824
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 1.20: The cost-effectiveness of tepotinib by decision problem subgroup

Population	Tepotinib ICER (ERG assumptions)	Tepotinib ICER (company assumptions)
Untreated		
Non-squamous PD-L1 ≥50%	Cost-effective (less costly and less benefit)	Cost-effective (less costly and less benefit)
Non-squamous PD-L1 <50%	Dominated	23,354
Adenocarcinoma/large cell carcinoma PD-L1 <50%	Dominated	23,354
Squamous PD-L1 ≥50%	Cost-effective (less costly and less benefit)	Cost-effective (less costly and less benefit)
Squamous PD-L1 <50%	Dominated	23,354
Treated		
Squamous PD-L1 ≥50%	55,879	24,824
Squamous PD-L1 <50%	55,879	£18,176
Source: Adapted from Table 1 in the Company Submission		

2. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	Adults with advanced non-small cell lung cancer (NSCLC) with mesenchymal–epithelial transition (MET) exon 14 skipping mutations	Adults with advanced non-small cell lung cancer (NSCLC) with mesenchymal–epithelial transition (MET) exon 14 skipping mutations	Population aligned with the NICE final scope	Population aligned with the NICE final scope
Intervention	Tepotinib	Tepotinib	Intervention aligned with NICE final scope	The intervention is in line with the NICE scope
Comparator(s)				
Untreated disease:			Aligned with NICE scope except for the omission of: Pembrolizumab with carboplatin and paclitaxel for people with squamous NSCLC - *this is because it is only available via the Cancer Drugs Fund.* Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566) – *not recommended by time of submission* Best supportive care (BSC) – *not considered a comparator, as patients with NSCLC harbouring METex14 skipping alterations who would*	Pembrolizumab with carboplatin and paclitaxel (subject to ongoing appraisal ID1683) was included in Table 1 in the CS, but the ERG believes that this was a typo. Only pembrolizumab monotherapy was listed as a comparator for people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score. The ERG believes that the omission of atezolizumab
For people with non-squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score:	• Pembrolizumab monotherapy • Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab monotherapy • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)	• As in scope except not Nivolumab plus ipilimumab		
For people with non-squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%:	• Pembrolizumab combination with pemetrexed and platinum chemotherapy • Atezolizumab plus bevacizumab, carboplatin and paclitaxel • Chemotherapy (docetaxel, gemcitabine, paclitaxel or	• As in scope except not Nivolumab plus ipilimumab		

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) o with or without pemetrexed maintenance treatment • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)		*receive tepotinib are highly unlikely to receive BSC instead of active treatment. In addition, there is no data available for BSC in the METex14 skipping alterations population either, therefore a comparison was not possible*	monotherapy was also a typo. Base case analyses were line, histology and PD-L1 status agnostic. This is potentially a serious limitation, although analyses according to whether untreated or pre-treated were presented in Appendix L (See Section 3.4)
For people with adenocarcinoma or large-cell carcinoma whose tumours express PD-L1 with a tumour proportion score below 50%	• Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) o with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment	• As in scope	Comparators were then placed into two groups for statistical comparison with tepotinib (see Section 3.4): Immunotherapies Chemotherapies An exploratory analysis comparing to immunotherapy plus chemotherapy was also conducted and provided in Appendix N of CS).	
For people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score	• Pembrolizumab monotherapy • Pembrolizumab with carboplatin and paclitaxel • Atezolizumab monotherapy • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)	• Pembrolizumab monotherapy		
For people with squamous NSCLC whose tumours express PD-L1 with a tumour proportion score below 50%	• Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)	• Chemotherapy (gemcitabine or vinorelbine) in combination		

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	• Pembrolizumab with carboplatin and paclitaxel (subject to ongoing appraisal ID1683) • Nivolumab plus ipilimumab (subject to ongoing appraisal ID1566)	with a platinum drug (carboplatin or cisplatin) • Pembrolizumab with carboplatin and paclitaxel (subject to ongoing appraisal ID1683)		
Previously treated disease:				
People with non-squamous NSCLC PD-L1 ≥50%	• Platinum doublet • Pemetrexed with carboplatin • Docetaxel, with (for adenocarcinoma histology) or without nintedanib • Best supportive care	As in scope except not BSC		
People with squamous NSCLC PD-L1 <50%	• Atezolizumab monotherapy • Nivolumab monotherapy • Pembrolizumab monotherapy • Docetaxel with (for adenocarcinoma histology) or without nintedanib • Best supportive care			
People with squamous NSCLC PD-L1 >50%	• Gemcitabine with carboplatin or cisplatin • Vinorelbine with carboplatin or cisplatin • Docetaxel • Best supportive care			

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life	As in scope	Aligned with NICE scope	The outcomes reported are in line with the NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	Not reported in Table 1	Not reported in Table 1.	Largely in line with the NICE Reference Case.
Subgroups to be considered	If evidence allows, subgroup analysis by:	Subgroup analysis presented by:	Sub-group data by PD-L1 expression was not collected as part of the VISION trial, so	Base case analyses were line, histology and PD-L1 status agnostic. Although

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	• previous therapy • tumour histology (squamous or non-squamous) • level of PD-L1 expression (strong positive or weak positive), The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	• previous therapy	sub-group analysis could not be conducted. There were only [redacted] patients ([redacted]%) in VISION Cohort A (1 Feb 2021 data cut-off) who were of squamous histology, and [redacted] ([redacted]%) who were sarcomatoid, so full sub-group analysis by histology was not possible. However, in Appendix E subgroup analysis for ORR by histology is reported.	analyses according to whether untreated or pre-treated were presented in Appendix L (See Section 3.4), this is potentially a serious limitation.
Special considerations including issues related to equity or equality	None specified.	None identified.	N/A – in line with the NICE final scope.	In line with the NICE scope

Based on Table 1 of the CS[1]

CS = company submission;; N/A = not applicable; NHS = National Health Service; NICE = National Institute of Health and Care Excellence; PAS = patient access scheme

2.1 Population

The population in the decision problem is aligned with that in the scope: Adults with advanced non-small cell lung cancer (NSCLC) with mesenchymal–epithelial transition (MET) exon 14 skipping mutations. However, subgroup analysis by which comparator was specified was limited (see Section 2.3). The company have interpreted advanced as stage IIIB to IV: "*The primary objective of treating advanced, recurrent, or metastatic NSCLC (Stage IIIb-IV) is to extend survival and improve the quality of life."* (p.28, CS), which was also the criterion for entry to the main trial, VISION.[1] ALK+ and EGFR+ patients are also excluded according to the statement by the company: "*The expectation is that tepotinib would replace non-targeted therapies (immunotherapies and/or chemotherapies) …"* (p.35, CS).[1]

ERG comment: It needs to be made clear that the population in the decision problem appears to be more specific than advanced disease: it is stage IIIB-IV excluding ALK+ and EGFR+ patients. Because this is not explicitly stated in the decision problem table, this is a key issue, which can be resolved by clarification by the company.

2.2 Intervention

The intervention (tepotinib) is in line with the scope.

2.3 Comparators

The NICE scope specifies a long list of potential comparators depending on PD-L1 status and histology (squamous, non-squamous or adenocarcinoma/large-cell carcinoma). All comparators in the decision problem are aligned with the scope except for two that are subject to the outcome of appraisals and, for previously treated disease only, BSC, because it is only uncommonly used and there are no data for it in the METex14 skipping alterations population. The CS[1] indicates the positioning of tepotinib as follows: "*The expectation is that tepotinib would replace non-targeted therapies (immunotherapies and/or chemotherapies) for patients with METex14 skipping alterations in all lines of treatment, in line with past recommendations for targeted treatments in EGFR, ALK and ROS1 NSCLC*." (p. 34) The company approach to estimating the treatment effect (relative to comparator) of tepotinib on OS and PFS was to be agnostic with regards to:

- comparator as except in terms of whether immunotherapy or chemotherapy (and the combination in an exploratory analysis)
- line of therapy (except in an additional analysis)
- histology
- PD-L1 status

ERG comment: The ERG agrees to the omission of comparators that remain subject to the outcome of appraisals. The ERG would also agree with the omission of BSC on the basis that this is not listed in the NICE Pathway for advanced NSLC.[2] It is not clear why atezolizumab monotherapy was not listed as comparator for people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score. Indeed, only atezolizumab monotherapy is listed in the NICE pathway as first-line treatment for both squamous and non-squamous.

Not differentiating according to subgroup in the scope in terms of PD-L1 status and histology might disguise a variation in treatment effect and cost effectiveness between these subgroups. The treatment effect and cost effectiveness relative to the mixture of either immunotherapies or chemotherapies might also be biased if the proportion of each of the individual treatments within the mixture is not as would

be observed in UK clinical practice. Therefore, lack of analysis by appropriate subgroup including comparators appropriate to that subgroup is potentially a serious limitation and thus a key issue.

2.4 Outcomes

The NICE final scope lists the following outcome measures:

- Overall survival
- Progression-free survival
- Response rate
- Adverse effects of treatment
- Health-related quality of life.

These were all assessed in the VISION trial and reported using data from the Cohort A. In addition, objective response, duration of response and best overall response were included as outcome measures. However, no subgroup analyses e.g., by line of therapy were performed for health-related quality of life.

2.5 Other relevant factors

According to the company, tepotinib was granted a Promising Innovative Medicine (PIM) designation from the Medicines and Healthcare products Regulatory Agency (MHRA) and awarded an Innovation Passport by the MHRA on 1 March 2021; and addresses a significant unmet need in patients with mesenchymal–epithelial transition (MET) exon 14 skipping mutations. A simple patient access scheme (PAS) discount of [redacted]% to the list price of tepotinib was applied.

3. CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

A systematic literature review (SLR) was performed to identify trial data for epidemiological, prognostic, clinical, humanistic, and economic burden of advanced NSCLC with MET gene alterations. However, the ERG required further clarification regarding the full SLR report mentioned in section D.1.1.4 of the CS, the application of eligibility criteria, quality assessments performed, as well as details regarding the data extraction process.

3.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical effectiveness, HRQoL and resource use presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[3, 4] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[5] The ERG has presented only the major limitations of each search strategy in the report.

Appendix D and Appendix 1 of the CS detail the systematic literature review (SLR) conducted to identify relevant burden of illness aspects of METex14 skipping alterations in NSCLC: epidemiological, prognostic, clinical, humanistic, and economic burden. This set of searches was therefore designed to identify health-related quality of life data (Appendix H) and cost and healthcare resource use (Appendix I). The SLR was conducted in four stages: an initial SLR on 22 January 2020 and two updates on 3 August 2020 and 8 June 2021. An additional 'top-up review' was conducted on 22 June 2021. The same search strategies were used in the original SLR and the two update searches, with additional search terms used for the top-up review. No language or date limits were applied to the searches. The bibliographies of systematic reviews and meta-analyses identified after an initial review of search results were searched for references to other potentially relevant studies.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the clinical effectiveness/HRQoL/resource use systematic review (as reported in CS)

	Resource	Host/Source	Date ranges	Dates searched
Electronic databases	Medline	Ovid PubMed Ovid Ovid	1946-01/20 1946-08/20 1946-11/06/21 1946-21/06/21	22/01/20 31/07/20 13/06/21 22/06/21
	Embase	Ovid Embase.com Ovid Ovid	1974-01/20 1974-08/20 1974-11/06/21 1974-21/06/21	22/01/20 03/08/20 08/06/21 22/06/21
	CENTRAL	EBM Reviews EBM Reviews Wiley	1991-01/20 1991-08/20 to 08/06/21	22/01/20 03/08/20 08/06/21
	CDSR	EBM Reviews EBM Reviews Wiley	2005-01/20 2005-08/20 to 08/06/21	22/01/20 03/08/20 08/06/21

	Resource	Host/Source	Date ranges	Dates searched
	DARE	EBM Reviews	1991-2015	22/01/20
	HTA Database	EBM Reviews	2001-2016	22/01/20
Conference proceedings	ASCO ESMO ISPOR WCLC	Not stated	All years	22/01/20 24/09/20 08/06/21
Additional resources	ClinicalTrials.gov	Internet	to 2021	24/11/20 08/06/21

CENTRAL = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects: HTA Database = Health Technology Assessment Database; ASCO = American Society of Clinical Oncology; ESMO = European Society of Medical Oncology; ISPOR = The Professional Society for Health Economics and Outcomes Research; WCLC = World Conference on Lung Cancer

ERG comment

- Searches were undertaken to identify burden of illness aspects of METex14 skipping alterations in NSCLC. The CS provided sufficient details for the ERG to appraise the literature searches.
- A good range of databases, conference proceedings and a clinical trials register were searched, and reference checking was conducted.
- Searches were clearly documented and structured, making them transparent and reproducible.
- Results were not limited by either publication date or language of publication.
- Overall, the search strategies appear very restrictive, as they will only have identified records containing both NSCLC and METex14 search terms. The ERG believes that a broader approach to search strategy design would have been beneficial. This would help identify records which did not necessarily contain both of these concepts in the title/abstract, but which may still have been of relevance to the SLR. Given the small numbers of records retrieved by the current searches, an increase in sensitivity is unlikely to have resulted in an unmanageable number of references to be screened.
- The ERG believes that it would also have been useful to include search terms for tepotinib as an addition to the strategies. Although 'tepotinib' was included as a search term in the second update search of conference proceedings, it would have been a useful addition to all searches, retrieving records which included terms for the intervention but not the population in their title/abstract. This addition to the search is unlikely to have produced a significant increase in screening burden but could well have retrieved additional useful references.
- Particularly for identification of records related to health-related quality of life and cost/resource use, the ERG believes that more useful data could have been retrieved from a strategy which combined a general search for non-small cell lung cancer with the relevant HRQoL/cost search filters. The existing searches found very little for economic or humanistic burden, suggesting a broader approach might have been helpful.
- Searches appeared to use appropriate free-text synonyms for non-small cell lung cancer and METex14. Additional terms such as 'malignan*' and 'lesion*' may have been helpful additions to the NSCLC facet. The MEDLINE searches throughout the submission include EMTREE (Non Small Cell Lung Cancer/) rather than MeSH (Carcinoma, Non-Small-Cell Lung/)

indexing terms. As mapping takes place between these terms, this will not have affected the recall of the searches, however it is good practice to use database-appropriate indexing terms.

- Given the points listed above, it is possible that potentially useful records may have been missed by the Company's approach to the SLR literature searches. Unfortunately, the ERG was unable to undertake independent searches and review the results within the STA timeline, as this would be outside of the ERG remit.

3.1.2 Inclusion criteria

The eligibility criteria used in the systematic review of observational and experimental evidence is presented in Table 3.2. Two independent reviewers screened titles and full-texts version of potentially eligible studies with any discrepant opinions being resolved through a consensus which appears adequate. Initially, the application of eligibility criteria, and exclusion of 79 studies based on 'outcomes' was unclear. However, the company clarified that certain "*adjustments were made to reasons for exclusion (highlighted in orange in the table in Appendix 2)*".[6]

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

	Description	Justification
Inclusion criteria		
Population	Patients with advanced NSCLC with MET exon 14 skipping alterations	Consistent with final scope
Interventions	Any therapy	Broader than final scope
Comparator	Not mentioned in the CS	N/A
Outcomes	**Prognostic:** PFS, OS, ORR **Efficacy:** OS, PFS, TTP, ORR, response rates, safety and tolerability **Humanistic:** PROs, carer burden, social burden/productivity **Epidemiological:** incidence, prevalence **Economic:** resource use/costs, disease complications, AEs, treatment response, disease progression, caregiver burden, social burden/productivity	Consistent with the final scope by NICE
Study design	**Prognostic and epidemiological:** Observational, real-world studies **Clinical and humanistic:** any design **Economic:** Observational/clinical studies or economic evaluations reporting cost and resource use data	Consistent with the final scope by NICE
Language restrictions	English language only	Please see the ERG comment below.
Exclusion criteria		
Population	Not mentioned	See the above inclusion criteria.

	Description	Justification
Interventions	Not mentioned	See the above inclusion criteria.
Outcomes	Studies not investigating prognostic, clinical, humanistic, epidemiological, and economic outcomes	See the above inclusion criteria.
Study design	Systematic reviews	See the above inclusion criteria.
Language restrictions	Full-text articles or abstracts published in non-English language	Not relevant to final scope by NICE

Source: Table 1 of the appendices[7]
Footnote: AE = adverse event; CS = company submission; ERG = Evidence Review Group; MET = mesenchymal–epithelial transition; N/A = not applicable; NICE = National Institute for Health and Clinical Excellence; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life; PROs = patient-reported outcomes; RCT = randomised controlled trial; TTP = time to progression

ERG comment: The ERG believes that narrowing down the inclusion criteria to only studies published in English language introduces potential biases and this is in line with the clarification response.[6] It is also not clear why studies of treatment not listed in the scope were included, the number out of 38 includes being: 13 (capmatinib), six (crizotinib), two (savolitinib), one (Mixed TKIs), two (Sym015). Therefore, after exclusion of five tepotinib studies, this leaves only nine possible comparator studies, three of which were chosen for an ITC (see Section 3.3).

3.1.3 Critique of data extraction

Information provided in the CS regarding data extraction was limited.[1]

ERG comment: The ERG requested further clarification from the company regarding data extraction e.g., whether a third researcher was involved in case of any disagreements in the extracted data.

3.1.4 Quality assessment

Quality assessment of the clinical evidence was conducted using the adapted Downs and Black adapted checklist.[8] Quality assessment of the included studies is presented in Tables 3.2. and 3.3.

ERG comment: It is unclear whether methods used for data extraction followed best practice; and details of the adaptation process were missing. However, the ERG does not consider this to have a substantial impact on the evidence submission.

3.1.5 Evidence synthesis

ERG comment: None of the included studies were synthesised quantitatively. The ERG agrees that any meta-analysis would not have been helpful, given insufficient data form the VISION (NCT02864992), single-arm, open-label, phase II study.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

3.2.1 VISION (NCT02864992) study

The evidence for the effectiveness of tepotinib came from the VISION (NCT02864992) study. This is a phase II, ongoing, single-arm, open label study in adults with advanced NSCLC with MET exon 14 skipping mutations or MET amplification. Tepotinib, 450 mg, was administered until progression of

the disease or undue toxicity (2 tablets, once daily; equivalent to 500 mg tepotinib hydrochloride hydrate). The study was conducted at 141 centres in 11 countries worldwide. A summary of the methodology of the trial is shown in Table 3.3.

Table 3.3: Trial design and methodology of the VISION (NCT02864992) study

Parameter	Description
Study objective(s)	To determine the objective response, partial response and/or complete response (by independent review) among patients who had undergone at least 9 months of follow-up
Trial design	Phase II, single-arm, open-label study
Trial drug	Tepotinib, 450 mg, administered until progression of the disease or undue toxicity (2 tablets, once daily; equivalent to 500 mg tepotinib hydrochloride hydrate)
Permitted and disallowed concomitant medication	**Permitted:** Treatment naïve patients in first-line or pre-treated patients with no more than 2 lines of prior therapy. **Disallowed:** Prior chemotherapy, biological therapy, radiation therapy, hormonal therapy (for anti-cancer purposes), targeted therapy, or other investigational anticancer therapy (not including palliative radiotherapy at focal sites) within 21 days prior to the first dose of trial treatment; Prior treatment with other agents targeting the Hepatocyte Growth Factor-C -Met pathway
Primary outcomes (including scoring methods and timings of assessments)	**Primary:** Objective response rate (ORR) determined according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 **Secondary:** Duration of response; best overall response; progression free survival; overall survival; health-related quality of life; adverse effects
Pre-planned subgroups	Age (above or below 65 years); sex; race; geographic region; ECOG; metastatic disease (yes/no); baseline brain metastases (absent/present); time from diagnosis to first dose (above or below 6 months); and smoking status.
Eligibility criteria for participants	Eligible: • Males or females 18 years of age or older • Measurable disease confirmed by an independent review committee in accordance with RECIST version 1.1 • ECOG Performance Status of 0 or 1 • Histologically or cytologically confirmed advanced (locally advanced or metastatic) NSCLC (all types including squamous and sarcomatoid) • Subjects with MET alterations, namely METex14 skipping alterations in plasma and/or tissue as determined by the central laboratory or by an assay with appropriate regulatory status Ineligible: • Subjects with characterized EGFR activating mutations that predict sensitivity to anti-EGFR-therapy • Subjects with characterized ALK rearrangements that predict sensitivity to anti-ALK therapy • Subjects with symptomatic brain metastases who are neurologically unstable

Parameter	Description
	• Any unresolved toxicity Grade 2 or more according to National Cancer Institute Common Terminology Criteria for Adverse Events from previous anticancer therapy • Need for transfusion within 14 days prior to the first dose of trial treatment • Subjects who have brain metastasis as the only measurable lesion • Inadequate haematological, liver, renal, cardiac function • Hypertension uncontrolled by standard therapies (not stabilized to < 150/90 mmHg) • Past or current history of neoplasm other than NSCLC, except for curatively treated non-melanoma skin cancer, in situ carcinoma of the cervix, or other cancer curatively treated and with no evidence of disease for at least 5 years • Medical history of difficulty swallowing, malabsorption, or other chronic gastrointestinal disease, or conditions that may hamper compliance and/or absorption of the test product • Major surgery within 28 days prior to Day 1 of trial treatment • Known infection with human immunodeficiency virus, or an active infection with hepatitis B or hepatitis C virus • Substance abuse, active infection, or other acute or chronic medical or psychiatric condition • Known hypersensitivity to any of the trial treatment ingredients • Participation in another clinical trial within the past 30 days
Based on section B.2.3.1. of the CS [1] and NCT02864992 ALK = Anaplastic Lymphoma Kinase; CS = company submission; ECOG = Eastern Cooperative Oncology Group; EGFR = Epidermal Growth Factor Receptor; MET = mesenchymal-epithelial transition; NSCLC = Non-small Cell Lung Cancer	

The patients in VISION were formed of three cohorts:

- **Cohort A:** Tepotinib 500 mg for METex14 skipping alterations
- **Cohort B:** Tepotinib 500 mg for MET amplification
- **Cohort C:** Confirmatory part for tepotinib 500 mg for METex14 skipping alterations

The eligibility criteria and schedule of assessments for Cohort C were the same as those for enrolment into Cohort A. Only the Cohort A efficacy data were reported in the CS document B and from two data cut-offs. These were 1 February 2021 (all patients who received a dose of tepotinib before 1 November 2020, N=152) and 1 July 2020 (patients who received the first dose of tepotinib before 02 October 2019, reported to ensure that the latest enrolled subject had a follow-up of at least nine months, which was expected to provide six months of follow-up beyond a possible onset of response, N=146). The cost effectiveness analysis was based on the former data-cut. The combined analysis of Cohorts A and C for efficacy (1 February cut-off, n=275) was reported in Appendix R.[7] In contrast to efficacy, the safety analysis of Cohorts A+C was reported in document B, although only the 1 July 2020 cut-off (n=255). The 1 February cut-off was reported in Appendix R, although for all patients who received a dose of tepotinib (n=291).[7]

3.2.2 Baseline characteristics of patients in the VISION study (Cohorts A and A+C)

Baseline characteristic for both Cohort A and Cohorts A+C are shown in Tables 3.4 (Cohort A) and 3.5 (combined A+C), as well as for two data cuts for the safety analysis (Tables 3.6 and 3.7).

Table 3.4: Demographics and baseline characteristics, VISION Cohort A – 1 February 2021 cut-off (efficacy outcomes)

	Overall N=152 (100%)	1L N=69 (100%)	2L+ N=83 (100%)
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Race, n (%)			
White	[redacted]	[redacted]	[redacted]
Black or African American*	[redacted]	[redacted]	[redacted]
Asian*	[redacted]	[redacted]	[redacted]
Not collected at site	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Age (years)			
Mean (StD)	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]
Age groups, n (%)			
<65 years	[redacted]	[redacted]	[redacted]
≥65 years	[redacted]	[redacted]	[redacted]
65 to <75 years	[redacted]	[redacted]	[redacted]
75 to <85 years	[redacted]	[redacted]	[redacted]
≥85 years	[redacted]	[redacted]	[redacted]
Country, n (%)			
Belgium	[redacted]	[redacted]	[redacted]
France	[redacted]	[redacted]	[redacted]
Germany	[redacted]	[redacted]	[redacted]
Italy	[redacted]	[redacted]	[redacted]
Japan	[redacted]	[redacted]	[redacted]
Poland	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
United States	[redacted]	[redacted]	[redacted]
South Korea	[redacted]	[redacted]	[redacted]
Taiwan	[redacted]	[redacted]	[redacted]
Netherlands	[redacted]	[redacted]	[redacted]
Israel	[redacted]	[redacted]	[redacted]
Geographic region, n (%)			
Europe	[redacted]	[redacted]	[redacted]
North America	[redacted]	[redacted]	[redacted]
Asia	[redacted]	[redacted]	[redacted]

	Overall N=152 (100%)	1L N=69 (100%)	2L+ N=83 (100%)
Histology subtype, n (%)			
Adenocarcinoma	[redacted]	[redacted]	[redacted]
Adenosquamous	[redacted]	[redacted]	[redacted]
Squamous	[redacted]	[redacted]	[redacted]
Sarcomatoid	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]

Source: Table 11, CS.[1]
*Values exchanged as revealed to have been swapped from original, as shown in CSR.[9]

Table 3.5: Demographics and baseline characteristics, VISION Cohort A + C – 1 February 2021 cut-off (efficacy outcomes)

	Cohort A+C [redacted]
Sex, n (%)	
Male	[redacted]
Female	[redacted]
Race, n (%)	
White	[redacted]
Black or African American	[redacted]
Asian	[redacted]
Not collected at site	[redacted]
Other	[redacted]
Age (years)	
Mean (StD)	[redacted]
Median (IQR)	[redacted]
Min, max	[redacted]
Age groups, n (%)	
<65 years	[redacted]
≥65 years	[redacted]
65 to <75 years	[redacted]
75 to <85 years	[redacted]
≥85 years	[redacted]
Country, n (%)	
Belgium	[redacted]
France	[redacted]
Germany	[redacted]
Italy	[redacted]
Japan	[redacted]
Poland	[redacted]
Spain	[redacted]

	Cohort A+C [redacted]
United States	[redacted]
South Korea	[redacted]
Taiwan	[redacted]
Netherlands	[redacted]
Israel	[redacted]
China	[redacted]
Switzerland	[redacted]
Geographic region, n (%)	
Europe	[redacted]
North America	[redacted]
Asia	[redacted]
Source: Table 69, Appendix R[7]	

Table 3.6: Demographic and baseline characteristics, VISION Cohort A + C (safety set) – 1 July cut-off

Characteristic	Cohort A+C (N=255)
Age (years)	
Median	72.0
Range	41; 94
Gender, n (%)	
Male	123 (48.2)
Female	131 (51.8)
Race, n (%)	
White	171 (67.1)
Black or African American	3 (1.2)
Asian	72 (28.2)
Not collected at this site	7 (2.7)
Other	1 (0.4)
Missing	1 (0.4)
Geographic region, n (%)	
Europe	128 (50.2)
North America	54 (21.2)
Asia	73 (28.6)
ECOG, n (%)	
0	71 (27.8)
1	184 (72.2)
Smoking history, n (%)	
Yes	121 (47.4)

Characteristic	Cohort A+C (N=255)
No	124 (48.6)
Prior therapy for advanced / metastatic disease, n (%)	
Untreated	125 (49.0)
Previously treated	130 (51.0)
Histology subtype, n (%)	
Adenocarcinoma	207 (81.2)
Squamous	25 (9.8)
Other	23 (9.0)
Stage at study entry, n (%)	
IIIb	8 (3.1)
IIIc	3 (1.2)
IV	243 (95.3)
Missing	1 (0.4)
Brain metastases as identified by IRC, n (%)	
Non-target lesion	INV: 31 (12.2) IRC: 31 (12.2)
Target lesion	INV: 1 (0.4) IRC: -

Source: Table 26, CS;[1]
ECOG = Eastern Cooperative Oncology Group performance scale; INV = investigator assessment; IRC = independent review committee

Table 3.7: Baseline characteristics, VISION Cohort A+C – 1 February 2021 cut-off (safety set)

	Cohort A+C [redacted]
Sex, n (%)	
Male	[redacted]
Female	[redacted]
Race, n (%)	
White	[redacted]
Black or African American	[redacted]
Asian	[redacted]
Not collected at site	[redacted]
Other	[redacted]
Age (years)	
Mean (SD)	[redacted]
Median (IQR)	[redacted]
Min, max	[redacted]
Age groups, n (%)	
<65 years	[redacted]
≥65 years	[redacted]

	Cohort A+C [redacted]
65 to <75 years	[redacted]
75 to <85 years	[redacted]
≥85 years	[redacted]
Geographic region, n (%)	
Europe	[redacted]
North America	[redacted]
Asia	[redacted]

Source: Table 9, Appendix F[7]
IQR=interquartile range, max=maximum, min=minimum, SD=standard deviation
*Values exchanged as revealed to have been swapped from original, as shown in CSR.[9]

ERG comment: There were no obvious differences in baseline characteristics between Cohort A and Cohorts A+C. Although smoking history, ECOG performance-status score, histologic subtype, NSCLC stage at study entry or presence of brain metastases are missing in the most recent cut-off, it is unlikely there would be much of a discrepancy given almost no difference in sample size.

3.2.3 Clinical effectiveness of tepotinib in the VISION study

Clinical outcomes

As can be seen in Table 3.8, the ORR in the Cohort A was 46.7% (95% CI: 38.6, 55.0) based on independent evaluation with a median duration of response of 15.4 months (95% CI: 9.7, 32.7). Also, a higher ORR was observed in the first line of therapy group compared to the second (or more) group 50.7% (95% CI 38.4, 63.0) versus 43.4% (95% CI 32.5, 54.7). As per Table 14 of the CS, none of the patients (0%) achieved complete response; 14.5% had progressed in their disease; 13.2% were not evaluable; 46.7% had partial response; and 25.7% had stable disease. As per Table 15 of the CS, the median PFS in the Cohort A was 10.8 months (95% CI 8.3, 12.4) (1 February 2021 cut-off). The median The OS in Cohort A was 19.1 months (95% CI 15.2, 22.1) in 1 February 2021 cut-off. Table 3.8 also shows that corresponding values for Cohort A+C, which appear to be very similar to those for Cohort A alone.

Table 3.8: Tepotinib outcomes, VISION (Cohort A – 1 Feb 2021 cut-off)

	Cohort	Overall	1L	2L+
N	A	[redacted]	[redacted]	[redacted]
	A+C	[redacted]	[redacted]	[redacted]
ORR n (%) [95% CI]	A	[redacted]	[redacted]	[redacted]
	A+C	[redacted]	[redacted]	[redacted]
Median DOR in months [95% CI]	A	[redacted]	[redacted]	[redacted]
	A+C	[redacted]	[redacted]	[redacted]
mPFS [a], months [95% CI] [b]	A	[redacted]	[redacted]	[redacted]
	A+C	[redacted]	[redacted]	[redacted]
Overall survival				
Patients with event, n (%)	A	[redacted]	[redacted]	[redacted]
	A+C	[redacted]	[redacted]	[redacted]
mOS time [a], months [95% CI] [b]	A	[redacted]	[redacted]	[redacted]
	A+C	[redacted]	[redacted]	[redacted]

Source: Tables 12, 13, 15 and 16, CS;1 Table 70,Appendix R[7]
1L=first line of therapy, 2L+=second or more lines of therapy; CI = confidence intervals; DOR = duration of response; ORR = objective response rate.
aProduct-limit (Kaplan-Meier) estimates.
b95% CI for the median calculated using the Brookmeyer and Crowley method.

Patient-reported outcomes: health-related quality of life

EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-LC13 were completed at baseline (before first dose of tepotinib), every six weeks for the first nine months and then every 12 weeks until disease progression, death or withdrawal of consent. The results presented in the CS were stated to be mostly for the 1 July 2020 cut-off because the *'…1 February 2021 PRO outcomes reporting are not currently as comprehensive.'* (p.70, CS).[1] The results are reported in Figures 17, 18, 19, 20, 21, 22 and 23 of the CS.[1] The CS states that the *'results were consistent across the three PRO tools and suggested that HRQL remains stable over time.'* (p.70, CS).[1] In EORTC QLQ-LC13, the company claimed that *'…a trend towards a clinically meaningful improvement in the coughing symptom scale was observed.'* (p.70, CS)[1] No analyses of subgroups, including line of therapy, were performed for PROs.

Adverse effects

A summary of treatment-emergent adverse events (TEAE) reported in the VISION study is presented in Table 3.9 below. For National Cancer Institute - Common Terminology Criteria for Adverse Events, 52.9% of patients experienced Grade ≥ 3 TEAE; and 25.1% experienced TRAE. A list of Grade ≥3 AEs from VISION was also presented in Table 28 of the CS, which showed that peripheral oedema was the most common Grade ≥3 AEs TEAE reported in 7.8% of patients. However, the AEs and frequency used in the cost effectiveness model were presented in Tables 41 and 42, which also included those for comparator treatments obtained from various literature sources. This table has been reproduced in Tables 3.10 and 3.11.

Table 3.9: Summary of treatment-emergent adverse events from the VISION study

	Tepotinib 500 mg (Cohorts A + C; N=255) n (%)
Any TEAE	246 (96.5)
TEAE, NCI CTCAE Grade ≥ 3	135 (52.9)
TEAE leading to treatment dose reduction	76 (29.8)
TEAE leading to temporary treatment discontinuation	112 (43.9)
TEAE leading to permanent treatment discontinuation[*]	52 (20.4)
Serious TEAE	115 (45.1)
TEAE with an outcome of death[#]	30 (11.8)

Legend: [*] = There was a difference to the number of patients with an AE as primary reason for treatment discontinuation' [#] = There was an additional TRAE leading to death by the cut-off date, which was not recorded in the clinical database. NCI CTCAE=National Cancer Institute - Common Terminology Criteria for Adverse Events, TEAE=treatment- emergent adverse event.

[redacted]Table 3.10: Grade ≥3 adverse event incidence – immunotherapies ± chemotherapy

Adverse event	Tepotinib	Pembrolizumab		Atezolizumab	Nivolumab		Pembrolizumab/ pemetrexed/ [illegible]	Atezolizumab/ bevacizumab/ [illegible]	Nivolumab/ ipilimumab
		Untreated	Previously treated		Non-squamous	Squamous			
Alanine aminotransferase) increase	[redacted]				0.3%				
Alopecia	[redacted]								
Amylase increase	[redacted]								
Anaemia	[redacted]	4.5%	0.9%	0.5%			18.3%	6.8%	1.4%
Asthenia	[redacted]	0.6%	0.3%		3.5%		6.7%		1.4%
Bilirubin increased	[redacted]							4.3%	
Cardiac failure	[redacted]								
Cough	[redacted]						0.0%		
Diarrhoea	[redacted]	6.5% [a]	3.5% [a]		1.0%		5.2%	3.0%	1.7%
Dyspnoea	[redacted]	1.9%			4.9%		4.2%		
Fatigue	[redacted]	1.3%	1.2%	1.7%	3.1%	0.8%	6.9%	3.3%	1.7%
Febrile neutropenia	[redacted]							10.3%	
Hyperglycaemia	[redacted]	2.6%			2.4%				
Hypertension	[redacted]							7.5%	
Hypoalbuminemia	[redacted]								
Hypomagnesemia	[redacted]								
Infection	[redacted]	0.6%							
Leukopenia	[redacted]					0.8%		2.0%	
Lipase increase	[redacted]								
Lymphocyte count decrease	[redacted]								
Nausea	[redacted]		0.3%				3.5%	4.0%	0.5%
Neuromotor	[redacted]								
Neurosensory	[redacted]								
Neutropenia	[redacted]			0.4%	0.3%		16.0%	16.5%	
Neutrophil count decrease	[redacted]							14.8%	
Oedema peripheral/other	[redacted]	0.6%					0.5%		
Pain	[redacted]	1.2%			2.1%		1.5%		
Platelet count decrease	[redacted]							5.8%	
Pleural effusion	[redacted]	3.9%							

Adverse event	Tepotinib	Pembrolizumab		Atezolizumab	Nivolumab		Pembrolizumab/ pemetrexed/ [illegible]	Atezolizumab/ bevacizumab/ [illegible]	Nivolumab/ ipilimumab
		Untreated	Previously treated		Non-squamous	Squamous			
Pneumonitis / pneumonia	[redacted]	4.5%		0.5%	3.5%	0.8%	3.0%		
Pulmonary/ respiratory tract infection	[redacted]			0.2%					
Thrombocytopenia	[redacted]						8.4%	4.8%	
Vomiting	[redacted]	0.6%					4.0%		0.3%
White blood cell count decrease								4.3%	
Source	VISION[10]	TA531[11]	TA428[12]	TA520[13]	TA484[14]	TA483[15]	Gadgeel et al, 2020[16]	TA584[17]	Hellmann et al, 2020[18]
Source: Table 41, CS[1]									

[redacted]Table 3.11: Grade ≥3 adverse event incidence - chemotherapies

Adverse event	Tepotinib	Docetaxel/ platinum	Gemcitabine/ platinum	Paclitaxel/ platinum	Vinorelbine/ platinum	Docetaxel monotherapy	Docetaxel/ [illegible]	Docetaxel/ gemcitabine	Vinorelbine monotherapy	Pemetrexed/ platinum	Pemetrexed maintenance
Alanine aminotransferase increase	[redacted]		3.0%				10.3 %				0.3 %
Alopecia	[redacted]	1.0%	1.0%			0.6 %			1.0%	15.8 %	
Amylase increase	[redacted]										
Anaemia	[redacted]	7.0%	25.0%		25.0 %	1.6 %	2.5 %	2.5 %			6.4 %
Asthenia	[redacted]	12.0 %			14.0 %	1.9 %		20.0 %	5.0%	3.5 %	
Bilirubin increased	[redacted]					3.2 %	15.9 %		5.0%		
Cardiac failure	[redacted]							7.5 %			
Cough	[redacted]							7.5 %			
Diarrhoea	[redacted]	7.0%	4.0%		3.0%	8.1 % [a]	34.1	5.0 %	1.0%	3.0 %	0.3 %

Adverse event	Tepotinib	Docetaxel/ platinum	Gemcitabine/ platinum	Paclitaxel/ platinum	Vinorelbine/ platinum	Docetaxel monotherapy	Docetaxel/ [illegible]	Docetaxel/ gemcitabine	Vinorelbine monotherapy	Pemetrexed/ platinum	Pemetrexed maintenance
							%[a]				
Dyspnoea	[redacted]		7.0%						2.0%	5.0 %	
Fatigue	[redacted]			13.0 %		3.6 %	2.2 %			3.5 %	4.7 %
Febrile neutropenia	[redacted]			2.0%		4.9 %	7.2 %	5.0 %			1.9 %
Hyperglycaemia	[redacted]		6.0%								
Hypertension	[redacted]		1.0%	0.7%							
Hypoalbumine mia	[redacted]										
Hypomagnesem ia	[redacted]		7.0%								
Infection	[redacted]	8.0%	5.0%	3.0%	8.0%		6.6 %				
Leukopenia	[redacted]		46.0%					2.5 %			2.2 %
Lipase increase	[redacted]										
Lymphocyte count decrease	[redacted]		43.0%								
Nausea	[redacted]	10.0 %	27.0%		17.0 %	0.3 %	1.5 %	7.5 %	1.0%	8.0 %	0.6 %
Neuromotor	[redacted]	3.0%	12.0%		6.0%			2.5 %			
Neurosensory	[redacted]	4.0%	12.0%		4.0%						0.3 %
Neutropenia	[redacted]	74.0 %	57.0%	17.0 %	78.0 %	12. 3%	9.1 %	27.5 %		12.4 %	5.8 %
Neutrophil count decrease	[redacted]					6.1 %					
Oedema peripheral/other	[redacted]										
Pain	[redacted]	1.0%		1.0%	1.0%			12.5 %	1.0%	2.0 %	1.1 %
Platelet count decrease	[redacted]										

Adverse event	Tepotinib	Docetaxel/ platinum	Gemcitabine/ platinum	Paclitaxel/ platinum	Vinorelbine/ platinum	Docetaxel monotherapy	Docetaxel/ [redacted]	Docetaxel/ gemcitabine	Vinorelbine monotherapy	Pemetrexed/ platinum	Pemetrexed maintenance
Pleural effusion	[redacted]	2.0%			2.0%						
Pneumonitis / pneumonia	[redacted]			3.0%						2.0 %	
Pulmonary/ respiratory tract infection	[redacted]							22.5 %			
Thrombocytopenia	[redacted]	3.0%	50.0%		4.0%		1.3 %	5.0 %		6.9 %	1.9 %
Vomiting	[redacted]	8.0%	23.0%		16.0 %	0.6 %		2.5 %	1.0%	3.0 %	0.3 %
White blood cell count decrease						3.2 %	15. 9 %				
Source	VISION, Cohort A[19]	Docetaxel prescribing information[20]	Gemcitabine prescribing label[21]	AVASTIN prescribing information[22]	Docetaxel prescribing information[20]	TA428[12]	TA347[23]	Casal et al 2007[24]	Vinorelbine prescribing information[25]	Scagliotti et al, 2008[26]	Paz-Ares et al 2013[27]

[redacted]**ERG comment:** The ERG would agree that Cohort B is outside of the scope. However, it is unclear how why Cohort A was preferred over combined Cohorts A+C for the efficacy analysis and why not all patients in Cohorts A+C were preferred for the safety analysis. However, as Table 3.9 shows, there appears to be little difference in all outcomes between Cohort A and Cohorts A+C. Therefore, it would seem reasonable to use Cohorts A+C for the ITC, the effect of which is uncertain and thus constitutes a Key Issue.

The ERG would agree that HRQoL measures appeared to be largely stable over the follow-up period. It also seemed to be the case that, according to Figure 21, there was an improvement in the coughing symptom scale of the EORTC QLQ-LC13, as indicated by a decrease in values. However, the limits of the bars corresponded to the standard error and not the 95% CI, the use of which would imply overlap with no change.

The ERG notes that the numbers presented for tepotinib in Table 41 do not match those in Table 28 of the CS. In fact, the Table 41 values all seem to be higher e.g. hypoalbuminaemia: 5.5% vs. [redacted]. There is a very large difference between peripheral oedema in Table 28 vs. Oedema peripheral/other, which is 7.8% vs. [redacted], although it is not clear what else the latter might include. The ERG can confirm that the values reported in Table 28 correspond to those from Cohort A+C and those in Table 41 are from Cohort A in the CSR with 1 July 2020 cut-off. [10]Although, as with efficacy, it is unclear why cohort A instead of cohort A + C was adopted, the ERG is reassured that the higher values seem to have been used in the cost effectiveness analysis. It is unclear how the sources of comparator AE data that were used in the economic model were obtained. It appears that mostly NICE TAs were used for the immunotherapies, which makes sense as these are likely to be a comprehensive source. Similarly, for

the chemotherapies prescribing information was used several times. The ERG would suggest that the lack of rationale is a source of uncertainty, which might be reduced by greater consistency in source of AE frequency estimates and therefore considers this to be a Key Issue.

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As referred to in Section 2, the following comparators, pembrolizumab with carboplatin and paclitaxel, nivolumab plus ipilimumab as well as best supportive care were omitted from the analyses. In terms of the remaining comparators, as per section B.2.9.1 of the CS, *"No head-to-head efficacy and safety data are available for tepotinib versus the comparators listed in the scope"*.(p.82) Even though comparison trial data were available for tepotinib versus immunotherapy and/or chemotherapy in wildtype NSCLC, clinical experts interviewed at the advisory board argued against such comparisons due to high uncertainty. However, patient level data (PLD) from three retrospective real-world studies, referred to as NIS-0015, NIS-0035 and COTA and conducted by the company were available to conduct the comparisons.[28] These plus patient-level data from British Columbia, Canada, by Wong et al. (2021)[29] were used for the main ITC reported in the CS. In section B.2.9.4 the company reported a brief description of each of the four real-world studies, which together formed the real-world cohort.

In addition, three published studies in the METex14 skipping alterations population were available.[30-32] Unanchored MAIC analyses using these studies were available in Appendix L (see ERG comment in Section 3.4.1).[7]

ERG comment: The choice of the particular PLD employed for the ITC was not justified by the company: it is likely that it was driven at least to some extent by availability, at least in the case of those studies conducted by the company. The choice of PLD is therefore a key issue of uncertainty.

The choice of studies for the MAIC was also not adequately justified, although many of them would not have been suitable for the decision problem because they included

3.4 Critique of the indirect comparison and/or multiple treatment comparison

3.4.1 ITC using propensity scoring

The company performed what they described as the primary ITC on OS and PFS using PLD from sources as listed in Section 3.2. The company argued that patient numbers were too small to compare tepotinib to individual comparator treatments, referring to Tables 20 and 21 in the CS (see Tables 3.12 and 3.13), and so grouped those comparator treatments to produce two main comparisons:

1. VISION versus immunotherapy
2. VISION versus chemotherapy

Table 3.12: Treatment regimens received in the chemotherapy treatment group

Line	Chemotherapy (n=66)	
	Frequency	Percent
Carboplatin & pemetrexed	[redacted]	[redacted]
Platinum doublet[a]	[redacted]	[redacted]
Bevacizumab, carboplatin & pemetrexed	[redacted]	[redacted]
Carboplatin & paclitaxel	[redacted]	[redacted]

Line	Chemotherapy (n=66)	
	Frequency	Percent
Docetaxel	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]
Cisplatin & pemetrexed	[redacted]	[redacted]
Pemetrexed & bevacizumab	[redacted]	[redacted]
Bevacizumab, cisplatin & pemetrexed	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Carboplatin & gemcitabine	[redacted]	[redacted]
Cisplatin & etoposide	[redacted]	[redacted]
Cisplatin & gemcitabine	[redacted]	[redacted]
Cisplatin & vinorelbine	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]
Gemcitabine & vinorelbine	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]

Source: Table 21, CS[1]

[a]The Wong et al data set only labelled treatments as per the treatment class.

Table 3.13: Treatment regimens received in the immunotherapy treatment group

Line	Immunotherapy (n=51)	
	Frequency	Percent
Pembrolizumab	[redacted]	[redacted]
Immunotherapy [a]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Ipilimumab & nivolumab	[redacted]	[redacted]
Durvalumab	[redacted]	[redacted]
Spartalizumab	[redacted]	[redacted]
Source: Table 21, CS[1] [a]The Wong et al data set only labelled treatments as per the treatment class.		

This approach was supported by precedent in the form of NICE TA531 in NSCLC and other oncology submissions (TA517, TA502 and TA541). [11, 33-35]Various studies were also cited to support the idea of similar efficacy between either chemotherapy or immunotherapy treatments. Finally, this approach was also validated at an advisory board.[36] It was however noted that the exception of similar efficacy was between platinum-based chemotherapy and single-agent chemotherapy, but this was considered to have little impact on the results given the rarity of the latter at this line of therapy, citing Table 20 in the CS. The company also claimed that patient numbers were too small for more than what was described as an exploratory analysis of the comparison with immunotherapy plus chemotherapy (Appendix N).[7] An additional analysis by whether untreated or pre-treated was also presented in Appendix L.[7]

Application criteria were applied to the real-world cohort to provide consistency with VISION:

- Age ≥ 18 years
- Exclude stages I-IIIA
- Exclude if missing both disease stage and advanced/metastatic disease status
- Exclude ECOG ≥ 2
- Exclude if missing both PFS/TTNTD and OS
- Include only the METex14 skipping alterations population
- Exclude anaplastic lymphoma kinase positive (ALK+)
- Exclude epidermal growth factor receptor positive (EGFR+)

This reduced the total number to be analysed from 360 patients (970 lines of therapy) to 140 patients (273 lines of therapy). Over half of the patients had missing ECOG status ([redacted] and [redacted] of chemotherapy and immunotherapy patients respectively), but these were not excluded, except in a sensitivity analysis (Appendix L).[7] However, limiting to MET skipping population had the largest effect, excluding 126 patients, with exclusion of states I-IIIA and ECOG ≥ 2 having the next largest impact (loss of 36 and 41 patients respectively). Application of the other criteria had little impact (no more than the loss of 9 patients), with missing outcome data have no impact.

The final data set for each of the comparisons (chemotherapy and immunotherapy) was compiled by selecting a maximum of only one line per patient. This was done to avoid including data for the same patient more than once and was achieved by randomly selecting lines where there was more than one per patient e.g. a patient with one line of immunotherapy followed two of chemotherapy would have their data included for the former and their data for only one of the two latter lines selected at random.[37] Following this sampling process, a total of 66 chemotherapy-treated patients and 51 immunotherapy-treated patients were available in order to conduct the primary ITC. The resulting patient characteristics are presented in Table 19 in the CS. The number of patients per treatment regimen in this dataset is shown in Tables 20 and 21 in the CS. Because of lack of PFS data, TTNTD or duration of treatment was used as a proxy and a sensitivity analysis reported in appendix L.[7] PFS data were available for the 0015 study and some patients in the COTA data. However, TTNTD had to be used for the 0035 study and some patients in the COTA data and time on treatment was used as a proxy for Wong et al.

In order to adjust for possible confounding, propensity scoring was employed to achieve balance of patient characteristics between tepotinib and comparators, which is an accordance with NICE TSD 17.[38] Matching was rejected because of loss of patients. The precise propensity score method chosen was to use Standardised Mortality Ratio (SMR) weights, citing a publication by Desai, 2019.[39] The ITC report (Appendix L) stated that this method was used to *"match to the treated i.e. tepotinib data…[which] means that the tepotinib data does not change…for instance comparing to the immunotherapy group, and the chemotherapy group…"* (p.25).[7] The characteristics that formed the covariates used to estimate the weights by logistic regression, obtained by interviews with two clinical experts, were:

- Prior treatment experience
- Age (as a mean)
- Metastatic/stage 4 disease (vs non-metastatic)
- Sex
- Histology (adenocarcinoma or not)
- Presence of smoking history

ECOG PS and other types of histology were also mentioned, but not used due to lack of data. The effect of weighting is shown in Tables 22 and 23 in the CS in terms of p value of test of difference and standardised mean difference (SMD).

3.4.2 ITC for VISION vs. immunotherapy chemotherapy combination

Because only five patients received an immunotherapy chemotherapy combination in the real world cohort, the company estimated the OS and PFS for the economic model by applying a HR to each of the curves with chemotherapy only estimated using the ITC (see Appendix N1.1.3).[7] These HRs were obtained from an RCT out of a choice of three:

- KEYNOTE-189 - Pembrolizumab with pemetrexed plus platinum therapy versus pemetrexed plus platinum for advanced non-squamous NSCLC without EGFR and ALK mutations.
- KEYNOTE-407 – Pembrolizumab with paclitaxel plus carboplatin versus paclitaxel plus carboplatin for stage IV squamous NSCLC
- IMPower-150 – Atezolizumab with bevacizumab plus carboplatin plus paclitaxel versus bevacizumab plus carboplatin plus paclitaxel for advanced non-squamous NSCLC, including patients with ALK and EGFR if they had progressed on tyrosine kinase inhibitor.

KEYNOTE-189 was chosen because of the higher occurrence of non-squamous patients in the METex14 skipping alterations population and because of the inclusion of pre-treated ALK and EGFR patients in IMPower-150. Also, the HRs from KEYNOTE-189 reported for the ≥ 65-year-old population were used in the economic model on the basis that patients with METex14 skipping alterations are typically older patients, which is reflected in VISION (mean age 73 years). The results for KEYNOTE-189 reports a HR for OS of 0.64 (95% CI: 0.43 – 0.95) and HR for PFS of 0.75 (95% CI: 0.55 – 1.02).

3.4.3 ITC using MAIC

This was conducted for OS and PFS (where available) and the methods were presented in Appendix L.[7] Because, unlike the propensity score method, PLD were not available for the comparator, those for VISION had to be adjusted to match the population characteristics of each of the three comparator studies, i.e. there were three MAICs. The characteristics included as covariates are the same as for the propensity score method (see above). Results were only presented as survival curves with no summary statistics.

ERG comment: The ERG agrees with the company that the ITC using propensity scoring is the more robust method. This is for several reasons:[40]

- The MAIC adjusts the intervention data to match the comparator trial population, which, given that only the patients in the intervention trail actually received the intervention would probably reduce the applicability of the results to the population most eligible for the intervention.
- Because there are more than one comparator, in this case immunotherapies and chemotherapies (the combination was not included in the ITC using propensity scoring), pooling comparator data for all comparators permits the adjustment of all comparator data to better match those of VISION and so facilitates comparability of treatment effect estimates for each of the comparators. This contrasts with a MAIC method whereby each comparator will have intervention data (from VISION in this case) that is adjusted to a different population, i.e. the population in each of the comparator trials.
- The degree to which balance has been achieved can be more clearly estimated, e.g. using standardised mean differences, given the availability of PLD for both intervention and comparator

Indeed, in referring to unanchored comparisons, TSD 18 states: *"because there is no analysis of the potential magnitude of residual bias, and hence no idea of the degree of error in the unanchored estimates [it is] most unlikely that systematic error has been eliminated. Hoaglin, in a series of letters critiquing an unanchored comparison by Di Lorenzo et al. based upon a matching approach similar to MAIC, remarked that, without providing evidence that the adjustment compensates for the missing common comparator arms and the resulting systematic error, the ensuing results "are not worthy of consideration*" (p.55)[40]

Given that the ITC using propensity scoring is the more robust method, and in accordance with the recommendation of TSD 18, only the results of the ITC using propensity scoring are presented in the ERG report.[40]

In terms of the ITC using propensity scoring, it is not clear that patient numbers would have been too small for an analysis of comparators by subgroup, specifically histology. There would probably be a

trade-off between the uncertainty and ability to discriminate between subgroups in terms of effectiveness and thus cost effectiveness. Analysis by PD-L1 status should also have been undertaken, as referred to in Section 2.3, but those data were not collected in VISION. This it therefore a key issue of uncertainty, which might be mitigated by further data and analyses.

The exclusion of patients from the PLD did seem reasonable in order to make the population more consistent with the scope i.e. adults with only the METex14 skipping alterations in stage IIIB-IV disease, excluding ALK+ and EGFR+.

Using propensity score weighting is a method of PLD analysis that is recommended in TSD 17.[38] However, it is not clear why SMRs were chosen instead of inverse probability of treatment, only the latter being recommended in TSD 17. Also, the former is limited to estimating the treatment effect only in the population that would receive the intervention i.e. the average treatment effect of the treated (ATT), in this case tepotinib, as opposed to the whole eligible population i.e. the average treatment effect (ATE). However, although not entirely clear, it does appear that estimating the ATT and by doing so not adjusting the tepotinib data enables separate analysis versus chemotherapy or immunotherapy. This implies that the estimates of treatment effect vs. either treatment group can also be compared to each other as if from the same population, which is those who received tepotinib in VISION. This then facilitates the full incremental analysis in the cost effectiveness analysis (see Sections 4 to 6). However, it is also not clear why regression adjustment (RA) or doubly robust methods of combining RA with IPW were not considered. Therefore, the method of PLD analysis remains a key issue of uncertainty, which might be mitigated by further explanation and analyses.

The characteristics used to calculate the propensity score were determined appropriately using clinical experience and the results of the adjustment demonstrated a reasonably close approximation of the weighted comparator data to the VISION data. However, one concern is the lack of inclusion of ECOG status due to its status being unknown for over 50% of comparator patients. Therefore, there is some value in considering the sensitivity analysis presented in Appendix L. Finally, no tests of overlap were explicitly reported, although the SMDs were for each of the adjusted characteristics. These values were low (well below 0.1) for all but metastatic disease presence ([redacted], and even this might be regarded as acceptable.[38]

In terms of the comparison with an immunotherapy chemotherapy combination, it does seem reasonable to conclude that there were too few patients in the PLD to perform an ITC as for the comparisons with chemotherapy or immunotherapy. However, it is unclear how those three trials listed in Appendix N were identified. It is also unclear why the HRs from only the non-squamous and not the squamous were used: one could have been used for an analysis in the former and the other in the latter subgroup. This is notwithstanding the limitations of the method of applying data from a non-METex14 skipping alterations population and, by using only the HR, assuming proportional hazards. The ERG regards the lack of justification of trials included as a Key Issue.

3.4.4 Results of the ITC using propensity scoring

Figures 24 to 27 were presented in the CS for OS and PFS showing the survival curves for tepotinib from VISION and separately for immunotherapy and chemotherapy, both before and after weighting. Table 3.14 shows a summary of the results. Tables 3.15 and 3.16 show those for the subgroups according to treatment experience.

Table 3.14: Summary of ITC efficacy results

	Tepotinib (n=151)	Chemotherapy (n=66, ESS=152)	Immunotherapy (n=51, ESS=150)
Overall survival			
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
RMST, months [a]	[redacted]	[redacted]	[redacted]
HR versus tepotinib (95% CI)	-	[redacted]	[redacted]
p-value	-	[redacted]	[redacted]
Progression-free survival			
[redacted]	[redacted]	[redacted]	[redacted]
RMST, months [a]	[redacted]	[redacted]	[redacted]
HR versus tepotinib (95% CI)	-	[redacted]	[redacted]
p-value	-	[redacted]	[redacted]

Source: Table 24, CS[1]
CI, confidence interval; ESS, effective sample size; HR, hazard ratio; ITC, indirect treatment comparison; RMST, restricted mean survival time
[a]RMST capped by maximum immunotherapy time (35.1 months for OS and 32.9 months for PFS)

Table 3.15: Summary of ITC efficacy results - untreated

	Tepotinib (n=69)	Immunotherapy (n=20, ESS=69)	Chemotherapy (n=49, ESS=68)
Overall survival			
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
RMST, months [a]	[redacted]	[redacted]	[redacted]
HR versus tepotinib (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
Progression-free survival			
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
RMST, months [a]	[redacted]	[redacted]	[redacted]
HR versus tepotinib (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]

Source: Table 22, CS[7]
CI, confidence interval; ESS, effective sample size; HR, hazard ratio; ITC, indirect treatment comparison; RMST, restricted mean survival time

Table 3.16: Summary of ITC efficacy results – previously treated

	Tepotinib (n=82)	Immunotherapy (n=32, ESS=80)	Chemotherapy (n=34, ESS=80)
Overall survival			
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
RMST, months [a]	[redacted]	[redacted]	[redacted]
HR versus tepotinib (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]
Progression-free survival			
Median, months (95% CI)	[redacted]	[redacted]	[redacted]
RMST, months [a]	[redacted]	[redacted]	[redacted]
HR versus tepotinib (95% CI)	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]

Source: Table 24, CS[7]
CI, confidence interval; ESS, effective sample size; HR, hazard ratio; ITC, indirect treatment comparison; RMST, restricted mean survival time

ERG comment: [redacted]. The summary statistics were not provided for PFS using only PFS data (as opposed to supplemented with TTNTD or time on treatment), but the survival curves appeared to be similar.[7] Similarly, the summary statistics were not provided using only patients with ECOG data: those survival curves do seem to show greater separation between tepotinib and either immunotherapy or chemotherapy, especially of OS versus immunotherapy. The subgroup analysis for the treated is largely in line with the overall population results for OS. [redacted]. Those for PFS in the previously treated are also very similar to the overall population results. [redacted]. Given that the comparators in the scope and as recommended by NICE are according to line of therapy, despite smaller patient numbers, the ERG would argue that the results by treatment experience are the most relevant.

3.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work was undertaken by the ERG.

3.6 Conclusions of the clinical effectiveness section

The company conducted a SLR to identify trial data for epidemiological, prognostic, clinical, humanistic, and economic burden of advanced NSCLC with MET gene alterations. The ERG considers that the eligibility criteria were largely in line with the scope. Thirty-eight publications were included

in the review, although only one trial of tepotinib, VISION, was included. None of the trials of comparator treatments were used for the primary ITC between tepotinib via VISION and any of the comparators since this was performed using PLD.

VISION is a phase II, ongoing, single-arm, open label study in adults with advanced NSCLC with MET exon 14 skipping mutations or MET amplification. Tepotinib, 450 mg, was administered until progression of the disease or undue toxicity (2 tablets, once daily; equivalent to 500 mg tepotinib hydrochloride hydrate). The study was conducted at 141 centres in 11 countries worldwide. The patients in VISION were formed of three cohorts, but only Cohort A and Cohort C included patients relevant to the decision problem, i.e. tepotinib 500 mg for METex14 skipping alterations. The company chose to analyse only cohort A for efficacy and using the February 2021 cut-off, although there were no differences in eligibility criteria or obvious differences in baseline characteristics or outcomes between Cohort A and Cohorts A+C. There was a discrepancy in AE percentages between the values reported in the Safety section of the CS, as supported by the CSR, and values used in the cost-effectiveness analysis, although the latter were higher. Also, there was no justification for and inconsistency in the sources of estimates for the comparators in the cost effectiveness analysis, which makes this a key issue of uncertainty that could be resolved by improving the consistency.

The company performed two types of ITC for the comparison with either chemotherapies or immunotherapies, the main one using propensity scoring combining PLD for the comparators with those from VISION. The second one employed a MAIC. The ERG agreed with the company that the former was clearly the more robust method. In line with the decision problem there were two comparisons with tepotinib: chemotherapy, immunotherapy. The choice of the PLD used for the propensity score matching ITC was not justified by the company: it is likely that it was driven at least to some extent by availability, at least in the case of those studies conducted by the company. The choice of PLD is therefore a key issue of uncertainty. It is also not clear that patient numbers would have been too small for an analysis of comparators by subgroup, specifically histology. This it therefore a key issue of uncertainty, which might be mitigated by further analyses. Use of propensity scores was the method of PLD analysis and it is recommended in TSD 17.[38] However, it is not clear why SMRs were chosen instead of inverse probability of treatment, only the latter being recommended in TSD 17. The ERG considers that the method of estimating the ATT as opposed to the ATE by weighting only the comparator data might have been employed to facilitate comparability between the treatment effects vs. each of the comparator groups. This is because estimates for both immunotherapy and chemotherapy have been adjusted to the same population, which is those of the patients treated with the intervention, in this case the VISION trial. It is also not clear why regression adjustment (RA) or doubly robust methods of combining RA with IPW were not considered. Therefore, the method of PLD analysis remains a key issue of uncertainty, which might be mitigated by further explanation and analyses. In terms of the comparison with an immunotherapy chemotherapy combination, it does seem reasonable to conclude that there were too few patients in the PLD to perform an ITC as for the comparisons with chemotherapy or immunotherapy. However, it is unclear how those three trials listed in Appendix N were identified. It is also unclear why the HRs from only the non-squamous and not the squamous were used: one could have been used for an analysis in the former and the other in the latter subgroup. This is notwithstanding the limitations of the method of applying data from a non-METex14 skipping alterations population and, by using only the HR, assuming proportional hazards.

According to the ITC using propensity scoring, it appears that [redacted]

[redacted]. The subgroup analysis for the treated is largely in line with the overall population results for OS. [redacted]. Those for PFS in the previously treated are also very similar to the overall population results. [redacted]. Given that the comparators in the scope and as recommended by NICE are according to line of therapy, despite smaller patient numbers, the ERG would argue that the results by treatment experience are the most relevant.

4. COST EFFECTIVENESS

4.1 ERG comment on company's review of cost effectiveness evidence

4.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS), was used to inform this critique.[3, 4] The submission was checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[5] The ERG has presented only the major limitations of each search strategy in the report.

Appendix G and Appendix 2 document a standalone literature search conducted to identify cost effectiveness evidence. Searches were conducted on 13 June 2021 with no language or date limits applied to the searches. The bibliographies of systematic reviews and meta-analyses identified after an initial review of search results were searched for references to other potentially relevant studies. As no cost-effectiveness analyses were identified in the database searches, a supplementary search of the NICE website was performed to identify prior health technology assessment (HTA) submissions.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the cost effectiveness systematic review (as reported in CS)

	Resource	Host/source	Date range	Dates searched
Electronic databases	Medline	Ovid	1946-11/06/21	13/06/21
	Embase	Ovid	1974-11/06/21	13/06/21
	CENTRAL CDSR	Wiley	Iss 6/12, June 2021	13/06/21
	DARE NHS EED HTA Database	CRD website	Not stated	13/06/21
Conference proceedings	ISPOR	Internet	2018-2021	13/06/21

CENTRAL = Cochrane Central Register of Controlled Trials; CDSR = Cochrane Database of Systematic Reviews; DARE = Database of Abstracts of Reviews of Effects: NHS EED = NHS Economic Evaluation Database; HTA Database = Health Technology Assessment Database; ISPOR = The Professional Society for Health Economics and Outcomes Research

ERG comment

- Searches were undertaken to identify cost effectiveness evidence in the METex14 skipping alteration NSCLC population. The CS provided sufficient details for the ERG to appraise the literature searches.
- A good range of electronic databases, conference proceedings were searched.
- Searches were clearly documented and structured, making them transparent and reproducible.
- Results were not limited by either publication date or language of publication.
- Search filters were applied to limit the results. The search filter for economic evaluations/costs/economic models developed by the CADTH was used for the MEDLINE and Embase searches.

- The searches conducted for cost effectiveness evidence appear identical to those searches used for clinical effectiveness/HRQoL/resource use, further limited by the addition of the search filter referenced above. The results of the cost-effectiveness searches are therefore a sub-set of those already found by clinical effectiveness/HRQoL/resource use searches.
- Due to the similarity of the searches, many of the ERG comments in Section 3.1.1 are also relevant to the cost-effectiveness searches, and the same limitations to this approach apply.

4.1.2 Inclusion/exclusion criteria

Eligibility criteria for the cost effectiveness systematic review presented in Table 4.2 (reproduced from Table 12 of Appendix G CS). The company considered National Institute for Health and Care Excellence (NICE) preferred methodological principles of conducting systematic reviews for undertaking systematic reviews in health care and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist for reporting the systematic review results.

The company noted the title and abstract of all hits found through the searches assessed by two researchers against eligibility criteria. The full-text of studies that meet the eligibility criteria, reviewed by two reviewers. The conflict between reviewers for both title/abstract and full-text review resolved by third reviewer.

Table 4.2: Eligibility criteria for the systematic literature reviews

Characteristic		Economic evaluations
Population	Inclusion criteria	Patients with advance non-small cell lung cancer with METex14 skipping alterations
Line of therapy	Inclusion criteria	Any line of therapy
Interventions	Inclusion criteria	No restrictions
Outcomes	Inclusion criteria	ICER: Cost per QALY ICER: Cost per LY Cost per QALY Cost per LY Cost-benefit Net present benefit
Study type	Inclusion criteria	Cost-utility analyses Cost-effectiveness analyses Cost-benefit analyses Non-randomised studies will be included (e.g. decision model based analyses, or analyses of patient-level cost and effectiveness data alongside observational studies)
	Exclusion criteria	Studies that measure only costs but not health benefits will be excluded except for stand alone cost analyses from the perspective of the UK NHS. Editorials or commentaries Systematic literature reviews
Year of Publication	Inclusion criteria	Full-text articles published any time Conference abstracts published any time

Characteristic	Economic evaluations
Source: Table 12 Appendix G of CS[1] ICER=incremental cost-effectiveness ratio; LY=life year; QALY=quality adjusted life year	

ERG comment: The ERG considers the company`s eligibility criteria to be satisfactory.

4.1.3 Conclusions of the cost effectiveness review

The CS reported that no relevant studies were included in the cost-effectiveness review.

ERG comment: The ERG has no comments to make.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Complied with reference case
Perspective on costs	NHS and PSS	The company provided NHS and Personal Social Services (PSS) perspective.
Type of economic evaluation	Cost utility analysis with fully incremental analysis	The company has provided a cost-utility analysis with indirect comparison treatment.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The company has provided lifetime horizon for base-case analysis
Synthesis of evidence on health effects	Based on systematic review	The company undertook a systematic review, and evidence from VISION study was the main source used to inform the model.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Yes (QALY based on EQ-5D-5L data from VISION study with a crosswalk to EQ-5D-3L)
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	No
Equity considerations	An additional QALY has the same weight regardless of the	Yes

Element of health technology assessment	Reference case	ERG comment on company's submission
	other characteristics of the individuals receiving the health benefit	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes (costs have been sourced using NHS reference costs, the PSSRU Unit Costs of Health and Social Care and published literature (table 52 p 177) and are reported in pounds sterling for a 2019/2020 cost year)
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

4.2.2 Model structure

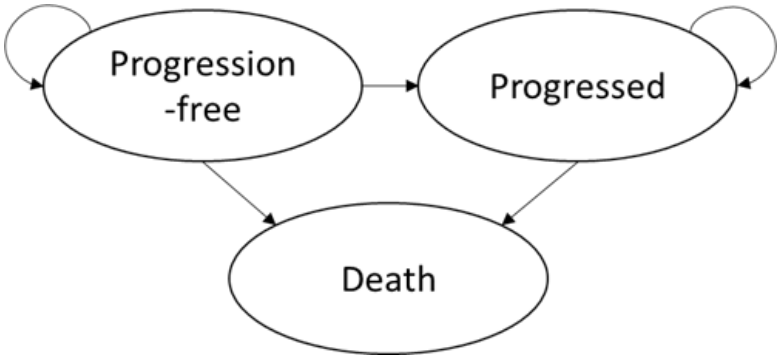
The company developed a de novo model in Microsoft Excel®. The model structure is presented in Figure 4.1. The model is a partitioned survival model (PSM), with three survival states: progression-free survival (PFS), post-progression survival (PPS) and death. All patients started in the progression free state, and they could transition from PFS to PPS or death, and from PPS to death. The time period was partitioned into seven-day periods. Health-related quality of life varied across states. Costs varied across states due to different treatment distributions and the associated monitoring protocols.

The proportion of patients in each state were estimated from the survival curves fitted to Kaplan-Meier curves for PFS and OS for each treatment. The proportion of patients in the PPS state was the difference between the estimates of patients in the OS and PFS states. An ITC based on the evidence identified in the systematic review was conducted to derive the Kaplan-Meier curves. Survival curves were fitted to the Kaplan-Meier curves to extrapolate OS and PFS beyond the follow-up periods of the included studies.

Patients in the progression-free state were given tepotinib until disease progression or toxicity. There were stopping rules for immunotherapy (two years) and chemotherapy (4-6 three-week cycles) in addition to disease progression or toxicity. The proportion of patients on treatment was estimated by modelling the 'on treatment' curve based on the time to stopping treatment data. No further treatment was given to the patients unless they progressed. A percentage of patients making the transition to progression or death from the progression-free state were modelled as receiving subsequent treatment with a one-off cost associated with the duration of the subsequent treatment regimens.

A proportion of patients experiencing an adverse event was modelled for each comparator and costs and utility decrements associated with adverse events were assigned as a one-off in the first cycle of the model.

Figure 4.1: Model structure



Source: Based on Figure 28 of the CS[1]

ERG comment: The ERG considers the company`s model to capture all relevant health states. The ERG also notes that partition survival models have been accepted in a wide variety of oncology settings submitted for NICE appraisal. However, the only justification presented by the company for the use of PSMs was the common use of the method. No argument for why a PSM is better than a state-transition model in this case was presented. The underlying assumptions that the PFS and OS outcomes were extrapolated and modelled independently were not stated.[41]

The ERG notes that including a one-off cost for subsequent treatment means that modelling subsequent treatment for patients departing the PFS state rather than when initial treatment is stopped due to adverse events does not underestimate time on subsequent treatment. Since some patients may die before completing the course of subsequent treatment, the ERG notes that the CS appropriately bases duration on subsequent treatment on published evidence for time on subsequent treatment, rather than recommended treatment regimens.

4.2.3 Population

Economic models with effectiveness evidence for three different populations were developed.

The population in the base-case model was adult patients with advanced NSCLC harbouring METex14 skipping alterations, regardless of treatment history (line agnostic) and histology. This was considered to be in line with the proposed license, final NICE scope and population of the Phase II VISION study. The population characteristics are those of the sample population of the VISION trial (see Section 3.2). The real-world data for the comparators were matched to the VISION trial data.

Subgroup analysis results were presented for untreated and previously treated patient populations. The same methods described below to derive the model parameter estimates apply to each subgroup as well as to the base case population.

A further subgroup of patients contra-indicated or unsuitable to immunotherapy, whether untreated or previously treated, is informed by the evidence from the results for the 3 different populations modelled.

In addition to a pair-wise comparison with chemotherapy for the above reasons, the company also presented a pair-wise comparison with immunotherapy both in the base case results and discussed in the end-of-life section. The ERG initially interpreted this to be for a population for which chemotherapy would be unsuitable; however, the company provided the clarification (to clarification point B26.b and

elaborated in the FAC) that this is not the case and that there is no subgroup for which immunotherapy would be the only comparator.[42]

The justification for not running analyses specifically for different patient groups defined by histology was twofold: firstly, the patient numbers to provide effectiveness evidence for would be too small; and, secondly, the company submission clinical experts stated that the results should be generalisable across histology groups.

The ERG's summary of the decision populations considered in the economic analysis is presented in Table 4.4.

Table .4: The ERG's summary of the decision populations in the economic analysis

Decision population	Comparators	Model population*	Analysis	Threshold (£/QALY)
Overall**	Immunotherapy, Chemotherapy	Overall (base-case)	Full incremental	30,000
Untreated	Immunotherapy, Chemotherapy, Immunotherapy + chemotherapy	Untreated	Full incremental	30,000
Treated	Immunotherapy, Chemotherapy	Treated	Full incremental	30,000
Contra-indicated to Immunotherapy	Chemotherapy	Overall	Pairwise	50,000***

* Based on the effectiveness evidence
** Adult patients with advanced NSCLC harbouring METex14 skipping alterations, regardless of treatment history (line agnostic) and histology
*** This analysis was considered eligible for end-of-life criteria
Source: Information compiled from Company submission

ERG comment: The ERG agrees that the base case population is in line with the population in the NICE scope for tepotinib. However, both in the NICE scope and in the Company's interpretation of the NICE scope, the relevant comparators differ according to untreated or treated status, and by the tumour proportion score for PD-L1. Since the comparators are categories of treatment (chemotherapy, immunotherapy, combined therapy) in the economic analyses rather than specific therapies (see Section 4.2.4), the decision populations in the scope paired with the relevant comparators described as categories are reproduced in Table 4.5. The company submission has not considered these subgroups.

The ERG notes that the company submission does consider a population that is contra-indicated or unsuitable to immunotherapy, which is not a subgroup mentioned in the scope. The company also presented a pair-wise analysis comparing tepotinib with immunotherapy, and the ERG initially interpreted this as an analysis for a population for which chemotherapy was unsuitable; however, the company clarified that there is no subgroup for which immunotherapy would be the only comparator.

Table 4.5: The decision problem subgroups with the relevant comparators

Population	Comparators
Untreated	
Non-squamous PD-L1 ≥50%	Immunotherapy or Immunotherapy + chemotherapy
Non-squamous PD-L1 <50%	Chemotherapy or Immunotherapy + chemotherapy
Adenocarcinoma/large cell carcinoma PD-L1 <50%	Chemotherapy
Squamous PD-L1 ≥50%	Immunotherapy or Immunotherapy + chemotherapy
Squamous PD-L1 <50%	Chemotherapy or Immunotherapy + chemotherapy
Treated	
Squamous PD-L1 ≥50%	Chemotherapy
Squamous PD-L1 <50%	Immunotherapy or Chemotherapy
Source: Adapted from Table 1 in the Company Submission	

4.2.4 Interventions and comparators

The intervention is tepotinib dosed at 450 mg daily until disease progression or toxicity in line with the proposed licence and dose received in the VISION trial. The comparators were the following three treatment categories: immunotherapy, chemotherapy, and combination of immunotherapy and chemotherapy. The relevant comparators varied according to the decision population. These are summarised in Table 4.5. For the overall and treated populations, both immunotherapy alone and chemotherapy alone were relevant comparators to tepotinib. For the untreated population, immunotherapy and chemotherapy combination therapy was a comparator as well as immunotherapy alone and chemotherapy alone. For the contra-indicated to immunotherapy population, the relevant comparator was chemotherapy alone. For the population for whom chemotherapy is not considered, the relevant comparator was immunotherapy alone.

The real-world data sets included in the ITC were considered to be too small for individual immunotherapy or chemotherapy treatments to be modelled separately (see Section 3.4.1). There were a mix of immunotherapy and chemotherapy treatments included in the real-world ITC data set. The treatment mix for the real-world data set for the effectiveness analysis used in the base case economic analysis is presented in Table 4.6.

The treatment distribution used in the economic model differs from the treatment distribution in the real-word data set matched to the VISION data set (CS Table 20 and Table 21). The company clarified in the Factual Accuracy Check (FAC) that weighted numbers were used in the economic model to produce treatment distributions to align with the weighted efficacy data. However, the ERG does not know how these weights were calculated. They could not be reproduced. The percentages used in the model differed slightly from those in Table 4.7 slightly, which was an error as they percentages did not sum to 100%. The method by which the proportions in Table 4.7 were derived was not perfectly clear, although the response to clarification point B8 presented how treatments in the data set were classified

as treatments in the economic model. An example (for the untreated population) on how treatments not used in the UK or treatments specified as a class (e.g. immunotherapy) were re-classified proportionally across the other treatments was presented in the response to clarification point B11. These details are reported in Appendix 2, along with an ERG attempt at recalculating the treatment distribution.

For the purpose of costing, the company also considered an alternative mix of treatments for UK clinical practice based expert opinion (see Section 4.2.6).

No stopping rule was applied in the model (base-case analysis or in scenario analysis) for tepotinib treatment discontinuation. Patients may stop treatment due to adverse events or progression. There were stopping rules for the comparators: two years for immunotherapy, and a maximum of six cycles for chemotherapy. Time on treatment (ToT) was modelled using the data from VISION for tepotinib and literature for the comparators (see Section 4.2.9).

Table 4.6: Treatment distributions for immunotherapy and chemotherapy included in the model base-case: previously treated

Category	Treatment	Real-world data (base case)	Clinical expert opinion (scenario)
Immunotherapy	Pembrolizumab	[redacted]	[redacted]
	Atezolizumab	[redacted]	[redacted]
	Nivolumab	[redacted]	[redacted]
	Nivolumab + ipilimumab	[redacted]	[redacted]
Chemotherapy	Docetaxel + platinum	[redacted]	[redacted]
	Gemcitabine + platinum	[redacted]	[redacted]
	Paclitaxel + platinum	[redacted]	[redacted]
	Vinorelbine + platinum	[redacted]	[redacted]
	Pemetrexed + platinum	[redacted]	[redacted]
	Docetaxel monotherapy	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]
	Docetaxel + gemcitabine a	[redacted]	[redacted]
	Gemcitabine monotherapy a	[redacted]	[redacted]
	Vinorelbine monotherapy a	[redacted]	[redacted]

Source: Table 33, CS[1]

ERG comment: The ERG notes that the individual comparators stated in the NICE scope were not included in the economic analysis. Immunotherapy and chemotherapy intervention categories were included rather than specific treatments. The company made the argument that the data set was too small to model specific treatments. Three specific treatments with more than 10 patients were included in the data set: carboplatin and pemetrexed (20), pembrolizumab (20), and nivolumab (11) (Table 20 and Table 21 CS).[1] The ERG agrees that the possibility of specific treatment comparisons is limited. For the decision populations that have been considered for analysis, the comparators appear to be appropriate, although the clinical context as to why immunotherapy alone might be the only relevant comparator to tepotinib in some circumstances was not explained. In the NICE scope, immunotherapy alone and chemotherapy alone are not both comparators for any one subgroup in the untreated population, but they are both relevant comparators for squamous, PD-L1 <50% patients in the treated group.

The method for calculating the proportions of treatments within the immunotherapy and chemotherapy categories was not clearly stated and the ERG could not reproduce the results; the ERG calculated a different distribution using the information presented by the company in the response to the letter of points for clarification. The company clarified that weighted numbers were used in the economic model to produce treatment distributions to align with the weighted efficacy data. However, the ERG does not know how these weights were calculated.

4.2.5 Perspective, time horizon and discounting

The analysis was performed from the UK National health Service (NHS) and Personal Social Services (PSS) perspective.

The time horizon in the model was stated to be 30 years in the company submission. The Excel model was programmed to run for 33.6 years from the starting age of 73 years., Costs and benefits were discounted at an annual rate of 3.5% as per the NICE reference case.[43][#NICE methods guide] A one-week cycle length was implemented in the model and no half-cycle correction was applied.

ERG comment: The ERG notes that the time horizon in the model was sufficiently long to capture the healthcare resource use and health outcomes affected by the interventions. It is in line with the NICE reference case. No half-cycle correction was necessary given the short cycle length.

4.2.6 Treatment effectiveness and extrapolation

The effectiveness data relevant to the model were the relative PFS and OS for tepotinib and the comparators. No relative effect data were included in the model. Instead, independent survival curves for each treatment for each outcome were included. The effectiveness evidence for tepotinib compared to immunotherapy and chemotherapy was obtained from the systematic review of clinical studies and ITC described in Sections 3.1 to 3.4. The process to derive the effectiveness data is summarised as follows:

- A systematic review of clinical studies
- Single arm studies with individual patient data were included for analysis
- Comparator data sets were matched to the tepotinib VISION trial population characteristics
- A data cleaning process adopted to identify relevant comparator treatment from comparator data sets
- Investigator assessment of PFS in VISION was selected over Independent Review Committee assessment as more likely to match PFS as reported in real-world data for comparators
- Time to next treatment or death (TTNTD) used for missing PFS data in real-world data sets
- Kaplan-Meier curves were generated for each treatment for PFS and OS
- To extrapolate survival beyond clinical follow-up, survival models (curves) fitted to data
- Several survival models (curves) were generated and compared to the Kaplan-Meier plots
- Clinical expert opinion alongside AIC and BIC statistics helped select the appropriate model
- The relative effect of tepotinib is the difference between the tepotinib and comparator curves over time

This section is concerned with fitting and selecting the survival models for each treatment. The company argued that investigator assessment of PFS in VISION is more closely aligned with the classification in the real-world data. The company also argued that the use of TTNDT as a proxy for PFS in the real-world data set is a conservative estimate of PFS with respect to tepotinib.

To extrapolate PFS and OS beyond the data collection period, the company followed the guidelines for survival model selection outlined in the NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 14 and 21.[44, 45] For this, Kaplan-Meier curves from VISION trial data (for tepotinib) and real-world data (for comparators) were produced. The company fitted different parametric survival models (PSMs), piecewise models and spline models to the individual patient data.

The model selection criteria were as follows. The same set of six parametric survival curves (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) were fit to the data for each outcome for each treatment. If these were considered a poor fit, spline models were fit to the data. Odds, hazard and normal restricted cubic spline models, varying from one to three knots, were fitted to the data, in line with NICE TSD 21.[45] If the spline models were also considered an extremely poor fit, piece-wise parametric curves were fit to the data. Models were fit using R. The AIC and BIC statistics for all the models that converged were reported.

The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness of fit statistics; the visual assessment of the appropriate diagnostic plot for the parametric model (log-cumulative hazard, logit survival, inverse normal survival, smoothed hazard); and expert opinion on the clinical plausibility of the long-term survival profile were considered in the selection of the survival model for use in the economic model. The expert panel comprised four clinical experts and two UK HTA experts. The cost-effectiveness results using alternative survival models were reported in scenario analyses (see Section 5.2).

Overall survival

For tepotinib, the PSMs were fitted to the data. These are presented in Figure 4.2. The best fitting model was the log-logistic model and this was selected for the economic analysis.

Figure 4.2: Parametric curve fits-tepotinib OS

(Source: Figure 30 CS[1])

For chemotherapy, PSMs were fitted to the data. These are presented in Figure 4.3. The best fitting model according to the AIC statistic was the generalised Gamma model. The best fitting model according to the BIC statistic was the log-normal model. The Weibull model was selected for the economic analysis based on expert opinion that considered overall survival prediction to be too high at five years (>12%).

Figure 4.3: Parametric curve fits-chemotherapy OS

(Source: Figure 32 CS[1])

For immunotherapy, spline models as well as PSMs were fitted to the data. These are presented in Figures 4.4 and 4.5. The best fitting model according to the AIC statistic was the generalised Gamma and normal two knot spline models. The best fitting model according to the BIC statistic was the generalised Gamma model followed by the normal two knot spline model. The one knot normal spline model was selected for inclusion in the model based on expert opinion as the best fitting models were considered to underestimate survival between three and eight years.

Figure 4.4: Parametric curve fits-immunotherapy OS

(Source Figure 33 CS[1])

Figure 4.5: Spline curve fits-immunotherapy OS

(Source: Figure 34 CS[1])

Progression-free survival

For tepotinib, only the PSMs were fitted to the data. These are presented in Figure 4.6. The best fitting model was the log-normal model and this was selected for the economic analysis.

Figure 4.6: Parametric curve fits-tepotinib PFS

(Source: Figure 38 CS[1])

For chemotherapy, spline models as well as PSMs were fitted to the data. These are presented in Figures 4.7 and 4.8. The best fitting model was the odds three knot spline model. This was followed by the odds one knot spline model. The odds one knot spline model was selected for the economic analysis based on expert opinion that considered an overall survival prediction of 1% at five years to be reasonable.

Figure 4.7: Parametric curve fits-chemotherapy PFS

(Source: Figure 40 CS[1])

Figure 4.8: Parametric curve fits-chemotherapy PFS

(Source: Figure 41 CS[1])

For immunotherapy, piecewise parametric models and spline models as well as PSMs were fitted to the data. The piecewise parametric models are presented in Figure 4.9. The best fitting model was the hazard one knot model. This was followed by the odds one knot and normal one knot spline models. The piecewise log-logistic model was selected for inclusion in the model based on expert opinion as it was expected that 1-4% would be progression free at five years.

Figure 4.9: Parametric curve fits (piece-wise)-immunotherapy PFS

(Source: Figure 42 CS[1])

Overall survival curve comparisons

The overall survival curves for tepotinib and chemotherapy selected for the economic analysis are presented in Figure 4.10.

Figure 4.10: Base-case OS extrapolations- chemotherapy

(Source: Figure 35 of CS[1])

The overall survival curves for tepotinib and immunotherapy selected for the economic analysis are presented in Figure 4.11.

Figure 4.11: Base-case OS extrapolations-immunotherapy

(Source: Figure 36 of CS[1])

Progression-free survival curve comparisons

The overall survival curves for tepotinib and chemotherapy selected for the economic analysis are presented in Figure 4.12.

Figure 4.12: Base-case PFS extrapolations-chemotherapy

(Source: Figure 43 of CS[1])

The overall survival curves for tepotinib and immunotherapy selected for the economic analysis are presented in Figure 4.13.

Figure 4.13: Base-case PFS extrapolations-immunotherapy

(Source: Figure 44 of CS[1])

Combined therapy (immunotherapy and chemotherapy)

Combined therapy was a comparator in the untreated population. Due to a lack of data with which to estimate the survival curves for combined therapy (immunotherapy and chemotherapy), a hazard ratio for combined therapy versus chemotherapy was applied to chemotherapy OS and chemotherapy PFS. The hazard ratios were obtained from KEYNOTE-189.[16][#Keynote] These were HR for OS of 0.64 (95% CI: 0.43 – 0.95) and HR for PFS of 0.75 (95% CI: 0.55 – 1.02).

Untreated and treated populations

The same process was followed for the untreated and treated subgroups. Treatment line in the real-world data sets was categorised in the same way as for the VISION data set: the first line of therapy was the first therapy received post diagnosis of advanced or metastatic disease.

ERG comment: The ERG notes that there is considerable uncertainty in the effectiveness of tepotinib compared to immunotherapy and chemotherapy in extending PFS and OS due to the issues identified in Section 3: the single-arm clinical evidence, limited follow-up periods, possible imperfect matching of real-world and VISION data sets, data cleaning issues and missing data. Uncertainty associated with these issues cannot be captured in the economic analysis results. The argument that TTNTD may be a conservative proxy for PFS for missing data in the real-world data set seems plausible.

The ERG notes that the CS follows recommendations in the Technical Support Documents 14 and 21 for the selection of the models to fit to the data, and for the selection of models to use in the economic analysis[44, 45]. The criteria for fitting piecewise models was not perfectly clear. The ERG also notes that the selected models for immunotherapy are conservative for tepotinib compared to the best fitting models, and the selected models for chemotherapy are favourable for tepotinib compared to the best fitting models.

The clinical experts have considered that the best fitting models under- or over-estimate PFS or OS at five years or between three and five years. On that basis they have selected alternative models. There are three possible reasons for the survival models under- or over-estimating PFS and OS beyond the data collection period: (1) the sample population in the VISION trial is not representative of the overall population, (2) the real-world data set for the comparators was inadequately matched to the VISION trial population, (3) another more flexible model is required to model survival but there is insufficient data to model it. An example of issue (2) is that the Company argue that the benefit of tepotinib may be underestimated due to the greater use of more aggressive treatments in the real-world data set. An example of issue (3) is that another survival model with another knot/piece near the end of data collection period may actually be a better fit, but of course there would not be any data to identify that knot/piece.

If the trial populations are representative of the UK decision population and issue (3) is the problem, then there is a trade-off between estimating relative effectiveness within the data collection period and beyond the data collection period: to improve long-term projections you need select the model that is not the perfect fit within the data collection period. If issue (2) were the problem then selecting another model based on clinical expert opinion goes part way to resolve it as you are potentially correcting for bias, although the selected model will not ideally model survival, and there is uncertainty in the expert assessment of future survival. If issue (3) were the problem then selecting another model based on clinical expert opinion for immunotherapy and chemotherapy but not for tepotinib means that you are trying to adjust for selection bias for one comparator but not for tepotinib, thus increasing bias in the relative effectiveness of tepotinib compared to the comparators. The experts have knowledge about long-term survival for the comparators but not for tepotinib.

Technical Support Document 21 notes that the model fit within the data collection period should remain good when using external data to model future outcomes.[45] The ERG notes that the selected models in some cases are not the best fit but that in most cases the fit statistics are within 5 points, suggesting multiple options are suitable. It is not known which of these issues or combination of issues is the problem, so the survival models used in the base case economic analysis may only be one of the plausible set of assumptions. The ERG considers an alternative set of survival assumptions in Section 6.

4.2.7 Adverse events

Both the utilities and costs of adverse events were included in the model. The dis-utilities of adverse events were included as a one-off utility decrement at the start of the model (see Section 4.2.8). The cost of adverse events were included as a one-off cost at the start of the model (see Section 4.2.9). Grade ≥3 adverse events with a prevalence greater than 5% were included in the economic analysis. The proportion of patients experiencing each adverse event were obtained from the VISION study for tepotinib and from previous NSCLC appraisals and literature for the comparators. The proportion of each adverse event for tepotinib, chemotherapy treatments and immunotherapy treatments has been reproduced in Tables 3.10 and 3.11 in Section 3.2.3. As discussed in that section, the percentages of adverse events used in the economic model differ from those reported in the CS Table 28.[1] The method was not described in the CS.

ERG comment: The ERG notes that the proportions of adverse events for the comparators may not always come from the studies with the same sample population characteristics as the decision population characteristics in this appraisal. It is, however, likely that the best available evidence was

used. The ERG also considers that while a 5% inclusion threshold is quite high, this may be due to small numbers and the ERG does not expect this assumption to materially impact the ICER.

The percentages of adverse events used in the economic model differ from those reported in the real-world data sets. The method for deriving the percentages was not reported. The difference in percentages may be related to the process of re-classifying non-UK treatments and treatments classified as a treatment class as one of the other treatments in the data set, proportionally according to the treatment prevalence. The result of this process is an increase in the proportion of patients on the remaining treatments. Proportions of adverse events would then be related to the included treatments and the percentage of patients receiving each treatment.

4.2.8 Health-related quality of life

Utility values for progression-free survival (PFS) and disease progression (PPS) health states were included in the model. Utility decrements were also included for the proportion of patients who experienced a Grade ≥3 adverse event. The utility for PFS applied for the duration in the PFS state, and the utility for OS applied for the duration in the OS state. The utility decrement for an adverse event was included at the beginning of the model as a one-off decrement. This was a weighted average of the utility decrements for the adverse events experienced by patients receiving tepotinib or a comparator. The proportion of patients experiencing an adverse event was discussed in Section 4.2.7 and the proportions were reported in Tables 3.10 and 3.11 in Section 3.2.2.

Progression-free survival and progression utilities

The utility values used in this model to represent progression free and progressing NSCLC are sourced from the VISION trial. Participants in this trial completed the EQ-5D-5L, EORTC-QLQ-C30 and EORTC QLQ-LC13. The questionnaires were to be completed every six weeks from Cycle 1, Day 1 until nine months and every 12 weeks thereafter until disease progression, death or withdrawal of consent. The study data recorded 973 EQ-5D-5L observations were available from 150 of the 151 patients. The majority of observations (808 observations, 150 patients) were in the pre-progression state and with the other observations being in the post progression (165 observations, 101 patients). The EQ-5D-5L data was cross walked to the existing EQ-5D-3L dataset as currently recommended by NICE using an established mapping algorithm.[46]

A linear mixed model was utilised to account for the overall mean pattern of change over time. Three models were utilised: progression, progression + baseline observation, and progression + baseline observation + treatment line. Treatment line in this instance relates to whether or not the patient had previous treatment or not. Whilst the inclusion of the baseline observation was found to be good predictor of utility values, treatment line was not found to improve the fit of the model. As such the for the base case of the model the progression + baseline observation were utilised. A summary of these utility values used in the cost effectiveness analysis is provided in Table 4.7.

For the purpose of conducting scenario analysis around the utility of progression-free and progressed states, the Company conducted a systematic literature review of studies estimating utility for these states in the decision population. No studies were found. The Company further conduced a target search for technology appraisals in this oncology area.

Table 4.7: Health state utility values

Health state	Utility value	Reference	Justification
Progression Free NSCLC	0.719	VISION trial Data	EQ-5D values derived from a relevant METex14 patient population
Progressing NSCLC	0.638	VISION trial Data	EQ-5D values derived from a relevant METex14 patient population
Source: CS[1]			

Disutility values

There are a number of adverse events which are included in this model. The disutility values for each of these events are presented below in Table 4.8.

Table 4.8: Health state disutility values

Health state	Disutility value	Reference	Justification
ALT increase	-0.050	Duration from VISION trial (54.8 days). Assumption based on TA347	Assumed equivalent to a similar adverse event
Alopecia	-0.045	Duration from VISION trial (37.2 days) disutility from Nafees et al. (2008)	Identified through targeted literature search and based on values
Amylase increase	-0.050	Duration from VISION trial (76.0 days) same assumption as ALT Increase	Assumed equivalent to a similar adverse event
Anaemia	-0.073	Duration from Vision trial (3.0 days) Assumed same as fatigue as per TA181	Assumed equivalent to a similar adverse event
Asthenia	-0.073	Duration from Vision Trial (52.0) Assumed same as fatigue.	Assumed equivalent to a similar adverse event
Bilirubin increased	-0.050	Duration based on mean duration of all AEs in VISION trial (Assumed same as ALT increase 37.2 days) Assumed same as ALT increase37.2	Assumed equivalent to a similar adverse event
Cardiac failure	-0.105	Duration based on VISION trial (9.5 days), values from McMurray et al, 2018)	Identified through targeted literature search.

Health state	Disutility value	Reference	Justification
Cough	-0.046	Duration based on VISION trial (22 days) Doyle et al. (2008)	Identified through targeted literature search.
Diarrhoea	-0.047	Duration based on VISION trial (3.0 days). Values from Nafees et al. (2008	Identified through targeted literature search.
Dyspnoea	-0.050	Duration based on VISION trial (18.8 days).Values from Doyle et al. (2008)	Identified through targeted literature search.
Fatigue	-0.073	Duration based on VISION trial (212.0).Values from Nafees et al. (2008).	Identified through targeted literature search.
Febrile neutropenia	-0.090	Duration based on TA628 (7.1 days). Values from Nafees et al. (2008)	Identified through targeted literature search and assumptions from previous TAR
Hyperglycaemia	-0.122	Duration based on VISION trial (1.0 days). Utilities based on Palmer et al. (2016) Currie et al. (2006)	Identified through targeted literature search
Hypertension	-0.030	Duration from VISION trial (150.0 days) Utilities from Paracha et al. (2018) (Nafees et al. 2016)	Identified through targeted literature search
Hypoalbuminemia	-0.050	Duration from VISION trial (344.1 days). Utilities assumed the same as white blood cell decrease	Assumed the same as similar utility.
Hypomagnesemia	-0.0028	Duration from VISION trial (7.0 days) From CADTH (2020) (based on Sullivan et al. (2011))	Identified through targeted literature search
Infection	-0.050	Duration from VISION trial (15.0 days). Assumption based on TA347	Assumptions from previous TAR
Leukopenia	-0.090	Duration from VISION trial (200.0	Assumed the same as similar utility.

Health state	Disutility value	Reference	Justification
		days). Assumed same as neutropenia as per TA520	
Lipase increase	-0.073	Duration from VISION trial (38.2 days) Assumed same as anaemia	Assumed the same as similar utility.
Lymphocyte count decrease	-0.05	Duration from VISION trial (46.0 days) Assumed same as white blood cell decrease.	Assumed the same as similar utility.
Nausea	-0.048	Duration from VISION trial (10.5 days) Nafees et al. (2008).	Identified through targeted literature search
Neuromotor	-0.150	Duration Assumed based on mean duration of all AEs in VISION (37.2 days). Tabberer et al. 2006	Identified through targeted literature search
Neurosensory	-0.150	Duration Assumed based on mean duration of all AEs in VISION (37.2 days). Tabberer et al. 2006	Identified through targeted literature search
Neutropenia	-0.090	Duration from VISION trial (158.0). Utilities from Nafees et al. (2008)	Identified through targeted literature search
Neutrophil count decrease	-0.090	Duration from VISION trial (2.5 days). Assumed same as neutropenia	Assumed the same as similar utility.
Oedema peripheral/other	-0.085	Duration from VISION trial (180.9 days). Utilities from Hagiwara et al. (2018)	Identified through targeted literature search
Pain	-0.069	Duration from VISION trial (31.0 days). Doyle et al. (2008)	Identified through targeted literature search
Platelet count decrease	-0.050	Duration assumed based on mean duration of all AEs in VISION (37.2 days) Assumed same as	Assumed the same as similar utility.

Health state	Disutility value	Reference	Justification
		white blood cell count decrease	
Pleural effusion	-0.008	Duration from VISION trial (125.1 days). Assumed same as pneumonia	Assumed the same as similar utility.
Pneumonitis / pneumonia	-0.008	Duration from VISION trial (19.6 days). Utilities from Marti et al. (2013) as per TA655 and TA520	Identified through targeted literature search
Pulmonary/respiratory tract infection	-0.186	Duration from VISION trial (33.9 days) Hunter et al. (2015) as per TA520	Identified through targeted literature search
Thrombocytopenia	-0.003	Duration assumed based on mean duration of all AEs in VISION (37.2 days) Utilities from Handorf et al. (2012)	Identified through targeted literature search
Vomiting	-0.048	Duration from VISION trial (2.0 days). Utilities from Nafees et al. (2008	Identified through targeted literature search
White blood cell count decrease	-0.050	Duration assumed based on mean duration of all AEs in VISION (37.2 days). Assumption based on TA347	Assumptions from previous TAR
Source: CS[1]			

ERG comment: The utilities used in the base-case analysis for the progression-free state and the progressed state were based on the results of the VISION trial. The company used the results of the linear mixed model that included progression and baseline observation to inform the model. The ERG considers the statistical analysis to estimate the utility values to be appropriate. However, the trial was ongoing and there may be significant missing follow-up data. Further data could significantly improve accuracy of estimates would be informative, particularly given the high frequency of data collection points and the large difference between observations in pre and post progression values.

The ERG notes that the utility values derived from literature for AEs may not be representative of the study population and may not be the preferred measure of utility for the NICE Reference case. However, the ERG notes that these may be the best available estimates and have been used in previous NSCLC NICE submissions. Examples of generalisability and NICE reference case issues follow.

Nafees et al (2008) is used to value a number of different states.[47] This study utilises a Standard Gamble technique on a sample of the general population recruited from a local London newspapers

and from an existing UBC database of willing survey participants. This study population is not fully representative of the UK population. It should also be noted that this study does not anchor the utility values at death, but rather in a "worst health" state which is painful and distressing state described by the authors. Given the shorter life expectancy of eight months, this could potentially make participants more reticent to trade compared to death and lower the resulting utility values. Doyle et al uses the same approach as Nafees et al (2008), a small sample (101) based on a SG not anchored to death. Similar issue may be present with these utility values.[48] Tabberer et al. was provided as a source, for disutility values for "Neuromotor" or "Neurosensory". This is conference abstract describing a study of 154 lay members of the public using the EQ-5d-3L there are no utilities in this study that match these descriptions.[49] Marti et al. is given as a source for "Pleural effusion" and "Pneumonitis / pneumonia", this value is from Bennett et al (2000).[50, 51] This is a study of 96 parents valuing health states via a computer based standard gamble exercise. As this is a proxy measure for a paediatric population these values may not be applicable in this population. The value for "Thrombocytopenia" is reported from Hunter et al (2015).[52] This study used a valuation Oppong et al (2013).[53] This value is derived form an expert opinion which is not an optimal evidence source.

4.2.9 Resources and costs

The company included the following costs in the economic model: testing for METex14 skipping alterations, drug acquisition and administration costs for tepotinib and the comparators, drug acquisition and administration costs for subsequent treatments, the cost of treating adverse effects, and terminal care costs.

Testing for METex14 skipping alterations

The company noted that Next generation sequencing (NGS) testing is already performed for non-squamous patients and based on clinical expert point of view the cost associated with METex14 skipping alterations testing in squamous patients was applied to the tepotinib arm as a one-off cost at the start of the model. The total cost is calculated using the expected incidence rate of METex14 skipping alterations in squamous patients and the cost of NGS provided in Table 54 in the CS.

Tepotinib and comparator drug costs

Time on treatment

Time on treatment was modelled using the same time to event (treatment cessation) analysis methods as described for PFS and OS survival analysis in Section 4.2.6. There is no specified time limit to receive tepotinib. In the model, a patient may remain on tepotinib until disease progression or adverse events.

For tepotinib, only the PSMs were fitted to the data. These are presented in Figure 4.14. The best fitting model according to the AIC statistic was the log-logistic model. The best fitting model according to the BIC statistic was the exponential model. The generalised Gamma model was selected for the economic analysis as expert opinion considered most people would be off tepotinib at five years.

Figure 4.14: Parametric curve fits-tepotinib ToT

(Source: Figure 45, CS[1])

For immunotherapy and chemotherapy, the company stated that the real-world data were too limited to estimate ToT curves, and instead they used estimates of mean and median duration on treatments from the literature (Table 39 in CS) to estimate ToT and then modelled exponential distributions using those data.[1] A cap was included to ensure that the proportion of patients on treatment was lower or equal to the proportion of patients in the PFS state. The company also presented other options for ToT for the comparators: (1) equating ToT with PFS (100% on treatment in the PFS state), and (2) applying the hazard ratio for ToT and PFS for tepotinib to the PFS for the comparators to get ToT for the comparators. These were alternatives in scenario analyses. While there was no time limit (stopping rule) for tepotinib, there were stopping rules for immunotherapy (two years) and chemotherapy (4-6 three-week cycles) in addition to disease progression or toxicity. The dosing schedule for each treatment was taken from the treatments summary of product characteristics (SmPC). The company also considered treatment stopping rules based on both SmPc and NICE guidance with a conservative approach (choosing higher end treatment cycle).

Dose intensity

The tepotinib dose is 450 mg daily and can be reduced to 225 mg in the case of adverse events of grade ≥ 3. In the VISION trial, doses could be reduced to 300 mg in the event of adverse events. Further reductions were by discussion. The dose intensity of tepotinib is significantly lower than the dose intensity for most comparator treatments. The company noted (in clarification response) that an explanation is that tepotinib is an oral therapy and it is easier to reduce the dose than for chemotherapy and immunotherapy treatments. Tepotinib had similar dose intensities to other oral treatments for NSCLC (e.g., brigatinib had a dose intensity of 88.9% and ceritinib had a dose intensity of 83.6%).

Table 4.9: Drug dose and intensity (adapted from CS Table 51)

Drug	Dose	Dose intensity
Tepotinib	500 mg once daily	[redacted]
Pembrolizumab	200 mg Q3W	99.2%
Atezolizumab	1,200 mg Q3W	97.7%
Nivolumab	240 mg Q2W	99.2%
Nivolumab	360 mg Q3W	99.2%
Ipilimumab	1 mg/kg Q6W	99.2%
Docetaxel	75 m^2 Q3W	94.0%
Cisplatin	75 m^2 Q3W	94.0%
Carboplatin	AUC 5 Q3W	93.0%
Gemcitabine	1,250 mg/m^2 Q3W day 1 and 8	85.8%
Cisplatin	80 m^2 Q3W	93.5%
Carboplatin	AUC 5 Q3W	93.5%
Paclitaxel	175 mg/m^2 Q3W	94.0%
Cisplatin	80 mg/m^2 Q3W	94.0%
Carboplatin	AUC 5 Q3W	93.0%
Vinorelbine	25 mg/m^2 day 1 and 8 Q3W	78.0%
Cisplatin	80 mg/m^2 Q3W	78.0%
Carboplatin	AUC 5 Q3W	78.0%
Docetaxel	75 m^2 Q3W	98.7%
Docetaxel	75 m^2 Q3W	98.1%
Nintedanib	200 mg twice daily days 2-21 Q3W	91.2%
Docetaxel	75 m^2 Q3W day 8	98.0%
Gemcitabine	1,000 mg/m^2 Q3W day 1 and 8	98.0%
Vinorelbine	30 mg/m^2 day 1 and 8 Q3W	93.0%
Pemetrexed	500 mg/m^2 Q3W	94.8%
Cisplatin	75 m^2 Q3W	95.0%
Carboplatin	AUC 5 Q3W	95.0%
Pemetrexed	500 mg/m^2 Q3W	93.7%
Pembrolizumab	200 mg Q3W	95.6%
Pemetrexed	500 mg/m^2 Q3W	95.6%
Cisplatin	75 m^2 Q3W	95.6%
Carboplatin	400 mg/m^2 Q3W	95.6%
Atezolizumab	1,200 mg Q3W	94.0%
Bevacizumab	15 mg/kg Q3W	93.8%
Carboplatin	AUC 6 Q3W	93.8%
Paclitaxel	200 mg/m^2 Q3W	93.8%

Acquisition costs

The unit costs of packets of tablets or different vial sizes (CS Table 50) were obtained from either the British National Formulary (BNF), the Drugs and pharmaceutical electronic market information tool

database (eMIT) for chemotherapy or immunotherapy treatments, or the Company for tepotinib.[54, 55] After the reduction in dose according to the dose intensity, the pack of 60 x 250 mg tepotinib tablets cost [redacted] or [redacted] with a [redacted] PAS discount. The PAS discount is indicative only and has been submitted to the Patient Access Scheme Liaison Unit (PASLU).

The quantity of each drug (tepotinib, specific immunotherapy and chemotherapy treatments) required for each dose according to the dosing schedule multiplied by the dose intensity for each patient in the VISION trial was estimated, and the cheapest number of tablets or vials required to achieve that dose was calculated.

The treatment regimens included in the economic analysis are summarised in Table 4.7, Section 4.2.4, along with the proportions of patients receiving each treatment. The proportion of treatments was derived from the real-world data set treatment distribution with ambiguous treatments within a class (e.g. immunotherapy) or treatments unavailable in the UK redistributed proportionally amongst treatments available in the UK. Each individual treatment was included in the model and the cost of immunotherapy was the weighted average of the individual immunotherapy treatment costs and the cost of chemotherapy was the weighted average of the individual chemotherapy treatment costs.

The distribution of chemotherapy and immunotherapy treatments will have affected both the survival outcomes and cost of immunotherapy and chemotherapy. The company elicited the opinions of clinical experts on the distribution of immunotherapy and chemotherapy treatments that reflect UK practice. These distributions are also reported in Table 4.7, Section 4.2.4. This distribution was used in scenario analysis.

Subsequent treatment costs

Subsequent treatment costs were calculated from the proportion of patients receiving each subsequent treatment, the mean duration of receiving that subsequent treatment, and the unit cost for the dosing schedule.

Subsequent treatment data from VISION were used to derive proportions of patients receiving each treatment as a subsequent treatment for tepotinib, and subsequent treatment data from the real-world data sets were used to derive proportions of patients receiving each treatment as a subsequent treatment for the comparators. The Company had to apply several assumptions in the data cleaning process to classify subsequent treatments given the ambiguity in the data sets. The percentages of patients receiving subsequent treatment for each initial therapy and for each population are reported in Table 4.10. Table 57 in the CS reports the percentages of each subsequent treatment for each initial treatment. Chemotherapy has the highest proportion of patients receiving subsequent treatment.

The company also produced scenarios which reflected subsequent treatment distributions in the UK by eliciting clinical expert opinion. The company noted that there is an inconsistency altering the cost of the distribution without altering the effectiveness.

The mean duration receiving the subsequent treatment was obtained from a variety of published studies.

Table 4.10: The percentages of patients receiving subsequent treatment and the unit cost per patient receiving subsequent treatment

Initial therapy	%	Cost/patient (£)
Tepotinib	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]

Initial therapy	%	Cost/patient (£)
Immunotherapy	[redacted]	[redacted]
Source: Table 57 CS[1]		

Administration costs

The company reported the administration costs for each treatment (CS Table 52). The administration cost for tepotinib is [redacted], based on 12 minutes of a band 6 radiologist time. The cost for infusion delivered immunotherapy and chemotherapy was obtained from HRG codes in the NHS Reference Costs.[56]

Monitoring and disease management costs

The estimated per week monitoring and disease management costs were £79.11 and £143.88 per week respectively, for progression-free and progressed period. The costs were derived from data obtained from the NHS Reference Costs and a health technology assessment for adult patients with advanced or metastatic NSCLC.[56, 57]

Adverse effects costs

The company presented adverse event costs included in the model (CS Table 55). The costs were obtained from HRG codes in the NHS Reference Costs.[56] The unit cost of each adverse event is applied to the incidence rate of the adverse event for each treatment (Table 41 and Table 42).[1] The total cost of adverse event for tepotinib £924.06.

Terminal care cost

The terminal care cost was £4,478.80 per patient. The calculation details were reported in CS Table 58.[1] The resource use frequencies are based on a health technology assessment for adult patients with advanced or metastatic NSCLC by Brown et al. (2013) and is consistent with the source used in other NSCLC appraisals.[57]

ERG comment: The treatment distributions for the immunotherapy and chemotherapy treatment classes, and the treatment distribution for the subsequent treatments, are all based on clinical studies conducted in countries other than the UK. While treatments not used in the UK were reclassified as comparable treatments used in the UK, the prevalence of the use of these treatments may not be representative of their use in the UK. The company produced alternative treatment distributions for both the comparator treatments and the subsequent treatments that were more likely to represent the UK use of these treatments. The company argued that for the subsequent treatments it is better to use the treatment distribution based on the real-world data set in the economic model in order to maintain the relationship between the effectiveness and cost outcomes. The ERG agrees with this. The company stated in the FAC that they did not make that argument for comparator treatment distributions as the comparators were grouped with treatments of similar efficacy.[42] The ERG considers that without evidence for equal efficacy the real world data treatment distribution are most appropriate.

There was some uncertainty in the cost estimates for immunotherapy and chemotherapy. The average cost for each of these was based on a weighted average of the cost of the individual treatments. Firstly, the Company first classified each of the treatments as a specific treatment for costing, and it was not clear why pemetrexed should be costed the same as Carboplatin and pemetrexed. Secondly, it was unclear how the treatment distribution percentages were derived. The ERG could not reproduce the distributions (see Appendix 1).

The ERG notes that while the Company selected the generalised Gamma model for ToT for tepotinib, the exponential model is the best fitting model according the BIC and the log-logistic model is the best fitting model according to the AIC statistic. While the cost-effectiveness results using the exponential model are similar to those using the generalised Gamma model, the cost-effectiveness results are very different when using the log-logistic model. The log-logistic model possibly over-fits the tail end of the distribution and a piece-wise parametric model or a spline model, which were not fit to the data by the Company, may have been a better fit.

It was not clear why the cost of febrile neutropenia was based on non-elective long stay hospital admissions only, when elective, non-elective short stay, day case and regular day or night admissions could have been included in the cost calculation. The ERG calculated the average cost for febrile neutropenia to be £1,628, compared to £2,880 in the CS. The ERG does not expect this to have a significant impact on the cost effectiveness results.

5. COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

In the presentation and interpretation of the results, the company consider five decision populations. These are reproduced in Table 5.1. Three different models were designed to provide evidence to these five decision populations. The deterministic results for the three models are presented in Tables 5.1-5.3. The probabilistic results for the three models are presented in Tables 5.4-5.6.

Table 5.1: The ERG's summary of the decision populations in the economic analysis

Decision population	Comparators	Model population*	Analysis	Threshold (£/QALY)
Overall**	Immunotherapy, Chemotherapy	Overall (base-case)	Full incremental	30,000
Untreated	Immunotherapy, Chemotherapy, Immunotherapy + chemotherapy	Untreated	Full incremental	30,000
Treated	Immunotherapy, Chemotherapy	Treated	Full incremental	30,000
Contra-indicated to Immunotherapy	Chemotherapy	Overall	Pairwise	50,000***

* Based on the effectiveness evidence
** Adult patients with advanced NSCLC harbouring METex14 skipping alterations, regardless of treatment history (line agnostic) and histology
*** This analysis was considered eligible for end-of-life criteria
Source: Information compiled from Company submission

5.1.1 Overall population (base-case)

For the overall population (adult patients with advanced NSCLC harbouring METex14 skipping alterations, regardless of treatment history (line agnostic) and histology), both immunotherapy and chemotherapy were comparators. The full incremental analysis from the base case model (overall population) was relevant to this decision population. Results for £30,000 cost effectiveness threshold were presented for this decision population. From the deterministic results, tepotinib was associated with [redacted] more than the next best comparator and [redacted] QALYs more. The ICER was £19,512. The probability that tepotinib was cost effective was 80.1% and 98.0% compared to chemotherapy and immunotherapy, respectively at the £30,000 WTP threshold.

Table 5.2: Base-case full incremental analysis (deterministic) for overall population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
Chemotherapy	[redacted]	[redacted]			
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£19,512
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Source: Table 61, CS[1]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

5.1.2 Untreated population

For the untreated population, immunotherapy, chemotherapy and combination of immunotherapy and chemotherapy were comparators. The full incremental analysis from the base-case model (overall population) was relevant to this decision population. Results for £30,000 cost effectiveness threshold were presented for this decision population. From the deterministic results, tepotinib was associated with [redacted] more than the next best comparator and [redacted] QALYs more. The ICER was £23,354.

Table 5.3: Base-case fully incremental analysis (deterministic) for untreated population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
Chemotherapy	[redacted]	[redacted]			
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£23,354
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£418,982
Immunotherapy + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,338

Source: Table 66, CS[1]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

5.1.3 Treated population

For the treated population immunotherapy, chemotherapy and combination of immunotherapy and chemotherapy were comparators. The full incremental analysis from the base-case model (overall population) was relevant to this decision population. Results for £30,000 cost effectiveness thresholds were presented for this decision population. From the deterministic results, tepotinib was associated with [redacted] more than the next best comparator and [redacted] QALYs more. The ICER was £18,176.

Table 5.4: Base-case fully incremental analysis (deterministic) for treated population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
Immunotherapy	[redacted]	[redacted]			
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£44,475
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£18,176

Source: Table 68, CS[1]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

5.1.4 Contra-indicated to immunotherapy population

For the contra-indicated to immunotherapy population, only chemotherapy was the comparator. The Pairwise analysis from the base case model (overall population) was relevant to this decision population. Results for £50,000 cost effectiveness thresholds were presented for this decision population. From the deterministic results, tepotinib was associated with [redacted] more than the next best comparator and [redacted] QALYs more. The ICER was £19,512.

Table 5.5: Pair-wise analysis (deterministic) for the contra-indicated to immunotherapy population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental LYG	Incremental costs (£)	Incremental QALYs	ICER

Chemotherapy	[redacted]	1.99	[redacted]		[redacted]	[redacted]	
Tepotinib	[redacted]	2.85	[redacted]	0.86	[redacted]	[redacted]	£19,512
Source: Tables 60 and 61, CS[1] ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

ERG comment: The ERG requested clarification on the decision populations that were to be informed by the three economic analyses (base case, untreated, treated) because relevant decision populations were implied by the economic analysis names, and in the write up of the results. The analysis populations were the overall population (adult patients with advanced NSCLC harbouring METex14 skipping alterations, regardless of treatment history (line agnostic) and histology), the untreated population, and the treated population. The principle write up in the cost effectiveness results focused on pair-wise analyses for a population contra-indicated to immunotherapy, and compared to immunotherapy. The company subsequently clarified that a pair-wise analysis compared to immunotherapy was not relevant as there is no subgroup for which immunotherapy would be the only comparatorIn the interpretation and conclusions section, conclusions are drawn for the base case (overall) population and for the untreated and treated subgroups. The response to the Letter for clarification, question 26 states that both chemotherapy and immunotherapy are relevant alternatives at any treatment line stage.[6] The four decision populations summarised here has been compiled by the ERG on the basis of the analyses presented in the CS and the company clarifications.

The ERG also notes that the cost effectiveness threshold was assumed to be £50,000/QALY for the comparison with chemotherapy because it is argued that this meets the end-of-life criteria. A £30,000/QALY threshold is assumed for a comparison with immunotherapy as it is assumed that this does not meet the end-of-life criteria (a pair-wise comparison with immunotherapy was subsequently discarded). No threshold is stated when both chemotherapy and immunotherapy are both comparators. This may be because the analysis includes a comparator for which the end-of-life criteria is not argued to be met. The ERG has therefore stated £30,000/QALY in Table 5.1.

The ERG notes that in Table 5.2, immunotherapy is dominated by extension and this is not mentioned in the table. The full incremental analysis is therefore not complete. The same applies for chemotherapy in Table 5.3. Only one probabilistic sensitivity analysis was reported. Consequently, the ERG requested probabilistic sensitivity analyses and full incremental analyses for all three models in the letter of points for clarification.

5.2 Company's sensitivity analyses

5.2.1 Probabilistic sensitivity analysis

Results of the company`s probabilistic sensitivity analysis (PSA), arising from 1,000 simulations, are summarised in Table 5.7.

Table 5.6: Mean results of PSA (1,000 runs)

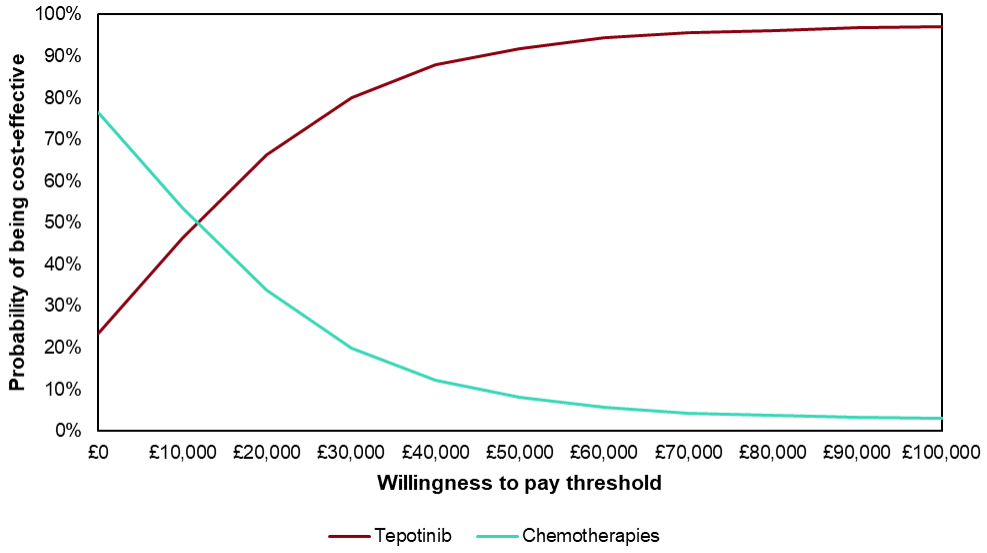
Technologies	Total costs (£)	Total QALYs	ICER (£)	NMB a
Versus chemotherapy				
Tepotinib	[redacted]	[redacted]		
Chemotherapy	[redacted]	[redacted]	£21,689	£12,074

Versus Immunotherapy				
Tepotinib	[redacted]	[redacted]		
Immunotherapy	[redacted]	[redacted]	Dominant	£21,119

Source: Table 62, CS[1]
DET, deterministic; ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life years
Notes: a Willingness-to-pay threshold is £30,000 versus immunotherapy and £50,000 versus chemotherapy

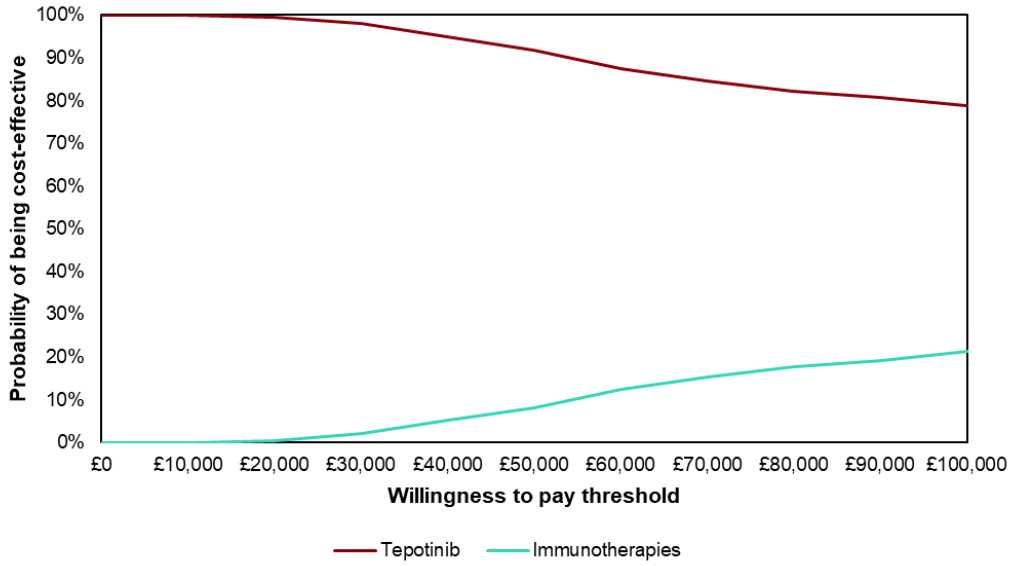
Cost effectiveness acceptability curve (CEAC) are presented in Figure 5.1 (tepotinib vs chemotherapy) and Figure 5.2 (tepotinib vs immunotherapy) in CS report. Based on this analysis, the probability of tepotinib being cost effective is 80.1% and 98.0% compared to chemotherapy and immunotherapy at the £30,000 WTP. The company also reported the probability of cost effectiveness at £50,000 WTP and noted tepotinib is 91.8% is likely to be cost effective vs chemotherapy.

Figure 5.1: Cost effectiveness acceptability curve – tepotinib versus chemotherapy



(Source: CS, Figure 48[1])

Figure 5.2: Cost effectiveness acceptability curve – tepotinib versus immunotherapy



(Source: CS, Figure 49[1])

The ERG considers the parameters and respective distributions chosen for PSA, outlined in Table 67 (Appendix Q) of the CS, to be generally sound. The ERG also considers the probabilistic results to be comparable to deterministic base-case results.[7]

5.2.2 Deterministic sensitivity analyses

The company conducted a range of one-way (deterministic) sensitivity analyses (OWSA) for upper and lower limits of the confidence interval of most parameters (presented in Appendix Q of CS) and presented the results as net monetary benefit (NMB) rather than ICER in tornado diagrams (Figure 50 and Figure 51 of CS).[1] The company noted tepotinib is cost effective in DSA at the £30,000 and £50,000 thresholds and the following parameters with the highest impact on NMB on OWSA as provided in tornado diagram:

One-way sensitivity analyses with greatest impact on NMB results for tepotinib vs chemotherapy (range varied in brackets) (see Figure 5.3).

- Proportion of patients receiving subsequent treatment – chemotherapies: crizotinib (21.7%-36%)
- Relative Dose Intensity (RDI) – tepotinib (65.5%-97.5%)
- Proportion of patients receiving subsequent treatment – tepotinib: crizotinib (6.3%-22.1%)
- Proportion of patients receiving subsequent treatment – chemotherapies: brigatinib (1.4%-7.4%)
- Proportion of patients receiving subsequent treatment – chemotherapies: nivolumab (18.7%-32.4%)
- Proportion of patients receiving subsequent treatment – tepotinib: pembrolizumab (5.9%-15.5%)
- Prevalence of MET mutation in NSCLC (0.6%-3.0%)
- Proportion of patients receiving subsequent treatment – tepotinib: nivolumab (2.0%-8.7%)
- Proportion of patients receiving subsequent treatment – chemotherapies: pembrolizumab (1.1%- 6.6%)

- Percentage of patients who are squamous (5.2%-14.4%)

Figure 5.3: Tornado diagram showing OWSA results on the NMB versus chemotherapy (WTP=£50,000)

(Source: CS, Figure 50[1])

One-way sensitivity analyses with greatest impact on NMB results for tepotinib vs immunotherapy (range varied in brackets) (see Figure 5.4).

- Proportion of patients receiving subsequent treatment – immunotherapy: crizotinib (14.6%-27.5%)
- Relative Dose Intensity (RDI) – tepotinib (65.5%-97.5%)
- Relative Dose Intensity (RDI) – pembrolizumab (79.8%-118.7%)
- Proportion of patients receiving subsequent treatment – tepotinib: crizotinib (10.2%-21.6%)
- Proportion of patients receiving subsequent treatment – immunotherapy: brigatinib (1.5%-7.6%)
- Proportion of patients receiving subsequent treatment – tepotinib: pembrolizumab (5.9%-15.5%)
- Prevalence of MET mutation in NSCLC (0.6%-3.0%)
- Relative Dose Intensity (RDI)– nivolumab (79.8%- 118.7%)
- Proportion of patients receiving subsequent treatment – tepotinib: nivolumab (2.0%-8.7%)
- Percentage of patients who are squamous (5.2%-14.4%)

Figure 5.4: Tornado diagram showing OWSA results on the NMB versus immunotherapy (WTP=£30,000)

(Source: CS, Figure 51[1])

5.2.3 Scenario analysis

The company undertook a series of scenario analyses (Table 63 & Table 64 in CS) to assess the impact of applying alternative efficacy evidence, these include:

- Different time horizon (10-20 years) and different discount rate (0.0%-6.0%)
- Weight data source (European patients)
- Excluding Drug wastage, Dose intensity, AE disutility, MET mutation testing
- Including Pemetrexed maintenance
- UK based subsequent treatment
- Different source of utility
- Different PSMs or Spline distributions for OS and PFS

The company noted tepotinib remained dominant over immunotherapy at the £30,000 WTP threshold and mainly cost effective versus chemotherapy at the £50,000 WTP threshold for all plausible scenarios. Also, using UK based subsequent treatment scenarios had the largest impact on the ICER versus chemotherapy.

5.3 Model validation and face validity check

For the model validation, the company stated that a technical review of the cost effectiveness model was conducted by an independent economist. Further the relevance of the model structure and assumptions were validated through consultation with UK clinicians; as noted in CS, four clinical experts from oncology and two HTA experts involved in clinical validation of ICT and cost effectiveness analysis.

The ERG reviewed the model and found most of the data to be correct and that the model to be correctly specified. There were a couple of minor data errors (see Section 6). The model was not designed to produce probabilistic sensitivity analysis results for multiple comparators, and the company revised the model in the response to the letter of points for clarification.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

This section describes the ERG base-case analyses and the scenario analyses conducted based on both the ERG base-case analyses and the company base-case analyses. The ERG base-case analyses are used to present cost effectiveness evidence for five decision questions identified in the CS that are informed by the company economic models. Both the ERG and company submission analyses are used to present cost effectiveness evidence for the subgroup decision questions specified in the NICE scope.

The details of how the ERG implemented the ERG analyses are stated in Appendix 3.

6.1.1 ERG base-case

The ERG considered that there was considerable uncertainty in the appropriate selection of statistical model for OS and PFS outcomes. The issue concerns the lack of randomised controlled trial data, and that clinical expert opinion was used to help select the survival curves for individual treatments based on single arm trial data.

If the survival model selections address bias associated with imperfect matching of populations in the VISION and real-world data sets, or if they address imperfect model choice due to insufficient follow-up data, then the clinical expert selections may be the most appropriate. If poor predictions of OS and PFS for the comparators of the best fitting models, according to the clinical experts, is due to poor generalisability of the VISION population to the decision population for this STA, or if the clinical experts inaccurately try to correct for bias, then the model selection choice could potentially introduce bias into the relative effectiveness of tepotinib compared to chemotherapy or immunotherapy.

The company conducted scenario analyses changing the statistical models one at a time, but the ERG considers that a model with an alternative selection of survival models based on the AIC and BIC statistics, visual inspection, ensuring that PFS and OS curves do not cross before eight years of follow-up, and where the model closest to clinical expert opinion is chosen in the event of different optimal models according to AIC and BIC, is an appropriate alternative model. The ERG selected model was either one of the best fitting models, or the next best based on the considerations stated. The ERG selected survival model was always an equal or better fit to the data than the company selected survival model.

OS and PFS curves crossing at or beyond eight years is not a concern because of the considerable uncertainty associated with long-term predictions, the numbers are small, the fact that the economic model includes a function that means that PFS is never greater than OS, and the company submission included survival models for chemotherapy where PFS and OS crossed at around nine years.

The ERG alternative base-case is not preferred to the company's base-case model. The differences in the results of the two models should reflect uncertainty in the independent selection of survival models for the intervention and comparators based on single arm trial data.

The company presented analyses based on three model populations in the CS: the base-case analysis (overall population), the untreated population analysis and the previously treated population analysis. The ERG selected alternative survival models for each of these populations. The survival models selected by the company and by the ERG for these three populations are presented in Tables 6.1, 6.2 and 6.3.

The ERG used the results of these three models to conduct a full incremental cost effectiveness analysis for the four decision questions presented in Table 6.4.

Since the probabilistic analysis results were similar to the deterministic results, and because using the deterministic results enabled the one-way sensitivity analysis results for the biggest drivers of the results to be presented explicitly, deterministic analyses were run.

Table 6.1: Base-case model (overall population): selected survival models for CS and ERG analyses

Technologies	CS models		ERG models	
	OS	PFS	OS	PFS
Tepotinib	Log-logistic	Log-normal	Log-logistic	Log-normal
Chemotherapy	Weibull	Spline 1- knot odds	Log-normal	Spline 3-knot odds
Immunotherapy	Spline 1- knot normal	Piece-wise log-logistic	Spline 2-knot normal	Piecewise log-logistic

Table 6.2: Untreated population model: selected survival models for CS and ERG analyses

Technologies	CS models		ERG models	
	OS	PFS	OS	PFS
Tepotinib	Log-normal	Log-normal	Log-logistic	Log-logistic
Chemotherapy	Weibull	Spline 2-knot odds	Log-normal	Spline 3-knot Odd
Immunotherapy	Spline 2-knot normal	Piece-wise Weibull	Spline 2-knot normal	Piece-wise log-normal

Table 6.3: Previously treated population model: selected survival models for CS and ERG analyses

Technologies	CS models		ERG models	
	OS	PFS	OS	PFS
Tepotinib	Log-normal	Log-normal	Log-normal	Log-normal
Chemotherapy	Weibull	Log-logistic	Log-normal	Log-logistic
Immunotherapy	Spline 1-knot normal	Spline 1-knot hazard	Exponential	Spline 1-knot hazard

Table 6.4: The ERG's summary of the decision populations and comparators in the economic analysis

Decision population	Comparators	Model population*	Analysis	Threshold (£/QALY)
Overall**	Immunotherapy, Chemotherapy	Overall (base-case)	Full incremental	30,000
Untreated	Immunotherapy, Chemotherapy,	Untreated	Full incremental	30,000

Decision population	Comparators	Model population*	Analysis	Threshold (£/QALY)
	Immunotherapy + chemotherapy			
Treated	Immunotherapy, Chemotherapy	Treated	Full incremental	30,000
Contra-indicated to Immunotherapy	Chemotherapy	Overall	Pairwise	50,000***

* Based on the effectiveness evidence
** Adult patients with advanced NSCLC harbouring METex14 skipping alterations, regardless of treatment history (line agnostic) and histology
*** This analysis was considered eligible for end-of-life criteria
Source: Information compiled from Company submission

6.1.2 ERG exploratory scenario analyses

This section describes the scenario and sensitivity analyses conducted by the ERG. All of these analyses were conducted using the base-case analysis (overall population), and tepotinib was compared to immunotherapy and chemotherapy as pairwise analyses, for ease of comparison with the results using the company base-case assumptions.

No model errors were identified by the ERG over and above any mentioned in the letter of points for clarification and corrected by the company in the response to the letter.

The ERG conducted one scenario analysis not conducted by the company: alternative treatment distribution assumptions for immunotherapy and chemotherapy.

The ERG also conducted scenario and sensitivity analyses conducted in the company submission for tepotinib compared to each of immunotherapy and chemotherapy comparators which changed the NMB compared the respective comparator by more than £5,000. The cost effectiveness thresholds used for the calculation of NMB in the scenario and sensitivity analyses in the company submission were £50,000/QALY for the chemotherapy comparison and £30,000/QALY for the immunotherapy comparison. The £50,000/QALY was used for chemotherapy because the company argued that the analysis compared to chemotherapy met the end-of-life inclusion criteria.

All of these scenario and sensitivity analyses are described below.

Alternative treatment distribution assumptions

It was not clear how the Company derived the treatment distributions for immunotherapy and chemotherapy. The ERG tried to reproduce the treatment distribution but could not (see Appendix 1). The company subsequently clarified that weighted numbers were used in the economic model to produce treatment distributions to align with the weighted efficacy data. However, the ERG does not know how these weights were calculated. The ERG distribution was included in a scenario analysis for the base-case model.

Table 6.5: Treatment distributions for immunotherapy and chemotherapy included in the model base-case: previously treated

Category	Treatment	Real-world data (Company base-case)	ERG recalculation
Immunotherapy	Pembrolizumab	[redacted]	[redacted]
	Atezolizumab	[redacted]	[redacted]
	Nivolumab	[redacted]	[redacted]
	Nivolumab + ipilimumab	[redacted]	[redacted]
Chemotherapy	Docetaxel + platinum	[redacted]	[redacted]
	Gemcitabine + platinum	[redacted]	[redacted]
	Paclitaxel + platinum	[redacted]	[redacted]
	Vinorelbine + platinum	[redacted]	[redacted]
	Pemetrexed + platinum	[redacted]	[redacted]
	Docetaxel monotherapy	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]
	Docetaxel + gemcitabine a	[redacted]	[redacted]
	Gemcitabine monotherapy a	[redacted]	[redacted]
	Vinorelbine monotherapy a	[redacted]	[redacted]

Source: Table 33 in CS[1]

Selected scenario analyses from those conducted by the Company

The scenario analyses conducted by the ERG are presented in Table 6.6. One analysis that met the inclusion criteria was excluded as a description of the analysis did not appear to be presented in the company submission. This was an analysis similar to the 'subsequent treatment has a UK based distribution' analysis, except that the name also mentioned that it matched subsequent lines. The results of the analysis were similar to the subsequent treatment results.

Table 6.6: Description of the scenario analyses conducted by the ERG

Analysis	Base-case description
Exclude dose intensity in cost calculations	In the base-case analysis, a dose intensity of 0.81 for tepotinib reduces the cost of tepotinib because fewer tepotinib tablets are consumed. Tepotinib has a lower dose intensity than the comparators in the model.
Discount rate is 0%	The base-case analysis includes an annual discount rate of 3.5%.
Subsequent Treatment has a UK based distribution	Following treatment cessation for tepotinib, immunotherapy or chemotherapy in the model, a percentage of patients are assumed to be given subsequent treatment. In the base-case model, this distribution is based on the treatment distributions used in the clinical trial evidence. In this scenario analysis, the distribution is based on the clinical expert assessment of treatment distributions in the UK.
Tepotinib ToT modelled with a log-logistic model	The base-case analysis used a generalised gamma model for ToT for tepotinib.

Analysis	Base-case description
Immunotherapy ToT assumption: treatment capped at PFS	In the base-case analysis, ToT was estimated using literature data and extrapolated assuming an exponential distribution.
Source: CS[1]	

The selection of sensitivity analyses conducted by the ERG is reported in Table 6.7. LB stands for the lower bound of the range of values considered. UB stands for the upper bound of the range of values considered.

Table 6.7: The sensitivity analyses conducted by the ERG

Analysis	Description
Subsequent Treatment for chemotherapy: crizotinib (LB)	The lower bound of the percentage of patients receiving crizotinib as subsequent treatment to chemotherapy, derived from the beta distribution with parameters based on the sample size in the cohort data.
Subsequent Treatment for chemotherapy: crizotinib (UB)	The upper bound of the percentage of patients receiving crizotinib as subsequent treatment to chemotherapy, derived from the beta distribution with parameters based on the sample size in the cohort data.
Subsequent Treatment for tepotinib: crizotinib (LB)	The lower bound of the percentage of patients receiving crizotinib as subsequent treatment to tepotinib, derived from the beta distribution with parameters based on the sample size in the cohort data.
Subsequent Treatment for tepotinib: crizotinib (UB)	The upper bound of the percentage of patients receiving crizotinib as subsequent treatment to tepotinib, derived from the beta distribution with parameters based on the sample size in the cohort data.
Subsequent Treatment for chemotherapy: briogatinib (UB)	The upper bound of the percentage of patients receiving brigatinib as subsequent treatment to chemotherapy, derived from the beta distribution with parameters based on the sample size in the cohort data.
RDI tepotinib (LB)	The lower bound of the dose intensity value for tepotinib.
RDI tepotinib (UB)	The lower bound of the dose intensity value for tepotinib.
Source: CS[1]	

6.1.3 ERG subgroup analyses

The ERG conducted a set of analyses to address the subgroup populations and comparators defined in the NICE scope. These subgroup populations and comparators are presented in Table 6.8. The untreated population and previously treated population models were used to inform these decision questions. The comparators varied by subgroup. The company did not produce results for these subgroups. Consequently, the ERG produced results for each decision question using the company survival model assumptions and the ERG survival model assumptions.

Table 6.8: The decision problem subgroups with the relevant comparators

Population	Comparators
Untreated	
Non-squamous PD-L1 ≥50%	Immunotherapy or Immunotherapy + chemotherapy
Non-squamous PD-L1 <50%	Chemotherapy or Immunotherapy + chemotherapy
Adenocarcinoma/large cell carcinoma PD-L1 <50%	Chemotherapy
Squamous PD-L1 ≥50%	Immunotherapy or Immunotherapy + chemotherapy
Squamous PD-L1 <50%	Chemotherapy or Immunotherapy + chemotherapy
Treated	
Squamous PD-L1 ≥50%	Chemotherapy
Squamous PD-L1 <50%	Immunotherapy or Chemotherapy
Source: Adapted from Table 1 in the company submission	

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

For the four decision questions addressed in the CS where chemotherapy is a comparator, tepotinib is not as cost effective based on the ERG analysis than on the company analysis. This is primarily because overall survival is greater in the long-run for chemotherapy using the ERG survival model than using the company survival model. The ICER varies from £19,512/QALY to £32,753/QALY.

The difference in the cost effectiveness of tepotinib between the ERG and company analyses is far greater in the untreated and treated populations than in the base-case (overall) population. This is due to a greater difference in the overall survival outcomes following chemotherapy between the ERG and Company survival models in both the untreated and treated populations. There is also a slight reduction in survival with tepotinib using the ERG survival model than using the company survival model in the untreated population. The company fitted survival models to the untreated and treated population subsets in the VISION and real-world data sets. When there are fewer data, it can be expected that there will be greater variation in predictions between survival models. This is reflected in the different survival model selections for the ERG and the company in these subgroups.

Tepotinib is no longer cost effective at a threshold of £50,000/QALY in the untreated and treated subgroups using the ERG survival model selections.

The full incremental cost effectiveness analyses for the NICE scope subgroup decision questions, conducted using both the ERG and company survival model assumptions, were based on the untreated and treated subgroup survival model selections. The untreated population subgroup analyses differ from each other only in the comparator selection. The cost effectiveness of tepotinib will be largely dependent on whether chemotherapy is a relevant comparator.

There are four scenario analyses that have a significant effect on the cost effectiveness of tepotinib when using either the ERG or company survival model assumptions. These are:

- The assumption of 100% dose intensity (RDI)
- The use of subsequent treatment distributions based on UK practice
- The use of subsequent treatment distributions based on UK practice, adjusting for the number of subsequent lines
- The use of a log-logistic model to model ToT for tepotinib.

The ERG agrees with the company that the two analyses involving subsequent treatment distributions are not useful analyses because it is the treatments used in the studies evaluating effectiveness outcomes that should be included in the cost analysis. The effectiveness and cost are related.

The company suggested that tepotinib has a lower RDI than for chemotherapy due to the fact that the mode of delivery is tablets and not infusion. Making the assumption of 100% RDI increases the cost of tepotinib relative to chemotherapy and immunotherapy and thereby reduces the cost effectiveness of tepotinib.

The company selected the generalised Gamma model for ToT for tepotinib. The use of the generalised Gamma model predicts a smaller percentage of patients receiving tepotinib treatment after two years than the use of the log-logistic model. The use of the log-logistic model therefore increases the cost of tepotinib and reduces the cost effectiveness of tepotinib. Tepotinib is no longer cost effective when using the ERG survival model selections and a log-logistic model for ToT for tepotinib. The ERG considers the log-logistic model may over-fit the tail end of the data, but that another model not fitted by the company may have better modelled ToT.

The cost-effectiveness of tepotinib is quite sensitive to the proportion of patients receiving subsequent treatment, especially crizotinib, one of the most common subsequent treatments in the analysis. Tepotinib becomes less cost-effective the lower the proportion of patients receiving crizotinib as this lowers the cost associated with the chemotherapy treatment.

6.2.1 ERG base-case results for four decision questions

The full incremental cost effectiveness results for the ERG base-case analyses for the four decision questions presented in Table 6.4 are presented in Tables 6.9-6.12. The company base-case ICERs are also presented for comparison as the ERG analyses are scenario analyses, not preferred analyses. Following each table of results for the base-case model (overall population), untreated population and the treated population, graphs of survival curves for comparators comparing the company selected model and the ERG selected model are presented where there is a difference in selected models. This is to facilitate interpretation of results.

Table 6.9: ERG base-case full incremental results for overall population and the company base-case ICER

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company base-case ICER (£/QALY)
Chemotherapy	[redacted]		2.45		[redacted]			
Tepotinib	[redacted]	[redacted]	2.85	0.40	[redacted]	[redacted]	32,753	19,512
Immunotherapy	[redacted]	[redacted]	2.02	-0.83	[redacted]	[redacted]	Dominated	Dominated

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

Figure 6.1: ERG comparison with CS OS curves: chemotherapy for Base-case population

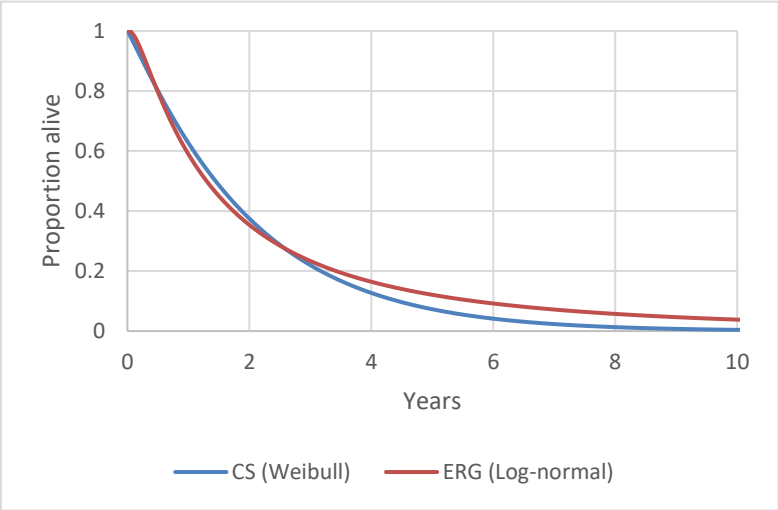


Figure 6.2: ERG comparison with CS PFS curves: chemotherapy for Base-case population

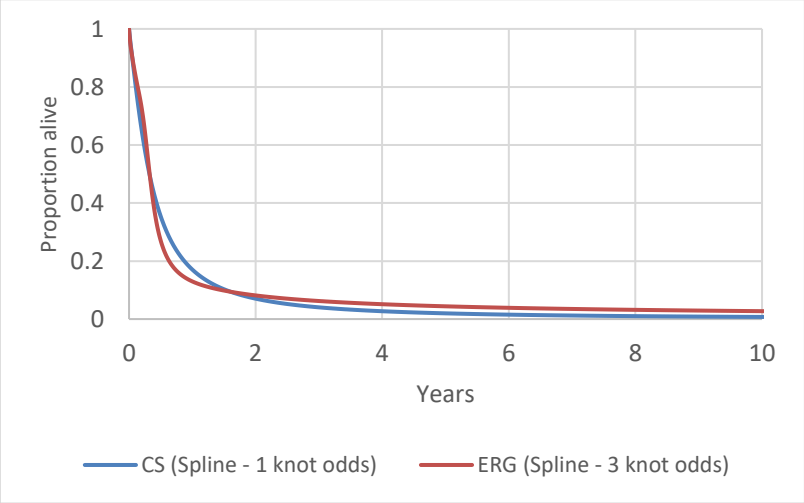


Figure 6.3: ERG comparison with CS OS curves: Immunotherapy for Base-case population

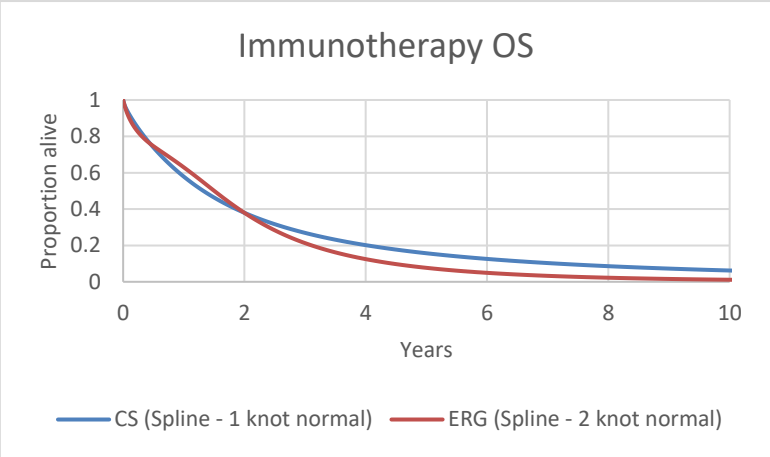


Table 6.10: ERG base-case full incremental results for Untreated population and the Company ICER

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company ICER (£/QALY)
Chemotherapy	[redacted]		3.18		[redacted]			
Tepotinib	[redacted]	[redacted]	3.06	-0.13	[redacted]	[redacted]	Dominated	23,354
Immunotherapy	[redacted]	[redacted]	3.45	0.39	[redacted]	[redacted]	Extendedly dominated	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	1.98	[redacted]	[redacted]	63,768	186,293

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

Figure 6.4: ERG comparison with CS OS curves: tepotinib for untreated population

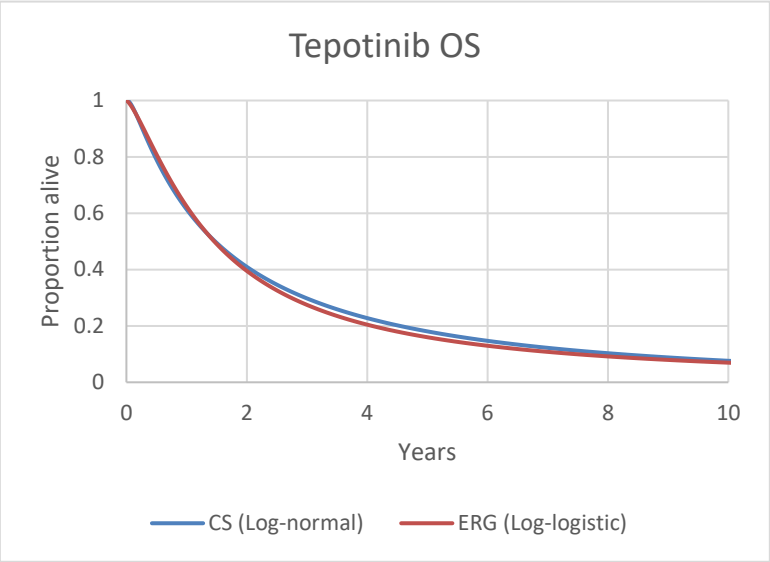


Figure 6.5: ERG comparison with CS PFS curves: tepotinib for untreated population

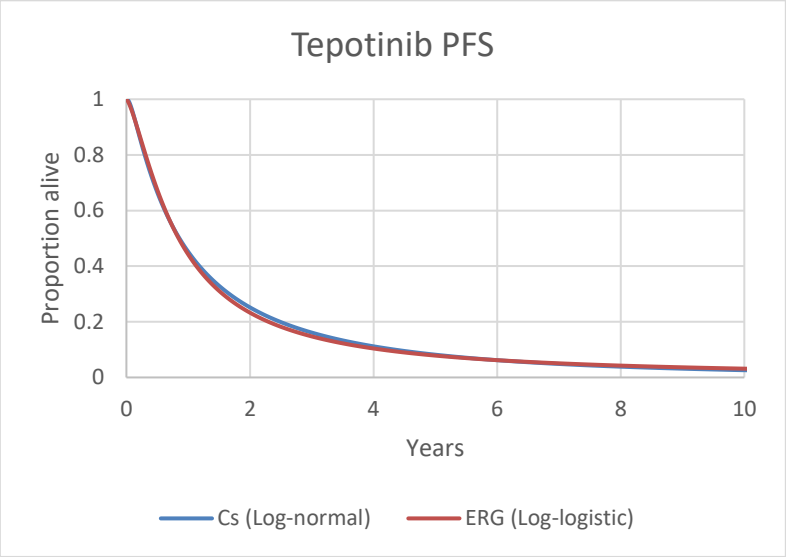


Figure 6.6: ERG comparison with CS OS curves: chemotherapy for untreated population

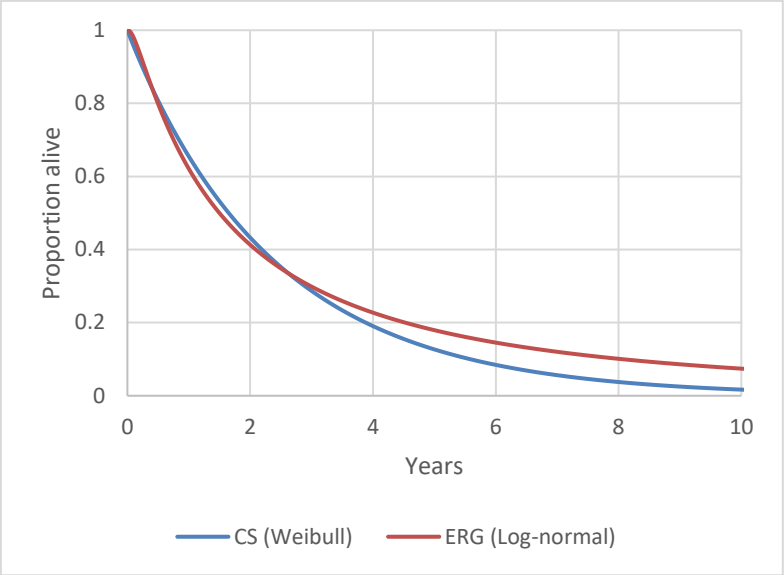


Figure 6.7: ERG comparison with CS PFS curves: chemotherapy for untreated population

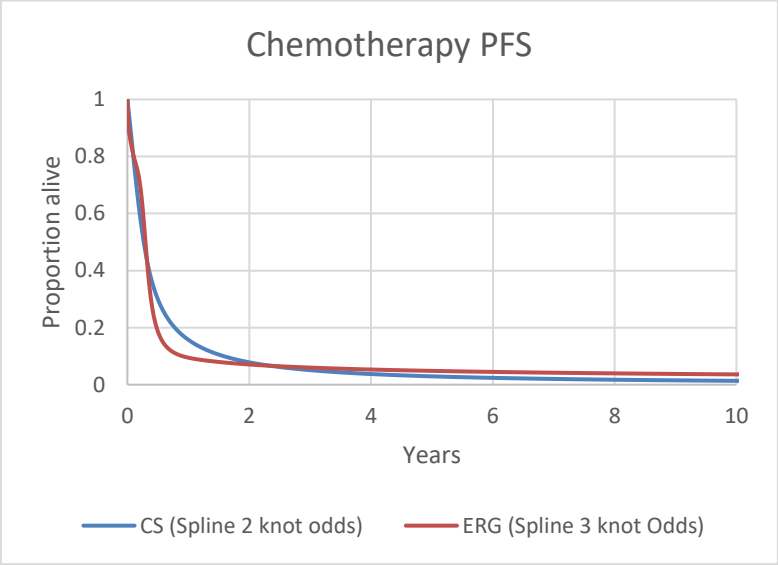


Figure 6.8: ERG comparison with CS PFS curves: chemotherapy for untreated population

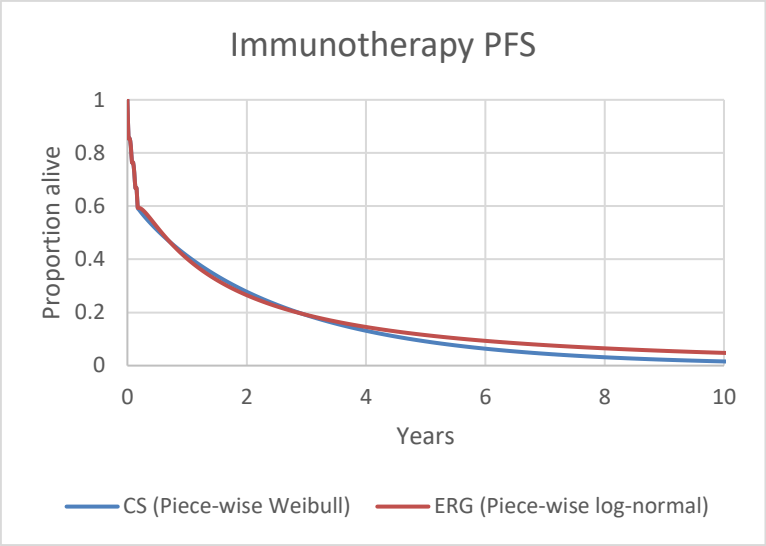


Table 6.11: ERG base-case full incremental results for treated population and the company ICER

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company ICER (£/QALY)
Immunotherapy	[redacted]		1.67		[redacted]			
Chemotherapy	[redacted]	[redacted]	2.58	0.92	[redacted]	[redacted]	17,363	Extendedly dominated
Tepotinib	[redacted]	[redacted]	2.61	0.02	[redacted]	[redacted]	55,879	£24,824

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

Figure 6.9: ERG comparison with CS OS curves: chemotherapy for treated population

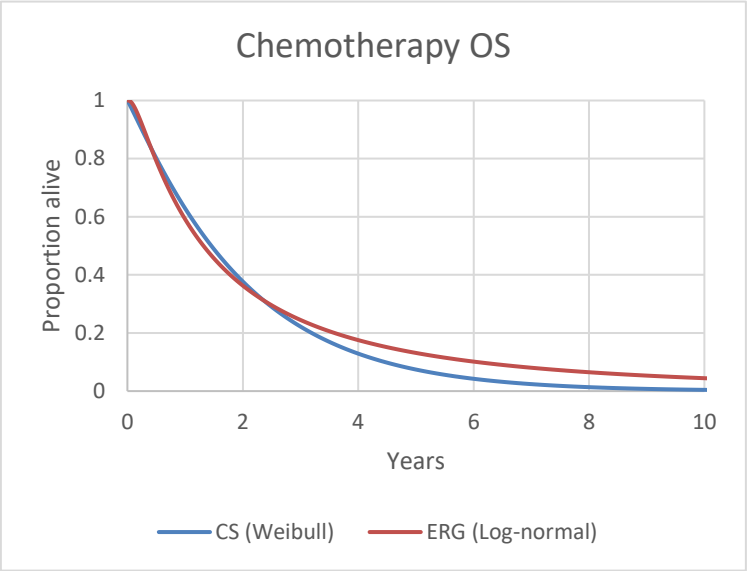


Figure 6.10: ERG comparison with CS OS curves: immunotherapy for treated population

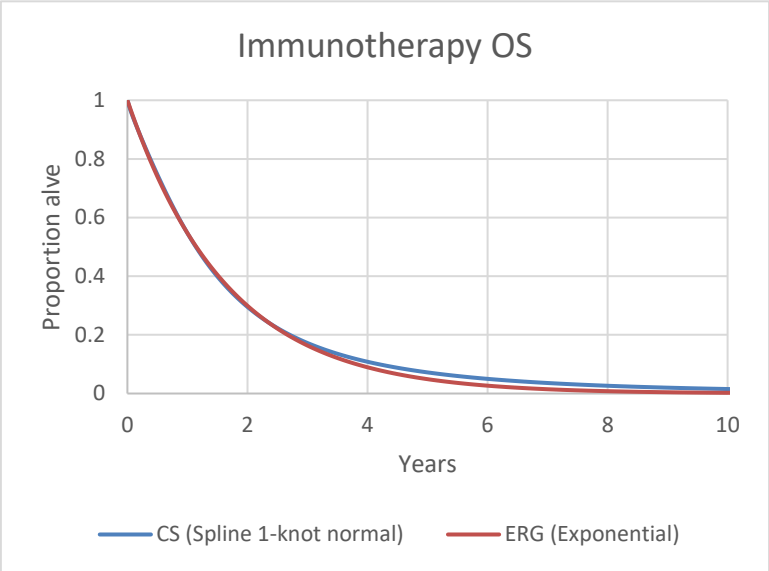


Table 6.12: ERG base-case full incremental results for contraindicated to immunotherapy population and the company ICER

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company ICER (£/QALY)
Chemotherapy	[redacted]		2.45		[redacted]			
Tepotinib	[redacted]	[redacted]	2.85	0.40	[redacted]	[redacted]	32,753	19,512
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

6.2.2 ERG scenario and sensitivity analyses' results

The results of the ERG scenario analyses are presented in Table 6.13 for both the ERG and company base-case models. The results of the ERG sensitivity analyses for tepotinib compared to chemotherapy are presented in Table 6.14 for both the ERG and company base-case models. The results of the ERG sensitivity analyses for tepotinib compared to immunotherapy are presented in Table 6.15 for both the ERG and company base-case models.

Table 6.13: Scenario analyses

Analysis	Technologies	ICER (Tepotinib vs comparator)	
		ERG	Company
Base-case	Immunotherapy	Dominant	Dominant
	Chemotherapy	32,753	19,512
ERG calculated treatment distributions	Immunotherapy	Dominant	Dominant
	Chemotherapy	32,696	19,512
Exclude dose intensity in cost calculations	Immunotherapy	30,209	Dominant
	Chemotherapy	65,583	36,287
Discount rate is 0%	Chemotherapy	£32,351	£19,378
Subsequent Treatment has a UK based distribution	Immunotherapy	Dominant	Dominant
	Chemotherapy	£159,726	£85,128
Subsequent Treatment has a UK based distribution matching number of subsequent lines	Immunotherapy	Dominant	Dominant
	Chemotherapy	£170,989	£90,877
Tepotinib ToT modelled with a log-logistic model	Chemotherapy	£65,381	£36,166
	Immunotherapy	Dominant	Dominant
Immunotherapy ToT assumption: treatment capped at PFS	Immunotherapy	Dominant	Dominant

Source: CS[1]

Table 6.14: Sensitivity analyses (tepotinib versus chemotherapy)

Analysis	ICER (£/QALY) (tepotinib vs comparator)	
	ERG	Company
Base case	32,753	19,512
Subsequent Treatment for chemo crizotinib (LB)	65,962	36,596
Subsequent Treatment for chemo crizotinib (UB)	Dominant	1,105
Subsequent Treatment for Tepotinib crizotinib (LB)	7,609	6,677
Subsequent Treatment for Tepotinib crizotinib (UB)	62,006	34,444
Subsequent Treatment for chemo briogatinib (UB)	2,357	3,873
RDI Tepotinib (LB)	3,680	4,672
RDI Tepotinib (UB)	61,826	34,352

Source: CS[1]

Table 6.15: Sensitivity analyses (tepotinib versus immunotherapy)

Analysis	ICER (Tepotinib vs comparator)	
	ERG	Company
Base case	Dominant	Dominant
Subsequent Treatment for immuno crizotinib (LB)	Dominant	Dominant
Subsequent Treatment for immuno crizotinib (UB)	Dominant	Dominant
RDI Tepotinib (LB)	Dominant	Dominant
RDI Tepotinib (UB)	Dominant	Dominant
RDI Pembrolizumab (LB)	Dominant	Dominant
RDI Pembrolizumab (UB)	Dominant	Dominant
Subsequent Treatment for Tepotinib crizotinib (LB)	Dominant	Dominant
Subsequent Treatment for Tepotinib crizotinib (UB)	Dominant	Dominant
Subsequent Treatment for immuno Brigatinib (UB)	Dominant	Dominant
Source: CS[1]		

6.2.3 ERG subgroup analyses' results

The results of the ERG subgroup analyses presenting both the life years gained and the ICER results for both the ERG and company base-case models are presented in Tables 6.16-6.22. The comparators are ordered according to increasing cost in the ERG analyses.

Table 6.16: ERG base-case results for untreated, non-squamous PD-L1 ≥50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Tepotinib	[redacted]	[redacted]	3.06				Cost-effective*	[redacted]	[redacted]	3.20				Cost-effective*
Immunotherapy	[redacted]	[redacted]	3.45	[redacted]	[redacted]	0.39	Extendedly dominated	[redacted]	[redacted]	3.45	[redacted]	[redacted]	0.25	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	1.98	57,774	[redacted]	[redacted]	3.79	[redacted]	[redacted]	0.35	186,293

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years
*Tepotinib is less costly and less effective and is cost-effective because the comparators are too costly given the additional benefit they provide

Table 6.17: ERG base-case results for untreated non-squamous PD-L1 <50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Chemotherapy	[redacted]	[redacted]	3.18					[redacted]	[redacted]	2.42				
Tepotinib	[redacted]	[redacted]	3.06	[redacted]	[redacted]	-0.13	Dominated	[redacted]	[redacted]	3.20	[redacted]	[redacted]	0.78	23,354
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	2.37	63,768	[redacted]	[redacted]	3.79	[redacted]	[redacted]	0.6	186,293

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

Table 6.18: ERG base-case results for untreated, adenocarcinoma/large cell carcinoma PD-L1 <50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Chemotherapy	[redacted]	[redacted]	3.18					[redacted]	[redacted]	2.42				
Tepotinib	[redacted]	[redacted]	3.06	[redacted]	[redacted]	-0.13	Dominated	[redacted]	[redacted]	3.20	[redacted]	[redacted]	0.78	23,354
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years														

Table 6.19: ERG base-case results for untreated squamous PD-L1 ≥50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Tepotinib	[redacted]	[redacted]	3.06				Cost-effective*	[redacted]	[redacted]	3.20				Cost-effective*
Immunotherapy	[redacted]	[redacted]	3.45	[redacted]	[redacted]	0.39	Extendedly dominated	[redacted]	[redacted]	3.45	[redacted]	[redacted]	0.25	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	1.98	57,774	[redacted]	[redacted]	3.79	[redacted]	[redacted]	0.35	186,293
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years *Tepotinib is less costly and less effective and is cost-effective because the comparators are too costly given the additional benefit they provide														

Table 6.20: ERG base-case results for Untreated Squamous PD-L1 <50% population

Technologies	ERG	Company

	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Chemotherapy	[redacted]	[redacted]	3.18					[redacted]	[redacted]	2.42				
Tepotinib	[redacted]	[redacted]	3.06	[redacted]	[redacted]	-0.13	Dominated	[redacted]	[redacted]	3.20	[redacted]	[redacted]	0.78	23,354
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	2.37	63,768	[redacted]	[redacted]	3.79	[redacted]	[redacted]	0.6	186,293
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years														

Table 6.21: ERG base-case results for treated squamous PD-L1 <50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Immunotherapy	[redacted]	[redacted]	1.67					[redacted]	[redacted]	1.87				
Chemotherapy	72,090	1.47	2.58	7,550	0.43	0.92	17,363	70,069	1.23	2.00	4,603	0.10	0.14	Extendedly dominated
Tepotinib	[redacted]	[redacted]	2.61	3,540	0.06	0.02	55,879	[redacted]	[redacted]	2.61	5,560	0.31	0.60	24,824
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years														

Table 6.22: ERG base-case results for Treated Squamous PD-L1 ≥50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	

Chemotherapy	72,090	1.47	2.58					[redacted]	[redacted]	2.00				
Tepotinib	[redacted]	[redacted]	2.61	3,540	0.06	0.02	55,879	[redacted]	[redacted]	2.61	[redacted]	[redacted]	0.61	£18,176
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years														

6.3 ERG's preferred assumptions

The survival model assumptions made by the ERG are not necessarily preferred to those made by company. The ERG believes these to be as plausible as those selected by the company. The ERG base-case analysis represents an alternative plausible scenario to the company base-case analysis, and the difference in the results reflects uncertainty associated with the independent survival model selection for the comparators based on single arm data.

6.4 Conclusions of the cost effectiveness section

The CS did not identify relevant economic models for the NICE scope decision question. Consequently, a *de novo* model was developed. All of the economic analysis components stated in the NICE Reference Case were adhered to, except for the source of preference data for valuation of changes in health-related quality of life. In the case of the source of preference data it may well be that the company used the best available data. The analysis was conducted from a NHS and PSS perspective. The time horizon was lifetime. The discount rate was 3.5% per annum.

The economic model was a partitioned survival model (PSM), where the progression-free survival and overall survival were estimated using survival modelling techniques and the proportion of the cohort that progressed was difference between the proportion still alive and the proportion with progression-free survival. There was no justification for the use of a PSM over a state transition model, but it was stated that PSMs are common in the clinical area. According to the ERG model checks, the model was mostly free from errors and was well executed. The one error identified was corrected in the response to the letter of points for clarification.

The decision questions addressed in the CS appeared to cover four populations: the overall population (adult patients with advanced NSCLC harbouring METex14 skipping alterations, regardless of treatment history (line agnostic) and histology); an untreated population; a previously treated population; and a population contraindicated to immunotherapy. These were informed by three analyses based on clinical evidence for the overall population, the untreated population, and the previously treated population. The comparators included immunotherapy, chemotherapy, and combined immunotherapy and chemotherapy. Combined immunotherapy and chemotherapy was only a relevant comparator in the untreated population group. For the population who are contraindicated or unsuitable to immunotherapy, there was only one relevant comparator.

The ERG had to compile the set of decision questions addressed because of the lack of clarity in the reporting of the results and the conclusions drawn. The main results focused on conclusions regarding populations who are contraindicated or unsuitable to one of the comparators, and for which pair-wise analyses were relevant. It was subsequently clarified that there was no subgroup for which immunotherapy was the only comparator. The interpretation and conclusions section drew conclusions regarding the overall population.

The set of decision questions differs from the decision questions in the NICE scope both in terms of the subgroups for which cost effectiveness conclusions were drawn and in terms of the comparators included in the analyses. The subgroups in the NICE scope were more specific than those in the economic analyses. It was argued in the CS that there were insufficient data to estimate effectiveness for those subgroups. The ERG considers this may be true. The comparators in the NICE scope were specific immunotherapy and chemotherapy treatments; whereas immunotherapy and chemotherapy classes were comparators in the CS. It was also argued in the CS that there were insufficient data to

estimate effectiveness for the individual comparators. The ERG agrees that few data were available for specific treatments.

The effectiveness evidence was derived from single-arm, patient-level cohort data in studies identified from a systematic review of the literature. An assumption regarding the progression-free survival outcome was made due to the data limitations. The ERG considers that a reasonable effort was made in the CS to produce comparable population data sets across comparators and that conservative assumptions with respect to tepotinib were sometimes made. There is significant uncertainty associated with the generalizability of the effectiveness evidence to the decision population.

The final part of the process in deriving the relative effectiveness of tepotinib compared to the comparators was based on the independent selection of survival models for each treatment. Clinical expert opinion was used to help select the survival models. Some of the criteria for model selection was the over or under estimation of survival for chemotherapy of immunotherapy comparators. The ERG considers this selection to be plausible, but that it is also possible that this selection may introduce bias if the reason for the poor predictions was either the VISION population was not generalisable to the NICE scope decision population or that the clinical experts inaccurately adjusted for bias. Consequently, the ERG selected an alternative plausible set of survival models for use in an alternative scenario analysis to help explore the impact on the cost-effectiveness of the uncertainty in survival model selection. The ERG also considers the modelling of the ToT for tepotinib to be a significant area of uncertainty. It is possible that a statistical model not fitted to the data by the company may be a better selection.

The ICER for tepotinib ranges from £19,512/QALY to £32,753/QALY between the company and ERG base-case models. The company produced models for the overall population, and the treated and untreated subgroups. The ERG considers the comparators stated in the NICE scope to be the most appropriate comparators for treated and untreated subgroups. The ICERs for tepotinib using the ERG and company survival model assumptions are presented in Table 6.23.

All of the cost-effectiveness results are based on an indicative PAS of [redacted]. Tepotinib is cost effective irrespective of survival model assumptions for subgroups where chemotherapy alone is not a relevant comparator. There is significant uncertainty in the cost effectiveness of tepotinib, whether using a cost effectiveness threshold of £30,000/QALY or £50,000/QALY, when chemotherapy alone is a relevant comparator.

The company considers a subgroup contraindicated to. There is considerable uncertainty in the cost effectiveness of tepotinib in this population.

Table 6.23: The decision problem subgroups with the relevant comparators

Population	Tepotinib ICER (ERG assumptions)	Tepotinib ICER (Company assumptions)
Untreated		
Non-squamous PD-L1 ≥50%	Cost-effective (less costly and less benefit)	Cost-effective (less costly and less benefit)
Non-squamous PD-L1 <50%	Dominated	23,354
Adenocarcinoma/large cell carcinoma PD-L1 <50%	Dominated	23,354
Squamous PD-L1 ≥50%	Cost-effective (less costly and less benefit)	Cost-effective (less costly and less benefit)
Squamous PD-L1 <50%	Dominated	23,354
Treated		
Squamous PD-L1 ≥50%	55,879	24,824
Squamous PD-L1 <50%	55,879	£18,176
Source: Adapted from Table 1 in the Company Submission[1]		

7. END OF LIFE

The company provided a summary of the justification as to the fulfilment of the end life criteria in Table 30 of the CS.[1] In terms of life expectancy, the ERG would agree that, according to the ITC, median survival is lower than 24 months. However, there is some doubt because of the uncertainty in the results of the ITC and because, according to the CEA, mean life years gained are very close to the threshold of 24 months.

In terms of survival gain, the company produced an economic model for the overall population, the untreated population and the treated population. The life years gained associated with chemotherapy were 1.99, 2.42 and 2 years, respectively. However, Table 3.14 shows that the difference in survival based on the ITC is [redacted] versus immunotherapy for the overall population and [redacted] Furthermore, with the ERG survival model assumptions the survival gain associated with tepotinib compared to chemotherapy is eliminated. This reflects the underlying uncertainty associated with the effectiveness evidence.

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Appendix 1: ERG treatment distribution calculations

Comparator treatments

The Company presented the treatment distribution used in the base-case as the real-world data distribution in Table 33 in the CS. These are reproduced here in Table A1.1.

Table A.1.1: Comparator groups and treatment mixes (compiled from Table 33 in CS and model data)

Category	Treatment	Real-world data (base-case)	ERG recalculation	Clinical expert opinion (scenario)
Immunotherapy	Pembrolizumab	[redacted]	[redacted]	[redacted]
	Atezolizumab	[redacted]	[redacted]	[redacted]
	Nivolumab	[redacted]	[redacted]	[redacted]
	Nivolumab + ipilimumab	[redacted]	[redacted]	[redacted]
Chemotherapy	Docetaxel + platinum	[redacted]	[redacted]	[redacted]
	Gemcitabine + platinum	[redacted]	[redacted]	[redacted]
	Paclitaxel + platinum	[redacted]	[redacted]	[redacted]
	Vinorelbine + platinum	[redacted]	[redacted]	[redacted]
	Pemetrexed + platinum	[redacted]	[redacted]	[redacted]
	Docetaxel monotherapy	[redacted]	[redacted]	[redacted]
	Docetaxel + nintedanib	[redacted]	[redacted]	[redacted]
	Docetaxel + gemcitabine a	[redacted]	[redacted]	[redacted]
	Gemcitabine monotherapy a	[redacted]	[redacted]	[redacted]
	Vinorelbine monotherapy a	[redacted]	[redacted]	[redacted]

Notes: [a] These treatments were not listed within the NICE final scope however are included as they are incorporated within the efficacy and therefore costed for.

Chemotherapy

The model provides a few treatment options in the costing for which 0% was allocated. There was no explanation for the exclusion of "Gemcitabine + vinorelbine" and "Pemetrexed" from the treatment options in the costing. These were treatments in the real-world data.

The Company provided the information presented in Table A.1.2 from the Company response to Question B8a in the Company response to the PfCs to help explain the classification of treatments in the base-case model. The ERG assumed that it was an error to state that "Carboplatin & paclitaxel" was reclassified as "Pemetrexed + platinum" because the model includes "Paclitaxel + platinum". The Company did not precisely explain how treatments classified as "Other" were redistributed across the other treatments in the base-case. However, the example given for immunotherapy for untreated patients in Table 16 in the Company response to Question B11 in the response to PfCs was that "Other" treatments were redistributed proportionally according to the prevalence of the other treatments.

The ERG attempted to reproduce the treatment distribution in the model by redistributing the treatments labelled "Other". The ERG assumed "Carboplatin & paclitaxel" was classified as "Paclitaxel + platinum", which seems consistent with classifying "Carboplatin & pemetrexed" as "Pemetrexed + platinum". The ERG treatment distribution estimate is presented in Table A1.1.

Table A.1.2: Re-distributions of chemotherapies for the economic model (reproduced from Table 13 in the response to PfCs)

Original treatment	Model treatment category	Chemotherapy (n=66)	
		Frequency	Percent
Carboplatin & pemetrexed	Pemetrexed + platinum	[redacted]	[redacted]
Platinum doublet a	Other	[redacted]	[redacted]
Bevacizumab, carboplatin & pemetrexed	Pemetrexed + platinum	[redacted]	[redacted]
Carboplatin & paclitaxel	Pemetrexed + platinum	[redacted]	[redacted]
Docetaxel	Docetaxel	[redacted]	[redacted]
Pemetrexed	Pemetrexed + platinum	[redacted]	[redacted]
Cisplatin & pemetrexed	Pemetrexed + platinum	[redacted]	[redacted]
Pemetrexed & bevacizumab	Pemetrexed + platinum	[redacted]	[redacted]
Bevacizumab, cisplatin & pemetrexed	Pemetrexed + platinum	[redacted]	[redacted]
Carboplatin a	Other	[redacted]	[redacted]
Carboplatin & gemcitabine	Gemcitabine + platinum	[redacted]	[redacted]
Cisplatin & etoposide	Docetaxel + platinum	[redacted]	[redacted]
Cisplatin & gemcitabine	Gemcitabine + platinum	[redacted]	[redacted]
Cisplatin & vinorelbine	Vinorelbine + platinum	[redacted]	[redacted]
Everolimus a	Other	[redacted]	[redacted]
Gemcitabine & vinorelbine	Docetaxel + gemcitabine	[redacted]	[redacted]
Vinorelbine	Vinorelbine monotherapy	[redacted]	[redacted]

Note: [a] The 'other' category are re-distributed proportionally between the remaining treatments

Immunotherapy

The Company provided the information presented in Table A.1.3 from the Company response to Question B8a in the Company response to the PfCs to help explain the classification of treatments in the base-case model.

The ERG attempted to reproduce the treatment distribution in the model by redistributing the treatments labelled "Other". The ERG treatment distribution estimate is presented in Table A.1.1.

Table A.1.3: Re-distributions of immunotherapies for the economic model (reproduced from Table 12 in the response to PfCs)

Original treatment	Model treatment category	Immunotherapy (n=51)	
		Frequency	Percent
Pembrolizumab	Pembrolizumab	[redacted]	[redacted]
Immunotherapy a	Other	[redacted]	[redacted]
Nivolumab	Nivolumab	[redacted]	[redacted]
Ipilimumab & nivolumab	Ipilimumab + nivolumab	[redacted]	[redacted]
Durvalumab a	Other	[redacted]	[redacted]
Spartalizumab a	Other	[redacted]	[redacted]

Note: [a] The 'other' category are re-distributed proportionally between the remaining treatments

Expert elicitation of distribution of comparator treatments

The opinions of experts were elicited to derive a distribution of comparator treatment likely to be seen in the UK. These estimates are presented in Table A.1.1. These estimates are mostly useful in evaluating whether the effectiveness estimates are generalisable to the UK context. Since the effectiveness estimates are based on non-UK treatment distributions, the costs in the model also need to be based on non-UK treatment distributions.

Subsequent treatments

The distribution of subsequent treatments was derived from the VISION trial and real-world data sets. Subsequent treatments listed are not routinely used for NSCLC patients in clinical practice or are not available in the UK were categorised as "Other" and redistributed among the other treatments. While every patient was classified as receiving one treatment combination, every patient was classified as receiving one or more individual subsequent treatments. The base-case distribution of subsequent treatments is presented in Table A.1.4.

Table A.1.4: Base-case distribution of subsequent treatments (reproduced from Table 57 CS)

Treatment category	Treatment	Tepotinib (VISION) N=151	Immunotherapy (real-world cohort data) N=150	Chemotherapy (real-world cohort data) N=152
Patient who had at least one subsequent treatment		[redacted]	[redacted]	[redacted]
Immunotherapy	Pembrolizumab	[redacted]	[redacted]	[redacted]
	Atezolizumab	[redacted]	[redacted]	[redacted]
	Nivolumab	[redacted]	[redacted]	[redacted]
Chemotherapy	Pemetrexed	[redacted]	[redacted]	[redacted]
	Vinorelbine	[redacted]	[redacted]	[redacted]
	Paclitaxel	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]
	Gemcitabine	[redacted]	[redacted]	[redacted]
Platinum	Cisplatin	[redacted]	[redacted]	[redacted]
	Carboplatin	[redacted]	[redacted]	[redacted]
Targeted	Brigatinib	[redacted]	[redacted]	[redacted]
	Nintedanib	[redacted]	[redacted]	[redacted]
MET inhibitor	Crizotinib	[redacted]	[redacted]	[redacted]
Total weighted cost per progressed patient		[redacted]	[redacted]	[redacted]

Expert elicitation of UK subsequent treatment distributions

The opinions of clinical experts were also elicited to derive UK-relevant distributions. These are presented in Table A.1.5.

The basic principles were reported as follows:

For immunotherapy, it is assumed that no patients will receive subsequent immunotherapy, therefore all these patients are proportionally re-distributed to the chemotherapy regimens.

For tepotinib it is assumed that the distribution of treatments from first-line and second-line would not be changed (with the exception of immunotherapy in combination with chemotherapy which are only available in untreated patients) therefore both immunotherapies and chemotherapies are included.

For chemotherapy, the distribution of previously treated estimates are used for this scenario.

These estimates are mostly useful in evaluating whether the effectiveness estimates are generalisable to the UK context. Since the effectiveness estimates are based on non-UK treatment distributions, the costs in the model also need to be based on non-UK treatment distributions.

Table A.1.5: Expert elicited distribution of subsequent treatments in the UK (reproduced from Table 66, CS Appendix P1.2)

Category	Treatment	Tepotinib	Immunotherapy	Chemotherapy
Immunotherapy	Pembrolizumab	[redacted]	[redacted]	[redacted]
	Atezolizumab	[redacted]	[redacted]	[redacted]
	Nivolumab	[redacted]	[redacted]	[redacted]
Chemotherapy	Pemetrexed	[redacted]	[redacted]	[redacted]
	Vinorelbine	[redacted]	[redacted]	[redacted]
	Paclitaxel	[redacted]	[redacted]	[redacted]
	Docetaxel	[redacted]	[redacted]	[redacted]
	Gemcitabine	[redacted]	[redacted]	[redacted]
Platinum	Cisplatin	[redacted]	[redacted]	[redacted]
	Carboplatin	[redacted]	[redacted]	[redacted]
Targeted	Brigatinib	[redacted]	[redacted]	[redacted]
	Nintedinib	[redacted]	[redacted]	[redacted]
MET inhibitor	Crizotinib	[redacted]	[redacted]	[redacted]
Total		[redacted]	[redacted]	[redacted]

Appendix 2: ERG survival model selections and the OS, PFS, and hazard ratio graphs

A2.1 Checks for PFS and OS curves crossing

A2.1.1 Base-case (overall population) survival curves

Table A.2.1: ERG & CS Distributions of Tepotinib OS & PFS

Tepotinib	CS	ERG
OS	log-logistic	log-logistic
PFS	log-normal	log-normal

Figure A.2.1: ERG & CS Extrapolation of Tepotinib OS & PFS

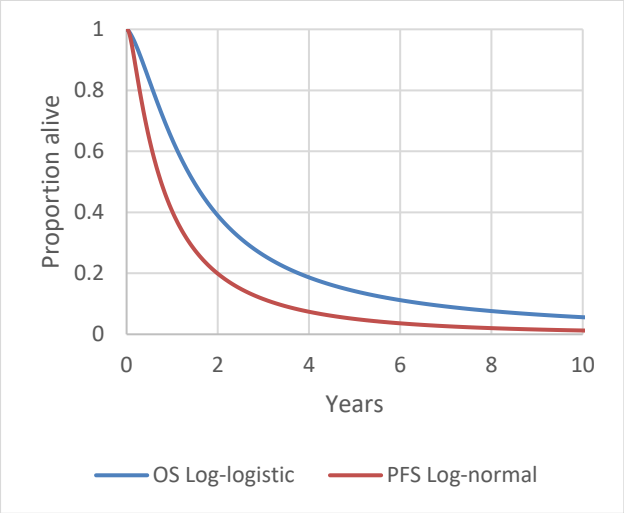


Table A.2.2: ERG & CS Distributions of chemotherapy OS & PFS

Chemotherapy	CS	ERG
OS	Weibull	Log-normal
PFS	One knot odds spline	Spline 3 knot odds

Figure A.2.2: CS Extrapolation of chemotherapy OS & PFS for general population

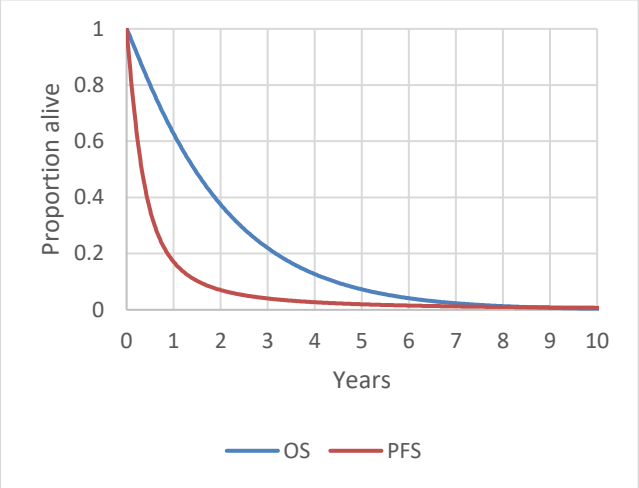


Figure A.2.3: ERG Extrapolation of chemotherapy OS & PFS for overall population

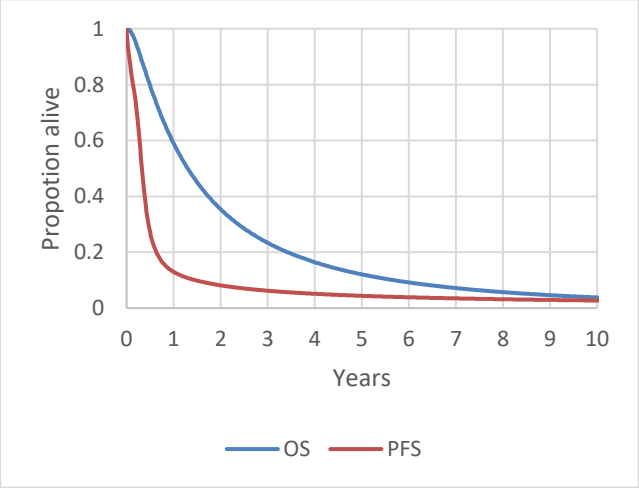


Table A.2.3: ERG & CS Distributions of immunotherapy OS & PFS for Overall population

Immunotherapy	CS	ERG
OS	Spline one knot normal	Spline 2 knot normal
PFS	Piece-wise log-logistic	piecewise log-logistic

Figure A.2.4: CS Extrapolation of immunotherapy OS & PFS for overall population

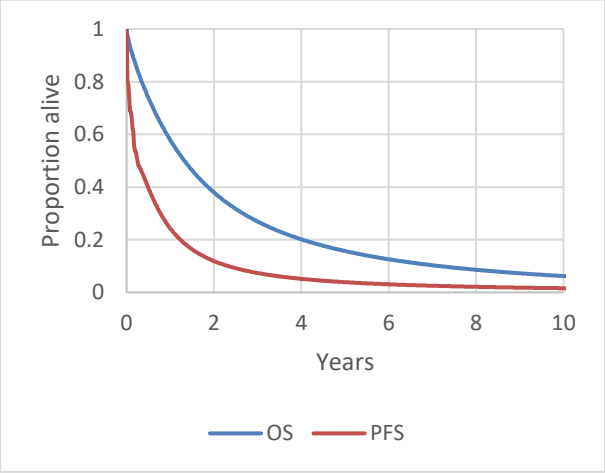
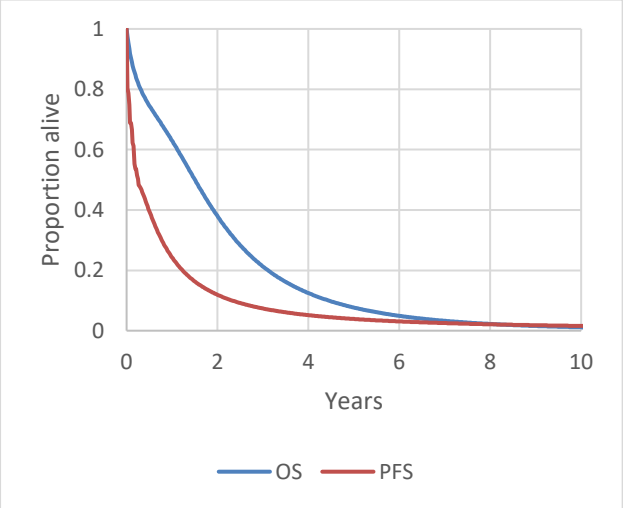


Figure A.2.5: ERG Extrapolation of immunotherapy OS & PFS for Overall population



A2.1.2 Untreated population survival curves

Table A.2.4: ERG & CS Distributions of Tepotinib OS & PFS for Untreated population

Tepotinib	CS	ERG
OS	Log-normal	Log-logistic
PFS	Log-normal	Log-logistic

Figure A.2.6: ERG & CS Extrapolation of Tepotinib OS & PFS for Untreated population

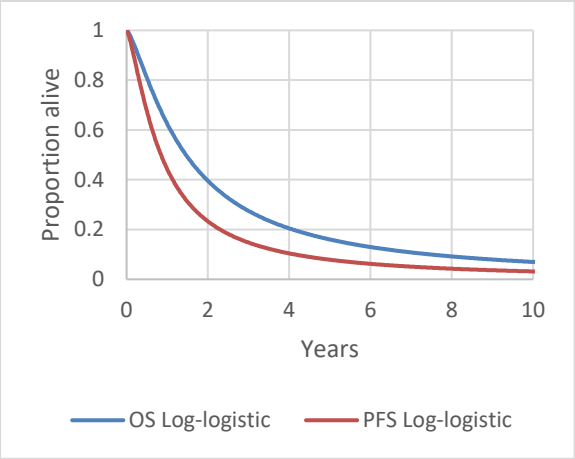


Table A.2.5: ERG & CS Distributions of Chemotherapy OS & PFS for Untreated population

Chemotherapy	CS	ERG
OS	Weibull	Log-normal
PFS	Spline 2 knot odds	Spline 3 knot Odds

Figure A.2.7: CS Extrapolation of Chemotherapy OS & PFS for Untreated population

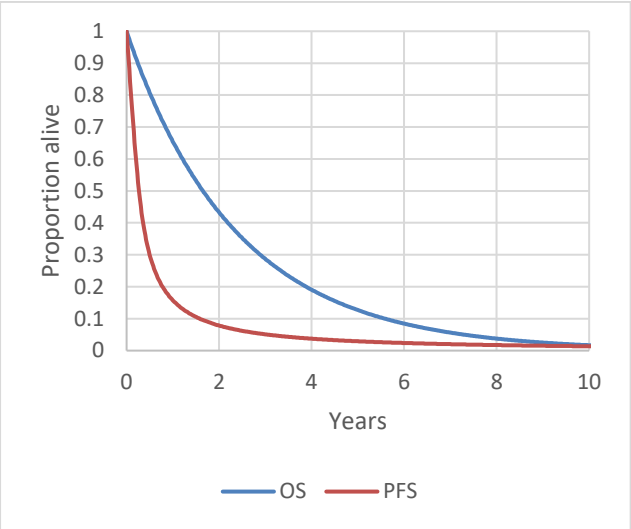


Figure A.2.8: ERG Extrapolation of Chemotherapy OS & PFS for Untreated population

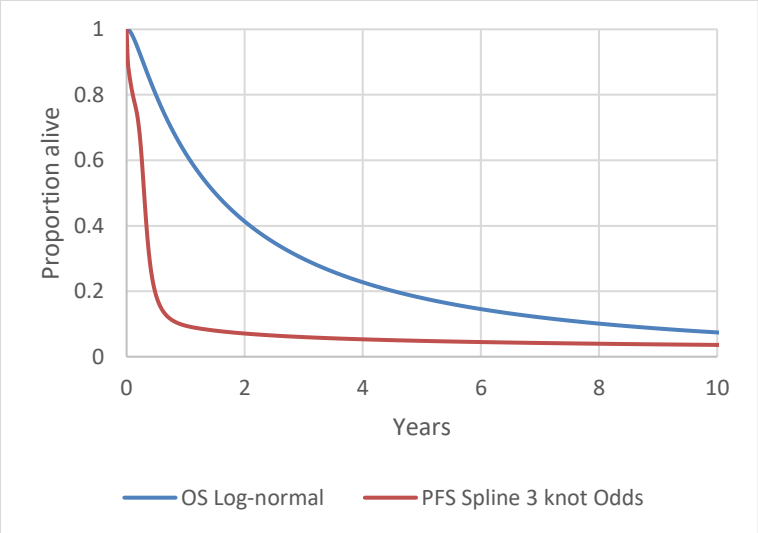


Table A.2.6: ERG & CS Distributions of Immunotherapy OS & PFS for Untreated population

Immunotherapy	CS	ERG
OS	Spline 2 knot normal	Spline 2 knot normal
PFS	Piece-wise Weibull	Piece-wise log-normal

Figure A.2.9: CS Extrapolation of Immunotherapy OS & PFS for Untreated population

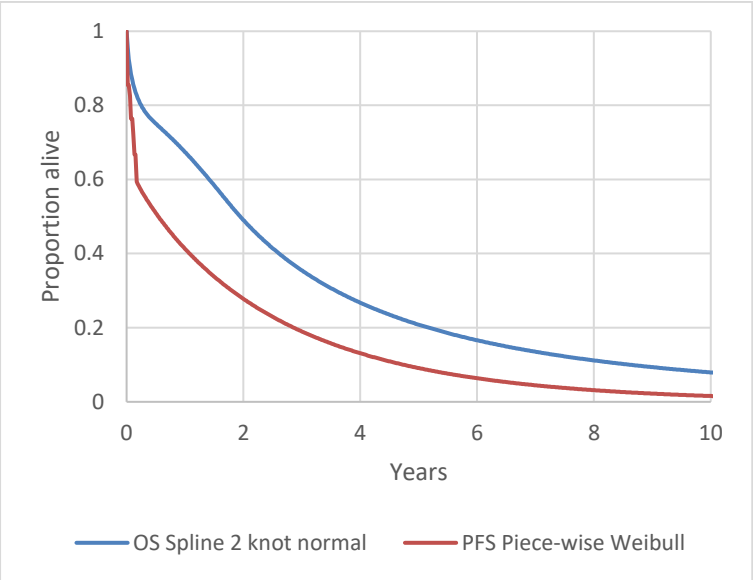
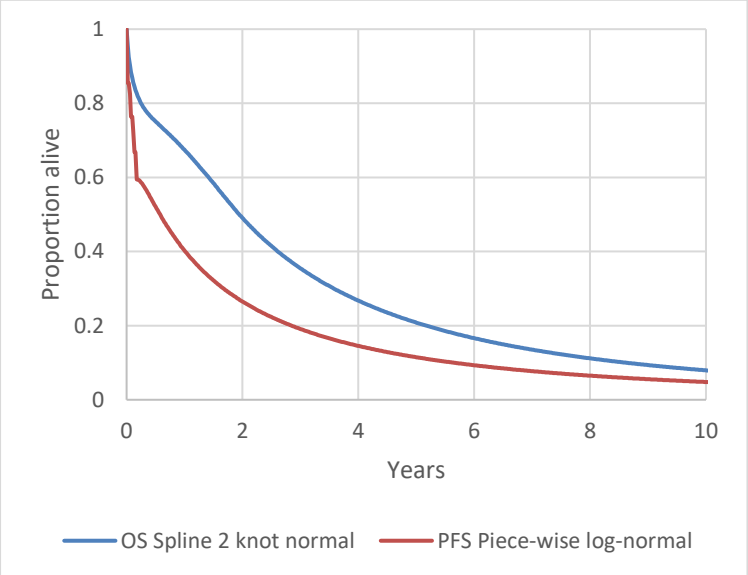


Figure A.2.10: ERG Extrapolation of Immunotherapy OS & PFS for Untreated population



A2.1.3 Treated population survival curves

Table A.2.7: ERG & CS Distributions of Tepotinib OS & PFS

Tepotinib	CS	ERG
OS	Log-normal	Log-normal
PFS	Log-normal	Log-normal

Figure A.2.11: ERG Extrapolation of Tepotinib OS & PFS for Treated population

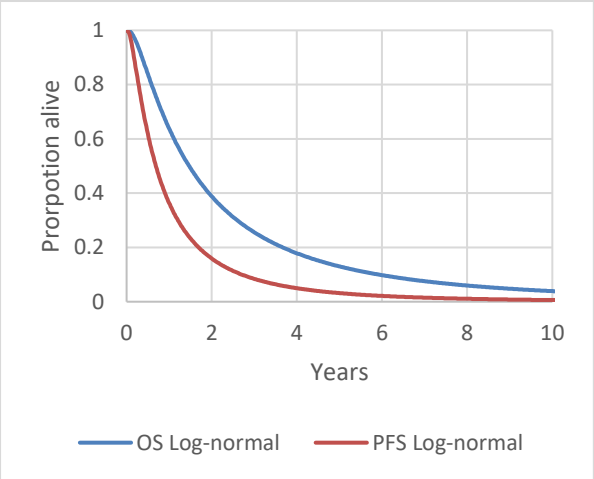


Table A.2.8: ERG & CS Distributions of Chemotherapy OS & PFS for Treated population

Chemotherapy	CS	ERG
OS	Weibull	Log-normal
PFS	Log-logistic	Log-logistic

Figure A.2.12: CS Extrapolation of Chemotherapy OS & PFS for Treated population

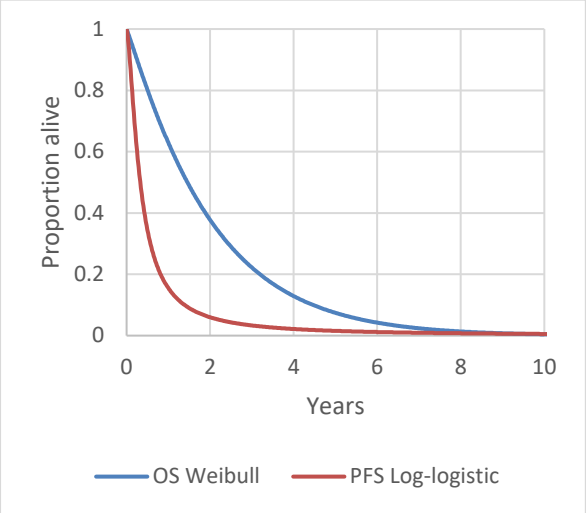


Figure A.2.13: ERG Extrapolation of Chemotherapy OS & PFS for Treated population

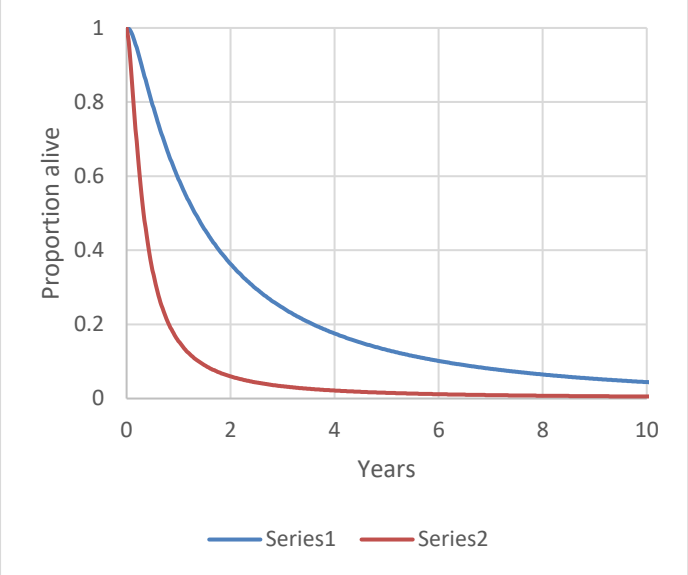


Table A.2.9: ERG & CS Distributions of Immunotherapy OS & PFS for Treated population

Immunotherapy	CS	ERG
OS	Spline 1-knot normal	Exponential
PFS	Spline 1 knot hazard	Gen-gamma

Figure A.2.14: CS Extrapolation of Immunotherapy OS & PFS for Treated population

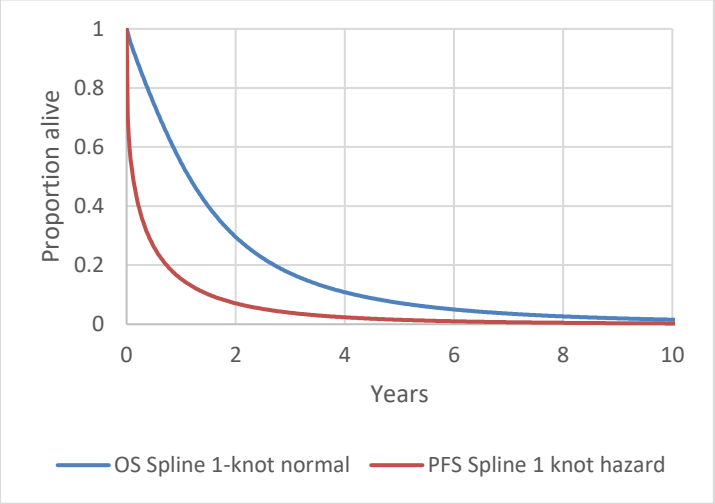
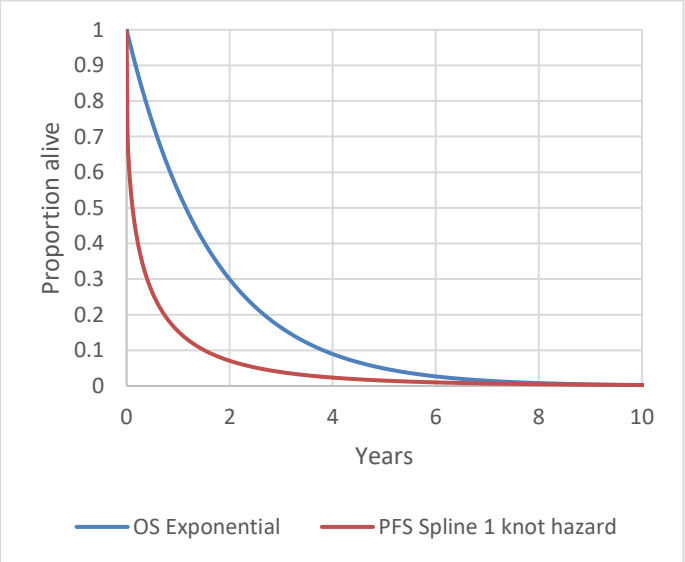


Figure A.2.15: ERG Extrapolation of Immunotherapy OS & PFS for Treated population



A2.2 Hazard ratio curves for the overall population

Figure A.2.16: CS Hazard ratio Tepotinib vs Chemotherapy for Overall population

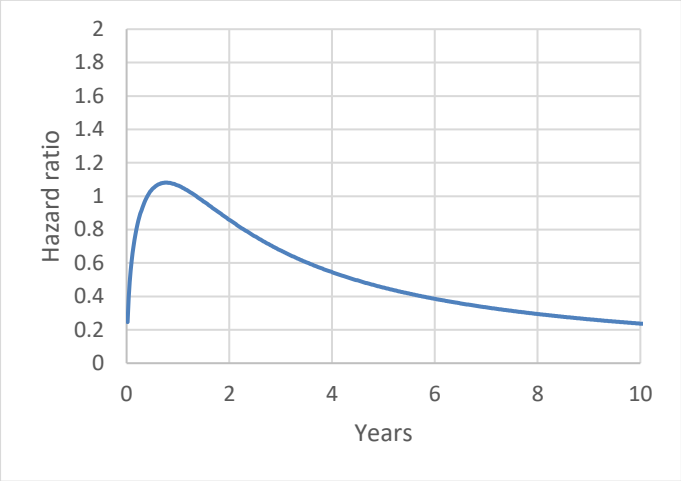


Figure A.2.17: ERG Hazard ratio Tepotinib vs Chemotherapy for Overall population

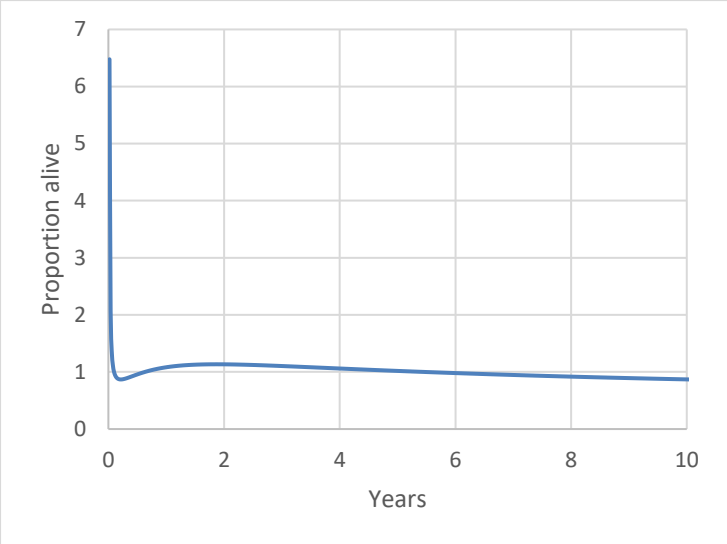


Figure A.2.18: CS Hazard ratio Tepotinib vs Immunotherapy for Overall population

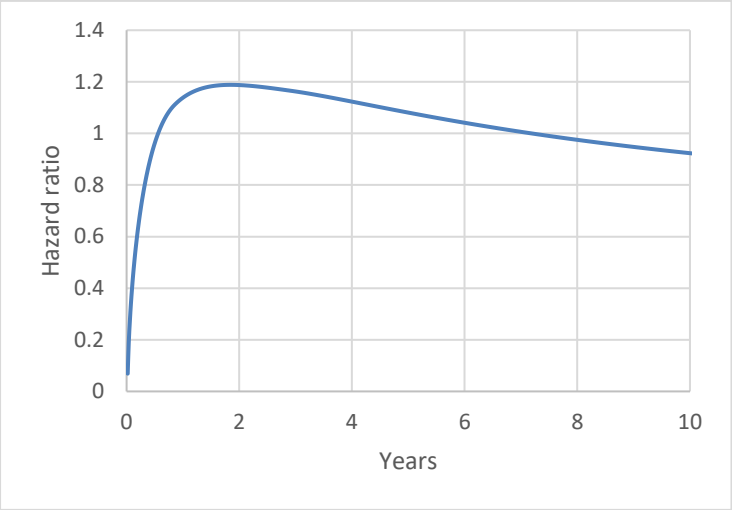
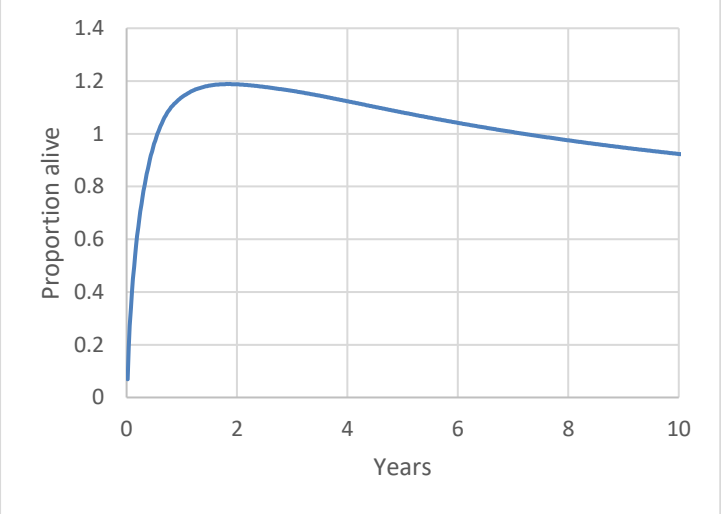


Figure A.2.19: ERG Hazard ratio Tepotinib vs Immunotherapy for Overall population



Appendix 3: Implementation of ERG analyses

To implement the ERG base-case, the ERG used the revised model submitted in the response to the letter of points for clarification. From the Control sheet, it then selected the population, then the comparator, and reset the parameters using the macro. Then the relevant survival models were selected for each comparator.

To implement the scenario analyses that the Company had conducted using the ERG selection of survival models, the Scenarios macro was run on the Scenarios sheet.

To implement the sensitivity analyses that the Company had conducted using the ERG selection of the survival models, the OWSA macro was run on the OWSA sheet.

To implement the treatment distribution scenario analysis, the ERG recalculated immunotherapy treatment percentages were entered in 'Treatment costs'!CellsF100-F115, and the ERG recalculated chemotherapy treatment percentages were entered in 'Treatment costs'!CellsL100-L115.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

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

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Wednesday 29 September 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Inaccuracies/typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 1.7, Table 1.17 – 1.20 Section 6.2, Tables 6.10 – 6.23	Incorrect reporting of results. Please see revised tables in the appendix	Some of the results appear to be incorrectly reported in the ERG report (both the ERG base case and company base case). Merck have checked these results in the latest economic model (post clarification, 27 August) and provided the correct results in the appendix of this document. The model results and 'incremental analysis' sheet have been used. For the ERG base case results, we selected the settings stated in the ERG report (described in Section 6.1.1). Results might be different due to rounding errors.	All of the tables have been edited accordingly. The Corrected tables presented in the Appendix in this document were correct.
Section 1.3, page 13, Table 1.2 *"…**estimated glomerular filtration rate** (EGFR)+"*	*"epidermal growth factor receptor (EGFR)+"*	Incorrect definition of EGFR	Corrected.
Section 3.2, page 39, Table 3.7 Black or African American [redacted] Asian [redacted]	The values for these rows should be swapped: [Asian = 88 (30.2), Black or African American (1.0)] Black or African American [redacted] Asian [redacted]	This was an error in the initial company submission, and was corrected and noted for in other patient characteristics tables. However, these revisions need to be carried across to this table too in the ERG report, for the Baseline	Corrected.

		characteristics, VISION Cohort A+C – 1 February 2021 cut-off (safety set)	
Section 3.4.1, page 49 *"Over half of the patients had missing ECOG status (**precise number not reported**), but these were not excluded, except in a sensitivity analysis (Appendix L)."*	*"Over half of the patients had missing ECOG status ([redacted] and 52.9% of chemotherapy and immunotherapy patients respectively), but these were not excluded, except in a sensitivity analysis (Appendix L)."*	The unknown ECOG status is reported in Table 20 of the CS (18 August version)	Corrected.
Section 3.4.3, page 51 *"This was conducted for OS **only** and the methods were presented in Appendix L."*	*"This was conducted for OS and PFS (where available) and the methods were presented in Appendix L."*	PFS was included in the MAIC for comparisons with Sabari et al.(1) and Guisier et al..(2) Awad et al.(3) did not present PFS therefore only OS was conducted for this comparison.	Corrected.
Section 3.6, page 55 [redacted]	[redacted]	Text error	Corrected.
Section 4.2.4, page 64 *"Time on treatment (ToT) was modelled using the data from **the ITC** (see Section 4.2.9)."*	*"Time on treatment (ToT) was modelled using the data from VISION for tepotinib and literature for the comparators (see Section 4.2.9)."*	Incorrect description of ToT. ToT data from the real-world cohort was not available to use to inform the model and therefore ITC data was not used.	Corrected.
Section 4.2.6, page 66 *"If these were considered a poor fit, **piecewise models and** spline models were fit to the data. Odds,*	*"If these were considered a poor fit, spline models were fit to the data. Odds, hazard and normal restricted cubic spline models, varying from one to three knots, were fitted to the data, in line with NICE TSD 21.[44] If the spline models*	Proposed amendment provides clarification on the approach to fit survival curves to the trial data.	Corrected.

*hazard and normal restricted cubic spline models, varying from one to three knots, were fitted to the data, in line with NICE TSD 21.[44] If the **parametric** models were considered an extremely poor fit, piece-wise parametric curves were fit to the data."*	*were also considered an extremely poor fit, piece-wise parametric curves were fit to the data."*		
Section 4.2.6, page 66 *"Models were fit using **STATA**."*	*"Models were fit using R."*	Incorrect software stated.	Corrected.
Section 4.2.6, page 73 *"The ERG also notes that the selected models for immunotherapy are conservative for tepotinib compared to the best fitting models, and the selected models for immunotherapy are favourable for tepotinib compared to the best fitting models."*	To update and correct this statement	This statement is conflicting, as in part it says the immunotherapy models are conservative for tepotinib, but then also says they are favourable for tepotinib.	Corrected to say, *"The ERG also notes that the selected models for immunotherapy are conservative for tepotinib compared to the best fitting models, and the selected models for **chem**otherapy are favourable for tepotinib compared to the best fitting models."*
Section 4.2.7, page 74 *"The ERG notes that the selected models in some cases are not the best fit but that the fit is not terrible."*	*"The ERG notes that the selected models in some cases are not the best fit but that the fit is not terrible, and in most cases the fit statistics are within 5, suggesting multiple options are suitable."*	To add clarification regarding the AIC and BIC fit statistics. In most cases, the AIC and BIC fit statistics are within 5 points, suggesting that there is little difference in statistical fit between the curves, and therefore it is irrelevant which has the smallest value.	Edited to say, *"The ERG notes that the selected models in some cases are not the best fit but that in most cases the fit statistics are within 5, suggesting multiple options are suitable."*
Section 4.2.7, page 74 *"The proportion of patients*	*"The proportion of patients experiencing each adverse event were obtained from the VISION study for tepotinib and from previous NSCLC*	Text error	Corrected.

*experiencing each adverse event were obtained from the VISION study for tepotinib and from previous **NSCLS** appraisals and literature for the comparators."*	*appraisals and literature for the comparators."*		
Section 4.2.7, page 74 *"The percentages of **adverse events** used in the economic model differ from those reported in the real-world data sets. The method for deriving the percentages was not reported. The difference in percentages may be related to the process of re-classifying non-UK treatments and treatments classified as a treatment class as one of the other treatments in the data set, proportionally according to the treatment prevalence. The result of this process is an increase in the proportion of patients on the remaining treatments. Proportions of **adverse events** would then be related to the included treatments and the percentage of patients receiving each treatment."*	First sentence to be removed, and clarification added about what this refers to (adverse events versus subsequent treatments). *"The method for deriving the percentages was not reported. The difference in percentages may be related to the process of re-classifying non-UK treatments and treatments classified as a treatment class as one of the other treatments in the data set, proportionally according to the treatment prevalence. The result of this process is an increase in the proportion of patients on the remaining treatments. Proportions of subsequent treatments would then be related to the included treatments and the percentage of patients receiving each treatment."*	This paragraph is incorrect. AEs were taken from the literature and not from the real-world data sets. The context of this paragraph makes sense if it is describing subsequent treatments, not adverse events. If this is correct then this is included in the wrong section of the report.	Corrected – this should have said Table 28 CS as opposed 'real world data sets'.
Section 4.2.8, page 79 *"The company chose the mean utility in the on-treatment dataset to inform the model."*	*"The company used the results of the linear mixed model that included progression and baseline observation."*	Initial statement incorrect. Correct statement proposed.	Corrected.
Section 4.2.9, page 80	*"A cap was included to ensure that the proportion of patients on treatment was lower or*	Initial statement incorrect. Correct	Corrected.

"The proportion of patients on treatment was lower than the proportion of patients in the PFS state."	*equal to the proportion of patients in the PFS state."*	statement proposed.	
Section 4.2.9, page 84 *"The ERG notes that while the company selected the generalised Gamma model for ToT for tepotinib, the exponential model is the best fitting model according to the AIC statistic. While the cost-effectiveness results using the exponential model are similar to those using the generalised Gamma model, the cost-effectiveness results are very different when using the log-logistic model. The log-logistic model possibly over-fits the tail end of the distribution and a piece-wise parametric model or a spline model, which were not fit by the company, may have been a better fit."*	Paragraph to be removed	This paragraph is repeated in the paragraph above, and so does not need to be stated twice	Paragraph removed.
Section 5.1.1, page 85 *"From the **probabilistic** results, tepotinib was associated with [redacted] more than the next best comparator and [redacted] QALYs more"* *Section 5.1.3, page 86* *"From the **probabilistic** results, tepotinib was associated with [redacted]*	*"From the deterministic results, tepotinib was associated with [redacted] more than the next best comparator and [redacted] QALYs more"* *"From the deterministic results, tepotinib was associated with [redacted] more than the next best comparator and [redacted] QALYs more. The ICER*	Incorrect description. Correct description proposed	Corrected.

more than the next best comparator and [redacted] QALYs more. The ICER was £18,176."	*was £18,176."*		
Section 5.1.4, page 87 *"Table 5.5: **Full incremental** analysis (deterministic) for the contra-indicated to immunotherapy population"* Section 5.1.5, page 87 *"Table 5.6: **Full incremental** analysis (deterministic) for the unsuitable for chemotherapy population (reproduced from CS Tables 60 & 61)"*	*"Table 5.5: Pair-wise analysis (deterministic) for the contra-indicated to immunotherapy population"* *"Table 5.6: Pair-wise analysis (deterministic) for the unsuitable for chemotherapy population (reproduced from CS Tables 60 & 61)"*	Incorrect description. Correct description proposed	Table headings edited accordingly.
Section 5.2.2, page 90 *"Proportion of patients receiving subsequent treatment – chemotherapies: crizotinib (19.4%-40.8%)"*	*"Proportion of patients receiving subsequent treatment – chemotherapies: crizotinib (21.7%-36.0%)"*	Incorrect values. Correct values proposed (see Appendix L or the model 'parameter' sheet) for reference.	Corrected.
Section 5.2.2, page 91 *"Relative Dose Intensity (RDI) – pembrolizumab (79.8%-118.7%)"*	To be removed	Repeated bullet point	Corrected.
Section 6.1.2, page 109, Table 6.15 *"Subsequent Treatment for chemo*	*"Subsequent Treatment for chemo brigatinib (UB)"*	Text error	Corrected.

***briogatinib** (UB)"*			
Section 6.4, page 115 *"The ERG had to compile the set of decision questions addressed because of the lack of clarity in the reporting of the results and the conclusions **drawen**."*	*"The ERG had to compile the set of decision questions addressed because of the lack of clarity in the reporting of the results and the conclusions drawn*."	Text error	Corrected.

Issue 2 Subgroups

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Multiple sections, related to Key Issue 2: Lack of subgroup (line of therapy, histological status, PD-L1 status) analysis according to scope *"Analysis by appropriate subgroup including comparators appropriate to that subgroup including PD-L1 status and histology is recommended." (pg 14)* *"In terms of the ITC using propensity scoring, it is not clear that patient numbers would have been too small for an analysis of comparators by subgroup, specifically PD-L1 status and histology, as referred to in Section 2.3." (pg 51)* *"It is also not clear that patient numbers would have been too*	It should be acknowledged in the ERG report that there were no data on PD-L1 expression available for the company to use within the indirect treatment comparisons, and so sub-group analysis for this in the indirect comparison was not possible.	PD-L1 expression was not collected as part of the VISION trial, and PD-L1 expression data was not available for the vast majority of patients in the real-world datasets either. It was already stated that histology sub-group analysis was challenging given the low numbers of patients with squamous disease in VISION (n=[redacted] %).	This is not a factual inaccuracy. However, the lack of subgroup data in VISION has now been added.

small for an analysis of comparators by subgroup, specifically PD-L1 status and histology" (pg 55)			
Section 4.2.3, page 61 *"A further subgroup of patients contra-indicated or unsuitable to immunotherapy, whether untreated or previously treated, is informed by the evidence from the results of the **3 different models**."* *Section 5.1, page 85* *"Three different models were designed to provide evidence to these five decision populations."*	Please re-phrase to make it clear that the company did not present three separate models for different subgroups	One model was submitted which included three sub-populations: - Overall (all patients) - Untreated - Previously treated	Edited to read, "A further subgroup of patients contra-indicated or unsuitable to immunotherapy, whether untreated or previously treated, is informed by the evidence from the results for the 3 different populations modelled." The report has been edited in several places accordingly.
Section 4.2.3, page 62 *"The ERG notes that **the company submission does consider a population that is contra-indicated or unsuitable to immunotherapy,** which is not a subgroup mentioned in the scope. In response to clarification point B26.b, the company clarifies that there is a population for whom chemotherapy would not be considered and therefore the only comparator is immunotherapy alone. This population is across histology groups, PD-L1 groups and treatment line. The clinical*	As per response to clarification point B26.b, the company would like to clarify that clinical expert opinion confirmed the vast majority of patients now receive immunotherapy or immunotherapy in combination with chemotherapy as a first-line treatment in advanced NSCLC (Appendix P, P.1.2) and only a small proportion receive platinum-based chemotherapy alone at first line (although this is higher for squamous patients), some of whom are contraindicated or unsuitable for immunotherapy. This also means that the vast majority of patients also receive some form of chemotherapy at second line, and very few receive immunotherapy.	This section of the ERG could be an incorrect interpretation of the clarification response previously provided by Merck. Therefore, we have provided additional clarification here about the pairwise comparisons to immunotherapy, and feedback on the treatment landscape.	The report has been edited accordingly to indicate that there is no subgroup where immunotherapy is the only comparator. Table 1.16, section 4.2.3, Table 4.4, Table 5.1, section 5.1.5 removed, section 6.1.1, Table 6.4, section 6.2, what was Table 6.12 removed, section 6.4.

context as to why chemotherapy would not be a relevant comparator for this subgroup was not explained." Section 4.2.4, page 64 *"For the decision populations that have been considered for analysis, the comparators appear to be appropriate, although the clinical context as to why immunotherapy alone might be the only relevant comparator to tepotinib in some circumstances was not explained."* Section 5.1.5, page 87 *"At no point does the company describe a population as unsuitable for chemotherapy. That appears to be the implication of the focus on a pairwise comparison."*	Therefore, chemotherapy and immunotherapy are both treatment options across lines of therapy, as tepotinib is expected to be. Therefore, full incremental cost-effectiveness analysis including all treatments is relevant and was provided in the updated model by 27 August 2021. Based on clinical expert opinion, there is unlikely to be a population that is considered unsuitable for chemotherapy, but would receive just immunotherapy. Therefore, this should not be a population, and this was not intended to be the implication. All pairwise and incremental results were provided for illustrative and completeness purposes.		

Issue 3 Comparators

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 2.3, page 28 *"It is not clear why **pembrolizumab combination with pemetrexed and platinum chemotherapy and** atezolizumab monotherapy were not listed as comparators for*	*"It is not clear why atezolizumab monotherapy was not listed as a comparator for people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score."*	Pembrolizumab in combination with pemetrexed and platinum chemotherapy should be removed from this statement. Pembrolizumab in combination with pemetrexed and platinum chemotherapy is not available for patients with squamous	Corrected.

people with squamous NSCLC whose tumours express PD-L1 with at least a 50% tumour proportion score."		NSCLC with PD-L1 ≥50%. Instead it is only available for non-squamous patients, as per the marketing authorisation, NICE recommendation and NICE guidelines. (4-6) Atezolizumab is an option for this population however and should remain in the statement.(7)	
Section 2.3, page 28 "*Indeed, only atezolizumab monotherapy, and* ***neither pembrolizumab monotherapy*** *nor pembrolizumab with carboplatin and paclitaxel is listed in the NICE pathway as first-line treatment for both squamous and non-squamous"*	"*Indeed, only atezolizumab monotherapy, is listed in the NICE pathway as first-line treatment for both squamous and non-squamous"*	Pembrolizumab monotherapy should be removed from this statement. Pembrolizumab monotherapy is available for the first line-treatment of non-squamous and squamous NSCLC patients, with PD-L1 expression ≥50%.	Corrected.
Section 6.1.3, page 98, Table 6.8 Section 6.2.3, page 112, Table 6.19	The comparator for the untreated adenocarcinoma/large cell carcinoma PD-L1<50% population should be changed to chemotherapy. This also impacts Table 6.19 in Section 6.2.3 and the results included for this subgroup.	Based on the NICE scope, the relevant comparator for this subgroup is: • Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) with (following cisplatin containing regimens only) or without pemetrexed maintenance treatment. Therefore, only chemotherapy should be included for this potential sub group. Immunotherapy or immunotherapy in combination with	The comparator has been changed to chemotherapy only.

		chemotherapy is not listed in the NICE scope here, and so should not be included as a comparator for this potential sub group.	

Issue 4 Clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 3.2.3, Page 47 *"The ERG notes that the numbers presented for tepotinib in Table 41 do not match those in Table 28 of the CS. In fact, the Table 41 values all seem to be higher e.g. hypoalbuminaemia: 5.5% vs.* [redacted] *There is a very large difference between peripheral oedema in Table 28 vs. Oedema peripheral/other, which is 7.8% vs.* [redacted] *although it is not clear what else the latter might include. The ERG can confirm that the values reported in Table 28 correspond to those in the CSR with 1 July 2020 cut-off. (8)Although it is unclear what the source of the values in Table 41 is, the ERG is reassured that the higher values seem to have been used in the cost effectiveness analysis."* Section 4.2.7, page 74 *"As discussed in that section, the*	Please remove this paragraph, as an explanation is provided below. Table 28 of the CS relates to Cohort A+C at the July 2020 data cut-off. This is consistent with other safety reporting from VISION. However, the AEs used in the cost-effectiveness model are using Cohort A only to match the source of the efficacy data used to inform tepotinib.	Clarification provided by Merck	Corrected.

percentages of adverse events used in the economic model differ from those reported in the real-world data sets (CS Table 28).[1]"			
Section 4.2.4, page 63 *"The treatment distribution used in the economic model differs from the treatment distribution in the real-word data set matched to the VISION data set (CS Table 20 and Table 21)."* Section 4.2.4, page 64 *"The method for calculating the proportions of treatments within the immunotherapy and chemotherapy categories was not clearly stated and the ERG could not reproduce the results; the ERG calculated a different distribution using the information presented by the company in the response to the letter of points for clarification."* Section 4.2.9, page 83 *"Secondly, it was unclear how the treatment distribution percentages were derived. The ERG could not reproduce the distributions (see Appendix 1)."* *Section 6.1.2, page 95* *"It was not clear how the Company derived the treatment distributions*	Please can this be re-phrased. Merck used the weighted numbers to produce the treatment distributions in the economic model to align with the weighted efficacy data.	Clarification. Please see attached spreadsheet of calculations for the treatment distributions.	The spreadsheet of calculations does not clarify the issue as we do not know how the weighted values in Column D are derived. It is not (n/N)*152. In addition, the model categories presented in the Excel spreadsheet provided as part of the FAC response are slightly different to those presented in the points for clarification. Vinorelbine monotherapy was specified in the company response to clarification model categories table (distinct from vinorelbine/ platinum) but not in the FAC model categories table. The paragraphs have been rephrased as follows: Section 4.2.4, page 63 *"The treatment distribution used in the economic model differs from the treatment distribution in the real-word data set matched to the VISION data set (CS Table 20*

for immunotherapy and chemotherapy. The ERG tried to reproduce the treatment distribution but could not (see Appendix 1). The ERG distribution was included in a scenario analysis for the base-case model."			*and Table 21).* ***The company clarified that weighted numbers were used in the economic model to produce treatment distributions to align with the weighted efficacy data. However, the ERG does not know how these weights were calculated. They could not be reproduced."*** Section 4.2.4, page 64 *"The method for calculating the proportions of treatments within the immunotherapy and chemotherapy categories was not clearly stated and the ERG could not reproduce the results; the ERG calculated a different distribution using the information presented by the company in the response to the letter of points for clarification.* ***The company clarified that weighted numbers were used in the economic model to produce treatment distributions to align with the weighted efficacy data. However, the ERG does not know how these weights were calculated."*** *Section 6.1.2, page 95*

			"It was not clear how the Company derived the treatment distributions for immunotherapy and chemotherapy. The ERG tried to reproduce the treatment distribution but could not (see Appendix 1). The ERG distribution was included in a scenario analysis for the base-case model. ***The company subsequently clarified that weighted numbers were used in the economic model to produce treatment distributions to align with the weighted efficacy data. However, the ERG does not know how these weights were calculated.****"*
Section 4.2.4, page 64 *"The ERG notes that the comparators stated in the NICE scope were not included in the economic analysis."*	"*The ERG notes that the individual comparators stated in the NICE scope were not included in the economic analysis."*	Amendment proposed to clarify that the comparators listed in the scope were included in the economic analysis but not included separately. Instead they were included as groupings by treatment class.	Corrected.
Section 4.2.6, page 73 *"In the real-world data sets, there was some ambiguity in classifying*	Please remove or clarify what is meant by this statement, as it is currently unclear.	Merck considers no issue in clarifying patients as treated or untreated from the real-world data sets.	Corrected to read, "Treatment line in the real-world data sets was categorised in the same way as for the VISION data

patients as untreated or treated."			set: the first line of therapy was the first therapy received post diagnosis of advanced or metastatic disease." Also changed sentence in Section 6.4 from: "Many assumptions regarding the classification of first-line and second-line treatments, and regarding the progression-free survival outcome were made due to the data limitations." to "An assumption regarding the progression-free survival outcome was made due to the data limitations."
Section 4.2.8, page 79 *"However, the ERG notes that these may be the best available estimates."*	*"However, the ERG notes that these may be the best available estimates and have been used in previous NSCLC NICE submissions."*	To clarify that sources identified have been used in previous appraisals	Edited accordingly.
Section 4.2.9, page 82 *"This distribution was used in scenario analysis, but the company noted that there is an inconsistency altering the cost of the distribution without altering the effectiveness."*	Please remove this statement from this location or insert on page 83 below the following statement: *"The company also produced scenarios which reflected subsequent treatment distributions in the UK by eliciting clinical expert opinion."*	This is only an issue when considering alternative distributions of subsequent treatments. Altering the distributions of the comparator treatments is likely to have little impact due to the comparators being grouped with treatments of similar efficacy. This was only flagged by the company in the context of subsequent treatments.	The statement has been moved to below the following statement as suggested by the company: *"The company also produced scenarios which reflected subsequent treatment distributions in the UK by eliciting clinical expert opinion."* In addition, the ERG comment in section 4.2.9 has been

			amended to read: “The company argued that for the subsequent treatments it is better to use the treatment distribution based on the real-world data set in the economic model in order to maintain the relationship between the effectiveness and cost outcomes. The ERG agrees with this. The company stated in the FAC that they did not make that argument for comparator treatment distributions as the comparators were grouped with treatments of similar efficacy. The ERG considers that without evidence for equal efficacy the real world data treatment distribution are most appropriate.”

Confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Section 1.7, Table 1.17 – 1.19	Life year and incremental life years are marked as confidential	Confidential marking can be removed from the life year outputs	Amended.
Section 3.4.1, Page 49, Table 3.13	Treatment group data from the real-world cohort has not been marked confidential	Please mark CIC	Amended.

Section 4.2.4, page 64, Table 4.6	Real-world data (base case) treatment distributions have not been marked as confidential	Please mark CIC	Amended.
Section 4.2.9, page 83	*"The estimated per week monitoring and disease management costs were* [redacted] *and* [redacted] *per week…"* *"The total cost of adverse event for tepotinib* [redacted] *."* *"The terminal care cost was* [redacted] *per patient."*	Confidential marking can be removed from these costs.	Amended.
Section 5.2.1, page 88	*"Based on this analysis, the probability of tepotinib being cost effective is 80.1% and* [redacted] *compared to chemotherapy and immunotherapy at the £30,000 WTP. The company also reported the probability of cost effectiveness at £50,000 WTP and noted tepotinib is* [redacted] *is likely to be cost effective vs chemotherapy."*	Confidential marking can be removed from these probabilities.	Amended.
Section 6.2.1, Table 6.9-6.23	Life year and incremental life years are marked as confidential	Confidential marking can be removed from the life year outputs	Amended.

Appendix: Corrected tables

Table 1.18: ERG base-case full incremental results for Untreated population and the Company ICER

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company ICER (£/QALY)

Chemotherapy	[redacted]		[redacted]		[redacted]			
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	23,354
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	63,768	186,293
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 1.19: ERG base-case full incremental results for Treated population and the Company ICER

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company ICER (£/QALY)
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,363	Extendedly dominated
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	55,879	£24,824
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 1.20: The cost-effectiveness of tepotinib by decision problem subgroup

Population	Tepotinib ICER (ERG assumptions)	Tepotinib ICER (company assumptions)
Untreated		
Non-squamous PD-L1 ≥50%	Cost-effective (less costly and less benefit)	Cost-effective (less costly and less benefit)
Non-squamous PD-L1 <50%	Dominated	23,354
Adenocarcinoma/large cell carcinoma PD-L1 <50%*	Dominated	23,354
Squamous PD-L1 ≥50%	Cost-effective (less costly and less benefit)	Cost-effective (less costly and less benefit)
Squamous PD-L1 <50%	Dominated	23,354

Population	Tepotinib ICER (ERG assumptions)	Tepotinib ICER (company assumptions)
Treated		
Squamous/non-squamous PD-L1 ≥50%	55,879	24,824
Squamous/non-squamous PD-L1 <50%	55,879	£18,176
Source: Adapted from Table 1 in the Company Submission *Please note that the difference from the ERG report is due to the comparator being corrected to chemotherapy		

Table 6.10: ERG base-case full incremental results for Untreated population and the Company ICER

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company ICER (£/QALY)
Chemotherapy	[redacted]	[redacted]	3.18		[redacted]	[redacted]		
Tepotinib	[redacted]	[redacted]	3.06	-0.13	[redacted]	[redacted]	Dominated	23,354
Immunotherapy	[redacted]	[redacted]	3.45	0.39	[redacted]	[redacted]	Extendedly dominated	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	1.98	[redacted]	[redacted]	63,768	186,293
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 6.11: ERG base-case full incremental results for Treated population and the Company ICER

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company ICER (£/QALY)
Immunotherapy	[redacted]	[redacted]	1.67		[redacted]	[redacted]		
Chemotherapy	[redacted]	[redacted]	2.58	0.92	[redacted]	[redacted]	17,363	Extendedly dominated
Tepotinib	[redacted]	[redacted]	2.61	0.02	[redacted]	[redacted]	55,879	£24,824
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 6.17: ERG base-case results for untreated, non-squamous PD-L1 ≥50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Tepotinib	[redacted]	[redacted]	3.06				Cost-effective*	[redacted]	[redacted]	3.20				Cost-effective*
Immunotherapy	[redacted]	[redacted]	3.45	[redacted]	[redacted]	0.39	Extendedly dominated	[redacted]	[redacted]	3.45	[redacted]	[redacted]	0.25	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	1.98	57,774	[redacted]	[redacted]	3.79	[redacted]	[redacted]	0.35	186,293
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years *Tepotinib is less costly and less effective and is cost-effective because the comparators are too costly given the additional benefit they provide														

Table 6.18: ERG base-case results for untreated non-squamous PD-L1 <50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Chemotherapy	[redacted]	[redacted]	3.18					[redacted]	[redacted]	2.42				
Tepotinib	[redacted]	[redacted]	3.06	[redacted]	[redacted]	-0.13	Dominated	[redacted]	[redacted]	3.20	[redacted]	[redacted]	0.78	23,354
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	2.37	63,768	[redacted]	[redacted]	3.79	[redacted]	[redacted]	0.60	186,293
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years														

Table 6.19: ERG base-case results for untreated, adenocarcinoma/large cell carcinoma PD-L1 <50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Chemotherapy	[redacted]	[redacted]	3.18					[redacted]	[redacted]	2.42				
Tepotinib	[redacted]	[redacted]	3.06	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	[redacted]	3.20	[redacted]	[redacted]	[redacted]	23,354
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years *Tepotinib is less costly and less effective and is cost-effective because the comparators are too costly given the additional benefit they provide														

Table 6.20: ERG base-case results for untreated squamous PD-L1 ≥50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Tepotinib	[redacted]	[redacted]	3.06				Cost-effective*	[redacted]	[redacted]	3.20				Cost-effective*
Immunotherapy	[redacted]	[redacted]	3.45	[redacted]	[redacted]	0.39	Extendedly dominated	[redacted]	[redacted]	3.45	[redacted]	[redacted]	0.25	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	1.98	57,774	[redacted]	[redacted]	3.79	[redacted]	[redacted]	0.35	186,293

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

*Tepotinib is less costly and less effective and is cost-effective because the comparators are too costly given the additional benefit they provide

Table 6.21: ERG base-case results for Untreated Squamous PD-L1 <50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Chemotherapy	[redacted]	[redacted]	3.18					[redacted]	[redacted]	2.42				
Tepotinib	[redacted]	[redacted]	3.06	[redacted]	[redacted]	-0.13	Dominated	[redacted]	[redacted]	3.20	[redacted]	[redacted]	0.78	23,354
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	2.37	63,768	[redacted]	[redacted]	3.79	[redacted]	[redacted]	0.60	186,293

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

Table 6.22: ERG base-case results for treated squamous and non-squamous PD-L1 <50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Immunotherapy	[redacted]	[redacted]	1.67					[redacted]	[redacted]	1.87				
Chemotherapy	[redacted]	[redacted]	2.58	[redacted]	[redacted]	0.92	17,363	[redacted]	[redacted]	2.00	[redacted]	[redacted]	0.14	Extendedly dominated
Tepotinib	[redacted]	[redacted]	2.61	[redacted]	[redacted]	0.02	55,879	[redacted]	[redacted]	2.61	[redacted]	[redacted]	0.60	24,824
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years														

Table 6.23: ERG base-case results for Treated Squamous and non-squamous PD-L1 ≥50% population

Technologies	ERG							Company						
	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY					Cost (£)	QALY	LY	
Chemotherapy	[redacted]	[redacted]	2.58					[redacted]	[redacted]	2.00				
Tepotinib	[redacted]	[redacted]	2.61	[redacted]	[redacted]	0.02	55,879	[redacted]	[redacted]	2.61	[redacted]	[redacted]	0.60	£18,176
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years														

Table 6.24: The decision problem subgroups with relevant comparators

Population	Tepotinib ICER (ERG assumptions)	Tepotinib ICER (company assumptions)
Untreated		
Non-squamous PD-L1 ≥50%	Cost-effective (less costly and less benefit)	Cost-effective (less costly and less benefit)
Non-squamous PD-L1 <50%	Dominated	23,354
Adenocarcinoma/large cell carcinoma PD-L1 <50%	Dominated	23,354
Squamous PD-L1 ≥50%	Cost-effective (less costly and less benefit)	Cost-effective (less costly and less benefit)
Squamous PD-L1 <50%	Dominated	23,354
Treated		
Squamous/non-squamous PD-L1 ≥50%	55,879	24,824
Squamous/non-squamous PD-L1 <50%	55,879	£18,176
Source: Adapted from Table 1 in the Company Submission		

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Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Monday 8 November 2021.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

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

NICE National Institute for Health and Care Excellence

About you

Your name	[redacted]
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**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Lack of clarity in the population	**NO**	The MHRA licence for tepotinib states: "*TEPMETKO (tepotinib) is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations.*" Therefore, Merck reflected the tepotinib license population in the decision problem as well as the population in the NICE scope. However, the ERG comments regarding the population in the ERG report are also correct: • The VISION trial included patients with stage IIIB to IV NSCLC, which is equivalent to 'advanced' disease • The VISION trial did exclude ALK+ and EGFR+ patients.
Key issue 2: Lack of subgroup (line of therapy, histological status, PD-L1	**NO**	Results by line of therapy (untreated and previously treated) were presented in Appendix N of the company submission.

status) analysis according to scope		While the company recognises that comparison by PD-L1 status was part of the NICE scope, we informed the NICE team and the ERG team at draft scope, ERG clarification questions and at TE that such a comparison was not possible due to the following reasons: (1) PD-L1 status was not collected in the VISION clinical trial and (2) there is limited reporting of PD-L1 available in the real-world cohort. Therefore, it was not possible to perform subgrouping based on PD-L1 status. Based on feedback from clinical experts, METex14 skipping mutation is now a targetable oncogenic driver mutation. If METex14 skipping mutation was detected through testing methods, the patient would be offered a targeted treatment such as tepotinib, irrespective of their PD-L1 status. This is supported by multiple studies which show patients with METex14 skipping alterations tend to respond poorly to current treatments, including immunotherapies, regardless of PD-L1 expression. [1-3]In one study (Negrao *et al*. 2021),[2] which assessed outcomes for 34 METex14 skipping patients treated with immunotherapies, patients with METex14 skipping alterations were found to have high PD-L1 expression although with low tumour mutational burden (TMB). However, this did not translate to better clinical outcomes on immunotherapy as demonstrated by the short PFS and low response rates.[2] This suggests that oncogene-specific factors other than TMB and PD-L1 expression also impact clinical outcome from immunotherapy treatment. In other oncogenic driver mutation NSCLCs, such as EGFR-mutant NSCLC, PD-L1 expression was also unlikely to be a predictive biomarker for prognosis, based on a meta-analyses of 18 separate studies in 1,986 patients.[4] In other oncogenic-driven NSCLCs such as EGFR, targeted treatments are recommended irrespective of PD-L1 expression.[5] With regards to histology, the majority of patients in VISION and the real-world cohort had adenocarcinoma ([redacted]% tepotinib, [redacted]% weighted chemotherapy and [redacted]% weighted immunotherapy). The squamous histology subgroup includes [redacted] patients treated with tepotinib, [redacted] unweighted, chemotherapy patients and [redacted] immunotherapy patients, which we did not consider feasible for making a reasonable comparison between tepotinib and the comparators. A comparison in the adenocarcinoma group would be possible, however this was not felt to be

		relevant by clinical experts consulted throughout submission development, as it accounts for the vast majority of the overall METex14 population anyway, and so was not performed. Expert clinical opinion indicated that if a targeted therapy for METex14 skipping alterations was available, this would be the preferred treatment for patients irrespective of PD-L1 status and histology. Furthermore, experts confirmed that although squamous patients tend to not perform as well on treatments as adenocarcinoma patients, the overall costs and outcomes are considered generalisable between groups. In addition, the approach of analysing squamous and non-squamous patients together was recently accepted by the committee in the recent NICE submission of selpercatinib for RET fusion-positive advanced NSCLC.[6] The ACD noted: *"The marketing authorisation for selpercatinib did not differentiate between people with squamous and non-squamous advanced NSCLC. However, because of the rarity of RET gene fusions in squamous NSCLC, clinical advice, and the very small number of people with squamous NSCLC in the LIBRETTO-001 trial, the company did not present any evidence on using selpercatinib to treat these tumours. The clinical expert said they might expect some difference in the effectiveness of selpercatinib in treating squamous advanced NSCLC. This is because people with squamous NSCLC may be older, have a higher chance of being smokers, and be less fit. However, they expected there would still be some level of response. The Cancer Drugs Fund clinical lead said that the NHS would expect to follow the same recommendation for people with squamous advanced NSCLC as for people with non-squamous advanced NSCLC. The committee agreed that the recommendations in this technology appraisal would apply to both squamous and non-squamous advanced NSCLC"* In this respect there are similarities between selpercatinib and tepotinib, including that the marketing authorisation provides no differentiation between histology groups, and there is a small proportion of patients with squamous NSCLC in the relevant clinical trials. Therefore, we anticipate the same approach is applicable for tepotinib in advanced NSCLC with METex14 skipping

		mutations, i.e. the technology appraisal would apply to both squamous and non-squamous patients, despite no sub-group analysis being done for squamous patients. **Conclusion** Given that tepotinib targets a rare type of NSCLC and has a line-agnostic marketing authorisation irrespective histology and PD-L1 expression, we anticipate that the decision to use tepotinib will be based on the presence of METex14 skipping alterations, regardless of the subgroup and comparators based on histology and PD-L1. Whilst Merck acknowledges the limitations with regards to histology and PD-L1 expression in this rare mutation with limited published data, the approach to modelling the population as a whole, irrespective of histology and PD-L1 expression, is considered appropriate and in line with previous NICE appraisals for targeted therapies as well as clinical expert feedback.
Key issue 3: Selection of analysis data set from VISION (cohort A instead of cohort A+C, and depending on length of follow-up)	**YES**	For the ITC and economic analysis, Cohort A from VISION was used. However, VISION also included Cohort C which also recruited patients with METex14 skipping mutations. At the February 2021 data cut-off, 152 patients were available from Cohort A, and 123 patients were available from Cohort C with at least 3 months of follow-up available for the efficacy analysis. The reason only Cohort A was used for the analysis instead of Cohort A+C was that patient level data for Cohort C only became available for analysis shortly before the submission deadline. As a result, there was little time to update the submission with the data from this cohort, as the following analyses would need to be performed: • Update to the ITC • Analysis of treatments received in the real-world cohort • Fitting of survival curves to tepotinib, chemotherapy and immunotherapy for the three populations available in the economic model (line agnostic, untreated and previously treated)

- Analysis of subsequent therapies received
- Analysis of adverse events experienced in the VISION data
- Utility analysis

Merck have compared the patient characteristics and clinical outcomes between Cohort A and Cohort A+C, to demonstrate the similarities between the groups. As the ERG stated within their technical report, there is little difference in all outcomes between Cohort A and Cohort A+C.

Firstly, the patient characteristics of Cohort A and Cohort A+C are shown in Table 1. Cohort A+C is across a larger cohort, but there are very similar patient characteristics (within a few percentage points) between the cohorts, for the characteristics which were deemed by clinical experts to be prognostic of disease outcomes when developing the ITC. These comprised:

- Prior treatment experience
- Mean age
- Disease stage
- Sex
- Histology
- Presence of smoking history

Table 1: VISION patient characteristics - Cohort A versus Cohort A+C

Characteristic	Cohort A	Cohort A + C
n	[redacted]	[redacted]
Age (mean, (SD))	[redacted]	[redacted]
Age over 75 (%)	[redacted]	[redacted]
Prior treatment	[redacted]	[redacted]

		Untreated (%)	[redacted]	[redacted]	
		Treatment Experienced (%)	[redacted]	[redacted]	
		Sex	[redacted]	[redacted]	
		Female (%)	[redacted]	[redacted]	
		Male (%)	[redacted]	[redacted]	
		Race	[redacted]	[redacted]	
		Asian	[redacted]	[redacted]	
		Black or African American	[redacted]	[redacted]	
		Other	[redacted]	[redacted]	
		White	[redacted]	[redacted]	
		Unknown	[redacted]	[redacted]	
		History of smoking (%)	[redacted]	[redacted]	
		No (%)	[redacted]	[redacted]	
		Yes (%)	[redacted]	[redacted]	
		ECOG	[redacted]	[redacted]	
		0	[redacted]	[redacted]	
		1	[redacted]	[redacted]	
		2	[redacted]	[redacted]	
		Stage (%)	[redacted]	[redacted]	
		IIIB/C	[redacted]	[redacted]	
		IIIB	[redacted]	[redacted]	
		IV	[redacted]	[redacted]	
		IVB	[redacted]	[redacted]	
		NA	[redacted]	[redacted]	
		Metastatic disease (%)	[redacted]	[redacted]	
		No (%)	[redacted]	[redacted]	
		Yes (%)	[redacted]	[redacted]	
		Histology	[redacted]		

		Adenocarcinoma	[redacted]	[redacted]
		Squamous	[redacted]	[redacted]
		Others	[redacted]	[redacted]
		Missing	[redacted]	[redacted]

The observed outcomes are also similar as seen in **Figure *1*** - **Figure *3*** below. Greater censoring is observed earlier in Cohort A+C (compared to Cohort A alone) due to enrolment in Cohort C occurring later than enrolment into Cohort A.

Figure *1* presents the OS Kaplan-Meier curves for Cohorts A and A+C, where very similar curves are observed over time. Median OS was [redacted] months (95% CI: [redacted] months) in Cohort A compared to [redacted] months (95% CI: [redacted] months) in Cohort A+C with a non-significant p-value of [redacted].

		Figure 1: VISION overall survival - Cohort A versus Cohort A+C 

		Similar to OS, the investigator PFS observed between Cohort A and Cohort A+C are closely aligned (Figure 2). Median PFS was [redacted] months (95% CI: [redacted] months) in Cohort A compared to [redacted] months (95% CI: [redacted] months) in Cohort A+C with a non-significant p-value of [redacted].

Figure 2: VISION progression-free survival - Cohort A versus Cohort A+C

Figure *3* presents a comparison of time on treatment (ToT) from Cohort A and Cohort A+C showing similar curves between the two cohorts. Median ToT was [redacted] months (95% CI: [redacted]

		months) in Cohort A compared to [redacted] months (95% CI: [redacted] months) in Cohort A+C with a non-significant p-value of [redacted]. **Figure 3: VISION time on treatment - Cohort A versus Cohort A+C** 

		Conclusion As the patient characteristics and outcomes between Cohort A and Cohort A+C are observed to be greatly similar, we do not anticipate the ITC or cost-effectiveness results would differ largely had the analysis been informed by Cohort A+C, compared to the results using Cohort A only. Despite this, there appears to be a minor improvement in median OS and lower median ToT for Cohort A+C compared to Cohort A, so if the ITC and economic model results were based on this analysis, we would expect that any direction of change would likely favour tepotinib.
Key issue 4: Selection of studies to obtain data for the ITC	**NO**	The ERG claimed that further justification is required for the inclusion of studies used for the ITC using patient-level data, therefore Merck would like to confirm how and why these data were chosen. A feasibility analysis of all data available to Merck in the METex14 skipping population was performed in order to determine how to proceed with performing comparisons to the relevant comparators as detailed in the NICE scope. Conducting an ITC using patient level data was the preferred option (in line with NICE DSU TSD17[7]), therefore we proceeded with this approach for the primary ITC analysis and prioritised the sourcing of patient-level data in the METex14 skipping NSCLC population. The sources of real-world data in the METex14 skipping NSCLC population that Merck was able to obtain access to included: • Merck sponsored studies – NIS 0015, NIS 0035 • Databases – COTA • Data from academic centres – Wong et al. Further data sources were explored, but unfortunately access to patient level data was not available elsewhere. These further data sources included:

		• The Flatiron database. The database agreement with Merck did not allow access to patient level data, so was not useable for the purposes of the primary ITC (using patient-level data) as part of this submission. • Published studies in the METex14 skipping NSCLC population which were identified in an SLR (see Appendix D). Requests to obtain patient level data from three of the most relevant publications (Sabari et al., Awad et al. and Guisier et al.) were sent to the authors however, permissions were not granted. Therefore, we performed MAICs to compare between the published studies and the VISION data, which were presented as a supplementary ITC analysis in Appendix L of the submission. • A dataset from French academic centres with patient-level data available. This data set was deemed to be appropriate for consideration, but was not available in time for inclusion into the submission. Instead the ITC is being updated in Q1 2022 to include these new real-world data. The available patient-level data sources were assessed for suitability in the primary ITC based on the following criteria: • The correct population and comparators • The availability of data within the submission timelines • The characteristics and outcomes reported Following this assessment, the NIS 0015, NIS 0035, COTA and Wong et al. data were included for the primary ITC which informed our base case analysis. Although Merck were not granted access to all patient-level data requested, this dataset is still the largest dataset for patients with NSCLC harbouring METex14 skipping mutations we are aware of, in this rare and relatively newly studied mutation. The availability of patient-level data allowed the use of more robust statistical techniques for matching patient cohorts, which is not always an option in other NICE submissions for treatments

		without a relevant head-to-head comparison.[8] Furthermore, the availability of METex14 skipping NSCLC patients for this comparator data is especially beneficial, allowing the characteristics and treatment effects of the specific decision problem population to be explored and accounted for. In previous NSCLC appraisals for targeted treatments, companies have been criticised for using data not in the specific mutation in the decision problem, resulting in high levels of uncertainty in the effectiveness analysis.[6;9] In this instance, patients used for the comparative efficacy are directly relevant to the licensed population, with patient-level data allowing them to be matched further to the VISION cohort. **Conclusion** Merck assessed all of the patient-level data available in the METex14 skipping population, against suitability criteria, and the relevant data sources were taken forward for the primary ITC. A SLR was also conducted to identify all published studies in the METEx14 skipping population, which were also assessed for suitability to take forward to the MAICs as part of the supplementary ITC. Therefore, systematic approaches have been taken to identify all data sources which could be used, for both the patient-level ITC and published data MAIC.
Key issue 5: Source of AE frequencies not justified	**NO**	The ERG was unclear how the sources of adverse event frequencies used in the economic model were obtained, and recommended a systematic approach to be taken to identify adverse event frequencies. Merck would like to clarify the approach taken to identify adverse event frequencies for the comparator treatments. Adverse event frequencies for the comparators were not available within the real-world data set and therefore needed to be sourced from the wider literature. A targeted literature approach was taken in order to source the most relevant adverse events for each comparator within the advanced and metastatic NSCLC setting. Firstly the NICE appraisal documents of the comparators were reviewed for adverse event frequencies, however in some cases these values were either redacted, unavailable or reported more substantially in the clinical trial publication. If that was the case, then either the clinical trial publication was used or an alternative source, such as the

		prescribing information, was used. Although the approach used to obtain the adverse event frequencies was not based on a systematic approach, the targeted review attempted to use the most up-to-date and relevant data for each comparator, and allowed us to obtain adverse event data from published pivotal clinical trial data in nearly all cases. Given the lack of adverse event information available from the METex14 specific population within the real-world data set, sourcing comparator adverse events from the literature is conservative, due to the limited reporting on certain adverse events in comparison to tepotinib, where all adverse events recorded in VISION can be included. This may have resulted in an underestimation of comparator adverse events compared to tepotinib. Another limitation is that the comparator adverse events are based on the wider NSCLC population, and it is unclear how comparator adverse events would differ in the METex14 skipping alteration patient group. Although there is limited evidence to draw conclusions, it could be expected the METex14 skipping NSCLC cohort might suffer from worse/more frequent severe adverse event burden from chemotherapy or immunotherapies, related to their older age compared to clinical trial cohorts in wildtype NSCLC. Again this could lead to an underestimation of comparator adverse events in the economic model. **Conclusion** Adverse events were derived from a targeted review of the wider literature and by choosing the most appropriate source. Despite not using a systematic approach, adverse events have very little impact on the overall cost-effectiveness results, therefore alternative sources for comparator adverse events are highly unlikely to impact decision making, despite potentially being underestimated for comparators.
Key issue 6: Selection of method of adjustment for confounding in the ITC	**NO**	The ERG queried why we used the standardised mortality rate (SMR) approach instead of the inverse probability of treatment. However, the ERG also acknowledged that this approach facilitates the full incremental analysis in the cost-effectiveness analysis. The ERG are correct that there are a number of approaches that could have been taken to adjust for differences between the

		studies. These could range from including patient characteristics in survival regressions, through to different methods of propensity scoring (such as propensity score matching).
		
		We consider the approach selected (reweighting comparator data to match tepotinib) to offer the following key advantages over these competing methods, as suggested by the ERG;
		
		• Interpretability
		  ○ All results can be compared, allowing the fully-incremental analysis preferred by the ERG to be performed
		
		• Consistency
		  ○ Tepotinib effectiveness remains consistent across comparisons meaning the long-term survival estimates do not change dependent on the selected comparator
		
		• Parametric curves
		  ○ Allows for the use of survival extrapolation using parametric curves, which may not otherwise have been possible depending on the method selected e.g., calculation of an effect size using doubly robust techniques.
		
		Had an Average Treatment Effect (ATE) or similar approach (i.e., standard Inverse Probability of Treatment Weighting [IPTW]) been used, consistent assumptions for tepotinib efficacy across comparisons would not apply, therefore losing that advantage, without gaining other advantages for such methods.
		
		Conclusion
		
		We acknowledge there are limitations to our selected approach, however these are far outweighed by the advantages described above. Therefore, Merck are satisfied with the approach taken versus alternatives, and consider other options, which equally could be used, do not necessarily add additional value compared to the approach taken.

Key issue 7: Lack of justification for partitioned survival model vis-à-vis a state transition model	**NO**	The ERG have requested more justification as to why a partitioned survival model was used to inform the economic analysis instead of a state-transition model. At model conceptualisation, both partitioned survival models and state-transition models were considered, acknowledging the limitations of both approaches. The main limitation of the state-transition model is the use of unclassified end points to model transitions such as post-progression survival. This is highly prone to bias due to the selection effects and informative censoring.[10] Moreover, post-progression outcomes are based on those patients who have progressed first (e.g., due to more severe disease or older age, etc.). Given that the data available for METex14 patients are based on small patient numbers, in addition to progressing early, the extrapolations of post-progression survival could be misleading. For the comparison with chemotherapies and immunotherapies the total number of patients is [redacted] and [redacted], respectively, thus the later model transitions (i.e., post-progression to death) would be based on even smaller patient numbers and subsequently small numbers of events, creating additional uncertainty in the extrapolated outcomes for later model transitions. This is not an issue when using OS directly from the start of the trial as required for a partitioned survival model, as all patients contribute to the function used to fit the curve. Therefore, selecting a state-transition model over a partitioned survival model would have likely resulted in greater uncertainty in OS, given the likely biased estimates these analyses will produce. Moreover, as the comparator data is based on real-world evidence, patients are not assessed for progression as routinely as in the VISION trial nor collected as routinely, if at all (see company submission Section B.2.9.8). Therefore, independent transitions between the different health states may not be comparable versus tepotinib. Another limitation of the state-transition model is that it does not negate the need to extrapolate data, therefore extrapolating more immature data (such as post-progression survival) produces more uncertain estimates for those particular transition probabilities and hence creating uncertain OS projections from the final model outputs.

		In addition to the above, further limitations to a state-transition model involve underlying data availability and complexity of the approach to allow for all possible transitions within the CE model itself. For a state-transition model, the development of a three-health state model using time-dependencies in event rates for each possible transition would add significant complexity based on the number of tunnel states that would be required to accurately model the transitions (i.e., tunnel state per cycle). This would create unnecessary computational complexity that would potentially make the model burdensome to run. **Conclusion** Based on the above points, the partitioned survival model structure was considered the most appropriate for this appraisal compared to a state-transition model. This is also consistent with the structure used in the majority of previous NSCLC NICE appraisals, which were considered appropriate by the committees of each appraisal.[11-19] Moreover, as stated in Section B.3.2.2, the partitioned survival model structure revolves around the key secondary endpoints from VISION (OS and PFS) and available outcomes for the comparator data using the real-world cohort.
Key issue 8: No analyses are considered for the subgroups stated in the decision problem	**NO**	Merck acknowledge the ERG's critique relating to the decision problem populations and comparators, and see value in the ERG's suggested approach to this. However, we would like to highlight that the ERG's decision problem 'subgroups' relating to treatment line (untreated/previously treated), histology (squamous/non-squamous) and PD-L1 expression (< 50%/ ≥50%) are not true subgroups as the underlying clinical data does not align with the subgroup defined, and in fact is the same data across all subgroups for each line of therapy group. The data used in the ERG's results are not split by histology or PD-L1 (as this is not available, as discussed in Key Issue 2 response) and instead uses the same data from the treatment line subgroups available in the model and just amends the comparator for each decision problem group to reflect the treatments relevant to that subgroup. For example, the efficacy data used to inform the 'untreated, non-squamous PD-L1≥50%' population are also used to inform the following other ERG subgroups, with just the comparators adjusted:

		• Untreated, non-squamous, PD-L1<50% • Untreated, adenocarcinoma/large cell carcinoma, PD-L1 <50% • Untreated, squamous, PD-L1 ≥50% population • Untreated, squamous, PD-L1 <50% population. As the comparators vary in each of the decision problem subgroups, we value the ERG's attempt to address this issue however, do not consider this to be a true subgroups analysis due to the lack of clinical subgroup data informing each separate subgroup analysis. As such, we request that these analyses are referred as 'subgroup scenario analyses'. The company did not present the cost-effectiveness results by the subgroups specified in the NICE scope for several reasons. Firstly, as discussed, data were not available to split patients by PD-L1 expression and not enough patients were in the squamous group to split by histology (see response to Key Issue 2). Thus, it was not possible to perform subgroup analysis as specified in the final scope. We were only able to split patients by treatment history (untreated or previously treated) but acknowledge that this analysis is still limited due to the small patient numbers for each group. Therefore, the line-agnostic population was presented as the base case analysis, and by line of therapy as sub-groups. Furthermore, tepotinib is licensed for all advanced NSCLC patients harbouring METex14 skipping alterations regardless of treatment line, histology and PD-L1 status. Therefore we consider it more appropriate to consider the 'all comers' approach in line with the label as the base case and not split results by decision problem subgroups where data is limited, and clinical input suggests it is not appropriate for decision making. This is in line with the latest NSCLC appraisals for targeted treatments, where the final scope outlines comparators for different groups of patients, but results are not split by these subgroups, based on their licence.[9;20;21] Moreover, clinical experts consulted at the advisory board and in separate validation calls agreed they would like the flexibility to use tepotinib at any treatment line and that if a patient is tested positive for METex14 then the targeted

		treatment (i.e., tepotinib) would be used over currently available therapies, regardless of histology and PD-L1 expression.[22] Therefore, this approach as the base case aligns with clinical need as well as the licence for tepotinib. Assessment by these subgroups causes further issues when considering the end of life criteria, as the data specifically for these subgroups within the METex14 NSCLC population are not available. METex14 skipping is a rare mutation within NSCLC, with limited available data, and so outcomes within the different subgroups proposed by the ERG are not currently available in the literature or in any real-world data known to Merck. Outcomes for patients in the larger wildtype NSCLC are available for these subgroups, however it is unknown how well METex14 skipping patients respond in comparison, although it is known that patients with METex14 skipping mutations generally have poorer outcomes compared to other types of NSCLC, including wildtype NSCLC.[1;3] Unfortunately, how much this differs by histology or PD-L1 status is currently not clear due to the lack of data (see response to Key Issue 2), and decision making using these sub groups would run into additional challenges when assessing end of life criteria. **Conclusion** Merck acknowledge that the ERG's attempt to address the decision problem by amending the comparator per subgroup could be a useful scenario analysis for consideration, and see value in the approach taken. However, for the reasons stated above, we continue to present our base case results using the overall population considering both chemotherapy and immunotherapy as comparators. Subgroup analysis by treatment line is also presented for completeness. Merck consider this approach sufficient to support decision making as it is reflective of how clinicians will choose tepotinib over the current comparators.
Key issue 9: No analyses were considered using the individual treatment comparators for which	**NO**	The comparators in the ITC were grouped by treatment class due to the limited number of patients receiving each individual treatment. The ERG noted that within the immunotherapy group, [redacted] patients received pembrolizumab and within the chemotherapy group, [redacted] patients received

there was enough evidence.		pemetrexed plus carboplatin. Based on these numbers, the ERG felt it is possible to conduct the ITC using these individual treatments in comparison to tepotinib. Although it would have been desirable to conduct comparisons against individual comparators, in what is a rare sub-population in NSCLC, Merck considers that insufficient data were available for any individual comparator. The largest group within the chemotherapy and immunotherapy categories is pembrolizumab, where [redacted] patients had PFS information available. These [redacted] patients were split between treatment naïve (n=[redacted]) and experienced (n=[redacted]) groups (thus preventing an analysis by line) and include a range of clinical characteristics which would confound any comparison. These numbers are even smaller for chemotherapy due to the number of possible regimens, with [redacted] naïve and [redacted] experienced patients receiving carboplatin + pemetrexed, and no other individual named treatment/combination having more than [redacted] patients ([redacted] patients received docetaxel monotherapy, and pemetrexed monotherapy). Based on these patient numbers, although it may be technically possible to perform comparisons against these two individual treatments, these would be extremely uncertain, and unlikely to meaningfully inform the decision problem. Furthermore, analysis by line of therapy would not be possible. As the comparators were weighted to match the tepotinib population, this would mean weighting [redacted] pembrolizumab patients and [redacted] pemetrexed plus carboplatin patients to 151 tepotinib patients to form a comparison. For this reason, the Merck considers that there was not enough evidence to perform such comparisons within the immunotherapy and chemotherapy classes and that these would not provide meaningful results for decision making. Even if just comparing in the line agnostic population, only pembrolizumab and pemetrexed + carboplatin comparisons would be technically possible, and all of the other comparators in the decision problem missed. Grouping the immunotherapies and chemotherapy treatments allowed for larger datasets to be used, and therefore increasing the robustness of the comparisons. These approaches were also considered appropriate by health economic experts and clinical experts at the advisory board.[22] The clinical experts considered that the treatments within each class have similar outcomes, and where appropriate, they tend to consider products by treatment class.[23-27] In addition, the grouping

		of treatments approach has been used in previous NICE submissions where the comparators are a mix of different treatments.[15;28-30] Conclusion Merck stand by their original approach and do not agree that comparisons against the individual treatments would be informative. These comparisons also would not allow for comparisons by line of therapy. The grouping approach mean that all treatment classes in the decision group can be compared to, and this approach has been supported by clinical experts and previous NICE appraisals.
Key issue 10: Potential bias from clinicians' selection of survival curves for the comparators, and lack of alternative scenario.	**NO**	**Comments on ERG's approach to best fitting curves** The ERG made several comments within their report regarding the approach to selecting the most appropriate curves, and noted that the clinical experts did not think the best fitting models represented the long term projections of OS and PFS. Merck disagree with the ERG's assessment of best fitting curves, noting that the only criteria the ERG appear to use are based on AIC and BIC assessment. Although AIC and BIC are a good statistical measure of how well the curves fit the observed data, NICE DSU TSD 14[31] specifies the need to also account for visual assessment and clinical plausibility as well as AIC and BIC to identify the most plausible curves. AIC and BIC provide a useful statistical test of the relative fit of alternative parametric models ordered by smallest value (best fitting) to largest value (worst fitting). While NICE DSU TSD 14 does not specify any fixed rules related to either AIC or BIC scores to compare specific models, a general 'rule of thumb' is proposed by Burnham & Anderson (2004)[32] regarding AIC scores. Based on the difference in the AIC scores for the 'best-fitting' model (i.e., the lowest AIC) and an alternative model, Burnham & Anderson suggest: • If the difference is ≤2, the models are essentially equivalent • If the difference is >2 but <10, the alternative model has less support, but may still provide a reasonable fit

		• If the difference is >10, the alternative model has essentially no support and should not be selected For BIC, a similar rule of thumb is proposed by Raftery (1995),[33] wherein differences in the BIC score of 0–2, 2–6, 6–10, and ≥10 are referred to as a means of justifying additional model complexity. **Comments on Merck's approach to best fitting curves** Merck considered the best fitting curves according to AIC and BIC alongside visual fit and clinical plausibility, obtained at an advisory board where clinicians validated the long term projections. In some cases the clinicians did not feel the curves identified as the statistically best fitting (according to AIC, BIC) were the most plausible and chose alternative curves. However, with the exception of chemotherapy the chosen curves are within a difference of 10 of the best statistical fitting, and visual fit was reasonable for all (see Table *2* and **Figure *17*** - **Figure *20***). Therefore, for tepotinib and immunotherapy the base case choices obtained by clinical validation do not penalise the plausibility of the data or suggest potential bias in the selection of curve fits. For chemotherapy, we acknowledge that the data from the real-world cohort may overestimate the survival projections compared to what would be expected in clinical practice and when compared to published data for chemotherapy, either in the METex14 skipping population and in wildtype NSCLC (see Section B.3.10 of company submission). This is possibly due to the high number of subsequent treatments given to these patients, including subsequent immunotherapies and MET inhibitors, some of which do not reflect UK practice and would not be available to UK patients (as the real-world cohort patients were primarily from the US). Therefore, for the chemotherapy base case, we selected curves which best represent expected long-term projections (as dictated by clinical expert opinion) over statistical and visual fit. However, despite the statistical fits not abiding the 'rule of thumb' (see Table 2), we consider that the visual fit of the selected curves versus the observed data are within reason (see **Figure *18*** and **Figure *19*** in the Appendix).

Table 2: AIC and BIC – best fitting versus selected models – overall population

Models	OS		PFS	
	AIC	BIC	AIC	BIC
Tepotinib				
Best fitting	Log-logistic (743.5)	Exponential (748.8)	Log-normal (776.5)	Log-normal (782.5)
Selected	Log-logistic (743.5)	Log-logistic (749.6)	Log-normal (776.5)	Log-normal (782.5)
Assessment	Best fitting selected	Within 1 score	Best fitting selected	Best fitting selected
Chemotherapy				
Best fitting	Generalised gamma (827.9)	Log-normal (832.61)	Odds 3 knot spline (726.2)	Odds 3 knot spline (737.2)
Selected	Weibull (842.1)	Weibull (846.5)	Odds 1 knot spline (739.2)	Odds 1 knot spline (745.7)
Assessment	>10 score difference	>10 score difference	> 10 score difference	> 10 score difference
Immunotherapy				
Best fitting	Normal 2 knot spline (748.6)	Generalised gamma (754.4)	Piece-wise log-logistic (376.3)	Piece-wise log-logistic (378.6)
Selected	Normal 1 knot spline (756.5)	Normal 1 knot spline (762.3)	Piece-wise log-logistic (376.3)	Piece-wise log-logistic (378.6)
Assessment	Within 8 score difference	Within 8 score difference	Best fitting selected	Best fitting selected

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

In conclusion, Merck consider the choice of base case curves for immunotherapy and tepotinib to be appropriate based on statistical fit, visual fit and clinical validation. The chosen curves for chemotherapy, did not pass the acceptability in terms of statistical fit, but still have a good visual fit

		and are substantially more clinically plausible than the statistically best fitting. Despite the chemotherapy curves being the most clinically plausible, they are still considered to overestimate the expected benefit of chemotherapy (see validation section of this response), thus the efficacy comparison between tepotinib and chemotherapy, and resulting benefit for tepotinib, is likely to be under-estimated resulting in a more conservative ICER. **Comments on the ERG's assessment** Merck would also like to address the three possible reasons the ERG provided for the statistically best-fitting survival models not aligning with the clinical experts selections, specifically that: 1. The sample population in VISION is not representative of the overall population 2. The real-world data was inadequately matched to VISION 3. Another more flexible model is required but there is not enough data to model Regarding the first reason, the patient characteristics of the VISION trial and real-world cohorts were considered representative of the METex14 skipping alterations NSCLC population based on the literature, which was agreed by the clinical experts at the advisory board (see Section B.2.3.1.2). Therefore, we do not believe this is a large issue. Regarding the second argument, we strongly disagree with the ERG's view here. The real-world cohort was adequately matched to the VISION trial using robust statistical techniques with the availability of patient-level data in line with the NICE DSU 17 guidance.[7] Regarding the final point, when selecting curves, Merck considered an array of options available give a good range of extrapolations to choose from based on both fitting to the observed data and long-term projections. In cases deemed necessary, more flexible models were included in line with NICE DSU 21.[34] Considering the chemotherapy OS, only parametric models were fit to the data after assessment concluded that further flexible models were not required (see Section B.3.3.1 of the company submission). Given that the issue with chemotherapy projected survival came from the observed real-world data itself, more flexible models would not resolve this. We do

		acknowledge that subsequent treatment use is one area where the real-world data differs from VISION and clinical practice in the UK and this is a limitation. However as stated earlier, the impact of this would be to underestimate the benefit of tepotinib vs. chemotherapy, and hence would represent a conversative assumption in the economic analysis. Overall, Merck disagree with the ERG's concerns regarding our approach to extrapolating OS and PFS. As discussed previously, the curves for tepotinib and immunotherapy in the base case analysis were selected based on clinical plausibility and were within the acceptable AIC and BIC score difference with reasonable visual fit to the data. For chemotherapy, clinicians noted that the subsequent treatments in the chemotherapy arm appeared more aggressive than what would be used in the UK which may have impacted OS. As such, the most plausible curve was selected for the chemotherapy arm, acknowledging that this may still overestimate the survival of the chemotherapy patients. Merck do not consider any bias to have been introduced by seeking clinical expert opinion for the validation of survival estimates. Clinicians used their experience of treating patients in the wider NSCLC population and knowledge of patients harbouring METex14 skipping alterations. Therefore, the experts were able to make informed estimates of survival for patients treated with immunotherapy, chemotherapy and targeted therapies, which have been used to inform Merck's base case. We acknowledge the ERG's conclusion that the set of curves we presented in our base case can be considered plausible, and below, share our comments on the alternative set of PFS and OS extrapolations presented by the ERG, and why we think these are not as plausible. **Comments on ERG's base case** The ERG chose another set of curves for their base case, based on AIC and BIC choice alone. As previously discussed, curves chosen based on AIC and BIC alone are not recommended by NICE DSU TSD 14. This suggests that where there is a need to extrapolate outcomes and a significant amount of censoring, then external data, clinical plausibility and external judgement should be all

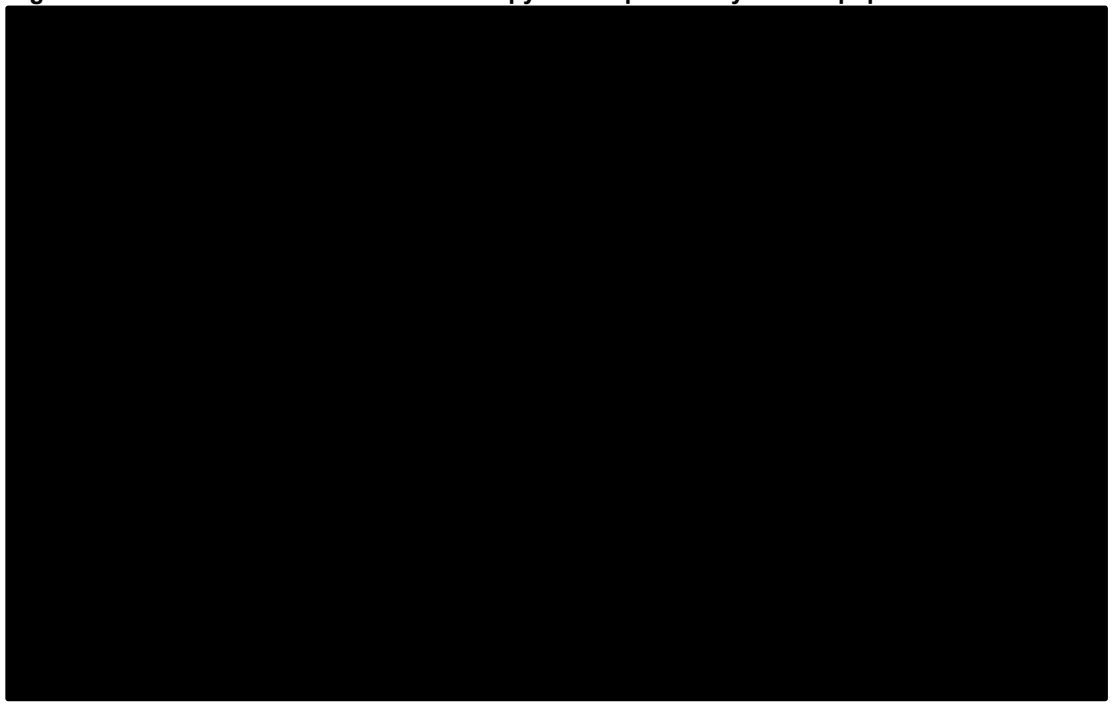
		used to assess the suitability and external validity of the alternative models.[31] Therefore, our critique and validation of the ERG's choices are discussed below. ***Tepotinib*** For the overall population and previously treated subgroup, the ERG chose the same curves as Merck's base case. For the untreated population, the ERG chose log-logistic for both PFS and OS instead of log-normal. The company chose log-normal for the base case as this appeared to have the better visual fit over the log-logistic distribution and was within 1 AIC and BIC score difference. Therefore, we stand by our choice of log-normal as our base case. ***Immunotherapy*** The ERG chose alternative immunotherapy curves for OS in the overall and previously treated populations, and PFS in the untreated population. These choices have been compared against external sources as per Section B.3.10 of the company submission. *Overall population* Figure 4 and **Figure 5** presents the ERG's projected OS for the overall population immunotherapy arm versus Merck's projected OS and published sources.

		Figure 4: External validation – immunotherapy – OS – overall population versus clinical trials  Abbreviations: 1L, first-line; 2L, second-line; OS, overall survival

		Figure 5: External validation – immunotherapy – OS – overall population versus real-world data  Abbreviations: 1L, first-line; 2L, second-line; OS, overall survival Similar to Merck's base case curve, in comparison to the clinical studies (Figure 4), the ERG's OS for the immunotherapy group projects lower survival compared to the pembrolizumab arm in KEYNOTE-024[35] and more in line with KEYNOTE-042.[36] Given that the KEYNOTE-024[35] and 042[36] populations are in first-line PD-L1 positive NSCLC without METex14 skipping alterations or other oncogenic driver mutations and are younger (median age 64.5 years and 63.0 years respectively compared to 72 years in the METex14 immunotherapy cohort), the survival for the METex14

		skipping alterations immunotherapy group is expected to be lower. In comparison to the previously treated clinical trials (KEYNOTE-010[37] and CheckMate 057/017[38]), the ERG's immunotherapy group survival projects better outcomes until around 3 to 4 years, after which the curve projects worse outcomes. Given the expectation of poorer outcomes for METex14 skipping alterations patients, and an older cohort, the survival would be expected to be either in line or lower than the immunotherapy arms from the published clinical trials in the previously treated group. Compared to published real-world data (**Figure 5**), the ERG's projected OS for the METex14 skipping alterations immunotherapy group appears in line with the two METex14 skipping alterations population sources (Guisier *et al.*[39] and Sabari et al.[3]), although underestimated compared to Sabari et al.[3] for the first two years and overestimated from one year compared to Guisier *et al.*[39] The ERG's immunotherapy OS curve sits consistently on the first-line real-world outcomes presented in Cramer-van der Welle *et al.*[40], however, compared to a wildtype NSCLC population, outcomes for a METex14 skipping alterations population are expected to be closer to the second-line projections. A similar conclusion was drawn from Merck's external validation of the base case choice, however the ERG's choice seems somewhat pessimistic compared to the feedback we received from clinicians at the advisory board who expected more of a plateau between five and eight years.

		Untreated population **Figure *6*** presents the ERG's projected PFS for the untreated population immunotherapy arm versus Merck's base case and first-line published sources. **Figure 6: External validation – immunotherapy – PFS – untreated population**  Abbreviations: 1L, first-line; PFS, progression-free survival The ERG's model projections are in line with the real-world outcomes in Cramer-van der Welle et al[40] and KEYNOTE-042. However the expectation would be that for the METex14 population, projections would be worse than those in the wider NSCLC group. In addition, the modelled PFS

		curve would be expected to be lower than KEYNOTE-042 given the age of the study populations and PD-L1 status. Therefore, this suggests that the ERG's PFS projections could be more optimistic than expected. This was also the conclusion of the Merck's base case curve (see Appendix N.1.1.8), therefore given the ERG's curve choice is slightly more optimistic than our base case, we consider the ERG's choice to be an implausible alternative. **Figure *7*** presents the ERG's projected OS for the previously treated population immunotherapy arm versus second-line published sources. **Figure 7: External validation – immunotherapy – OS – previously treated population**  Abbreviations: 2L+, second-line plus; OS, overall survival

		Similarly to Merck's base case, the ERG's model survival projection looks to be as expected compared to KEYNOTE-010[37] although predicting lower OS from two years. Compared to the second-line data from Cramer-van der Welle,[40] the survival looks to be overestimated and more in line with the immunotherapy trial studies. This is slightly higher than would be expected given the poorer response associated with METex14 skipping alterations patients in comparison to wildtype NSCLC. Given the similarities to our base case curve, we consider the ERG's choice to be a plausible alternative but note that the underlying assumptions of the exponential distribution (i.e., constant hazards) may not be appropriate for long term projections of immunotherapy as per the diagnostic plots (see Appendix N.1.1.8). ***Chemotherapy*** The ERG chose alternative curves for the OS and PFS in the overall and untreated population, and OS in the previously treated population. These choices have been validated against external sources as per Section B.3.10 of the company submission. *Overall population* **Figure *8*** and **Figure *9*** presents the ERG's projected OS for the overall population chemotherapy arm versus Merck's base case and published sources, respectively.

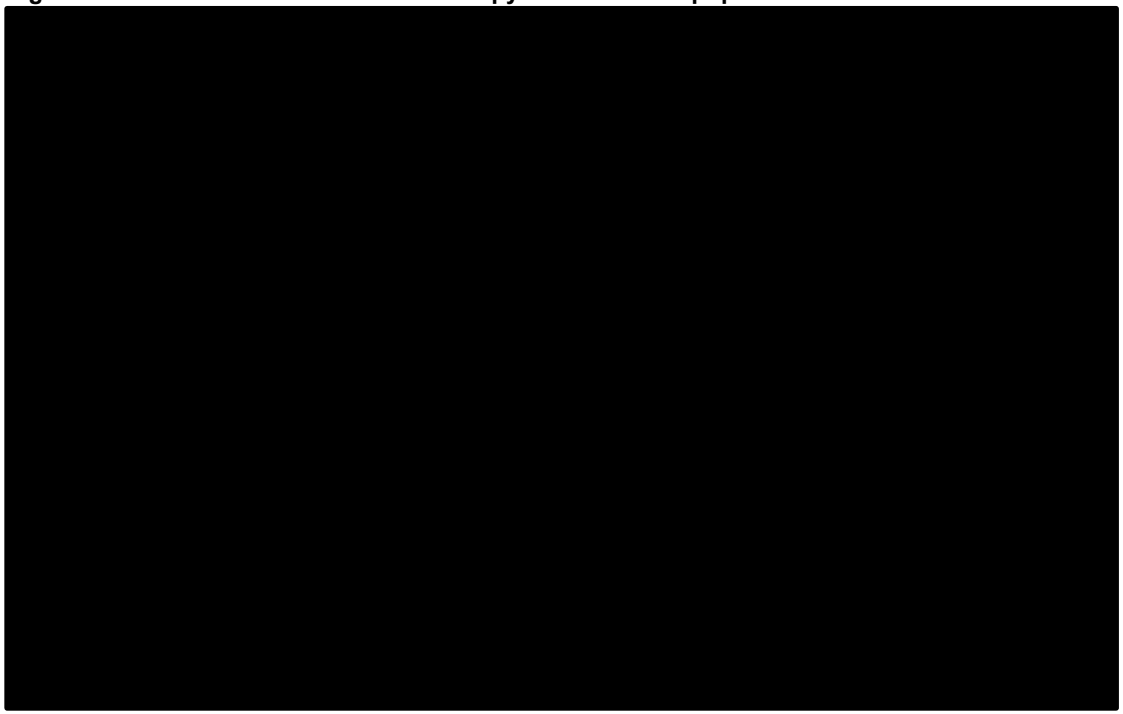
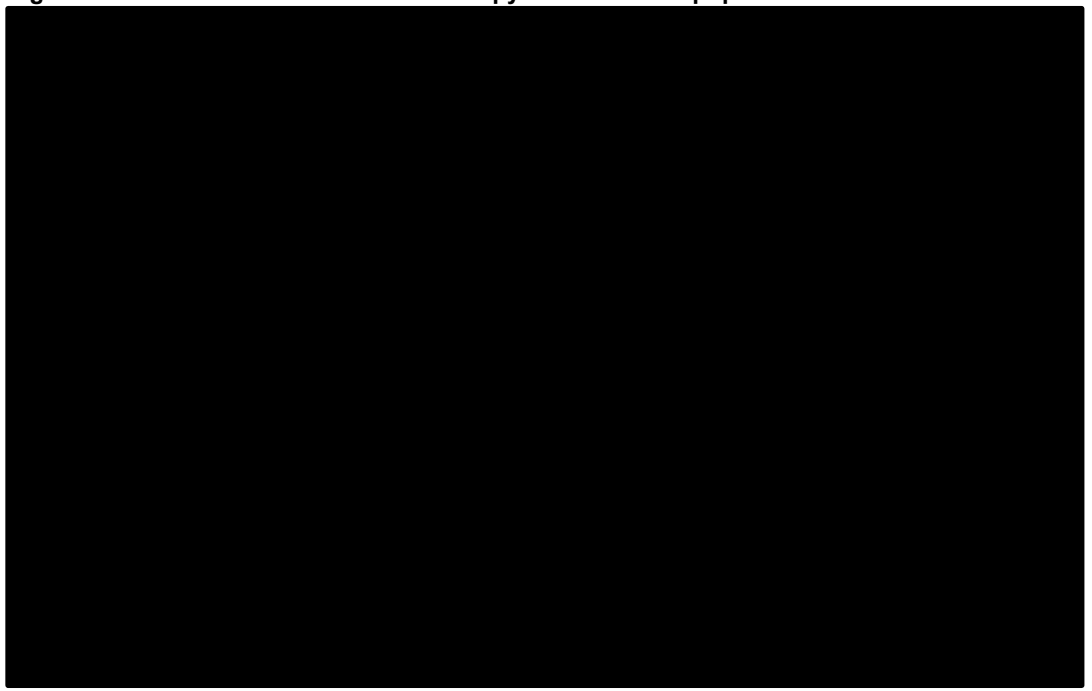
		Figure 8: External validation – chemotherapy – OS – overall population – versus clinical studies  Abbreviations: 1L, first-line; 2L+, second-line plus; OS, overall survival

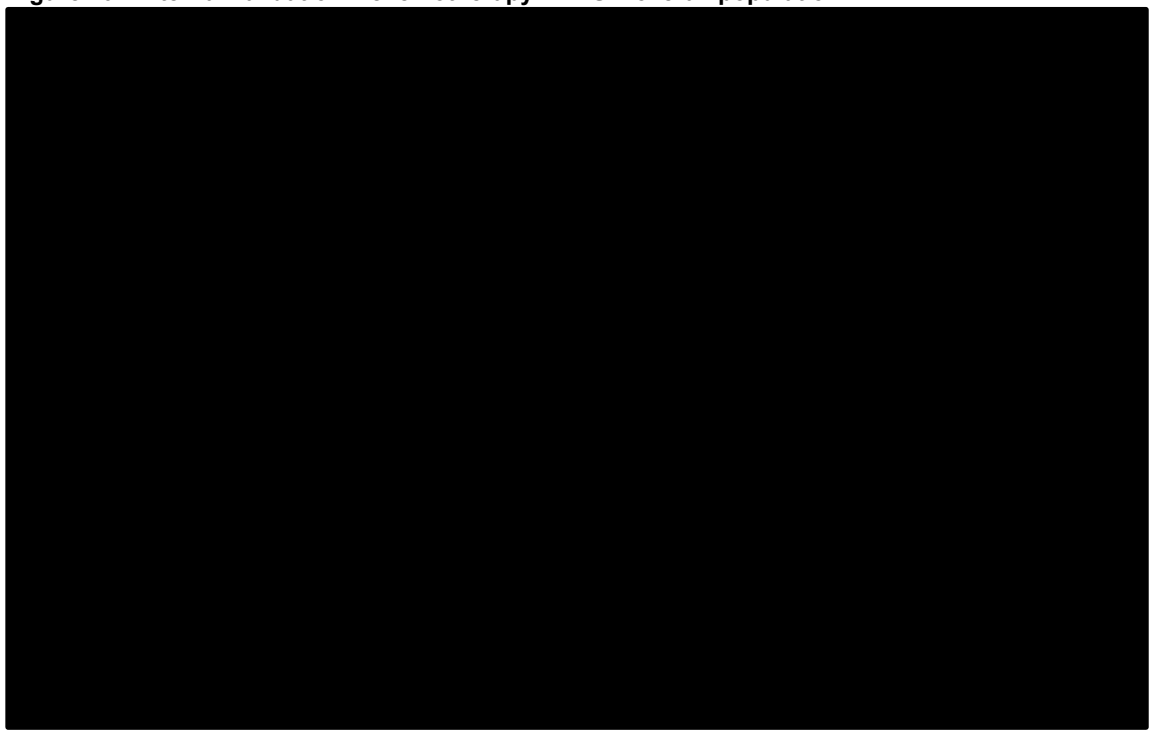
Figure 9: External validation – chemotherapy – OS – overall population – versus real-world data



Abbreviations: 1L, first-line; 2L+, second-line plus; OS, overall survival

Compared to clinical studies (**Figure *8***) the ERG's OS curve from the model projects greater survival compared to any of the chemotherapy clinical trials, although close to KEYNOTE-189.[41] At around three years the survival then projects lower estimates in comparison to KEYNOTE-189, but remains higher than any other study.[41] Based on the mix of untreated and previously treated patients, and a generally older cohort, the modelled chemotherapy OS would be expected to sit more closely with the previously treated published data (i.e., KEYNOTE-010[37] and CheckMate 057/017[38]). Additionally, compared to real-world studies (**Figure *9***), the ERG's modelled OS looks

		overestimated when compared to the real-world study Awad *et al*,[41] which is a mix of both untreated and previously patients and the study from Gajra *et al*.[42] of older patients. In conclusion, the ERG's OS looks substantially overestimated when comparing against external sources for chemotherapy (clinical trials in wildtype NSCLC and published real-world studies in METex14 skipping alterations patients), particularly in the long term. As discussed in Section B.3.10 the high estimates of survival are mainly driven by the real-world data as opposed to the curve selected. This could be largely due to subsequent treatments which will differ by study and will be dependent on the time period of the studies. Clinical experts at the advisory board noted the aggressive subsequent treatment usage in the real-world data sets which is not in line with UK clinical practice (e.g., high use of targeted MET inhibitors) which is likely having an impact on the survival. Subsequent treatments from the published METex14 skipping alterations studies are not available therefore it is not possible to compare appropriately what impact subsequent treatments may be having. Similar conclusions were reached for Merck's base case using the most pessimistic curve for the chemotherapy arm, and that even these could be overstated. Therefore, given the ERG's curve is one of the most optimistic options, we consider the ERG's choice to be highly implausible and also does not align with clinical advice that expected survival at 5 years is around 5% (log-normal estimates 12% 5-year survival). The higher long term survival estimates in the ERG curve are particularly implausible based on clinical expert feedback. **Figure *10*** presents the ERG's projected chemotherapy PFS curve versus Merck's base case and published sources.

		Figure 10: External validation – chemotherapy – PFS – overall population  Abbreviations: 1L, first-line; 2L+, second-line plus; PFS, progression-free survival Similar to Merck's base case, the ERG's PFS looks mostly in line with the external sources as they all project similar outcomes when naively compared in the first year. However the ERG's curve looks largely overestimated than would be expected after one year and into the long-term in comparison.

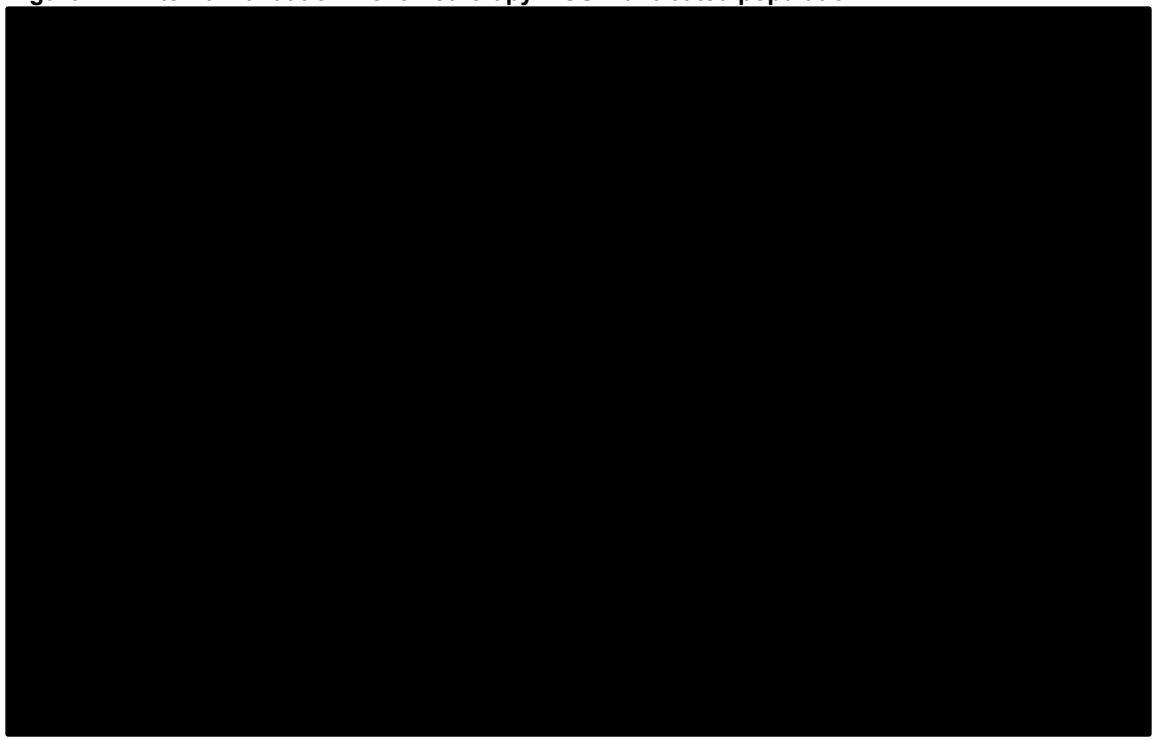
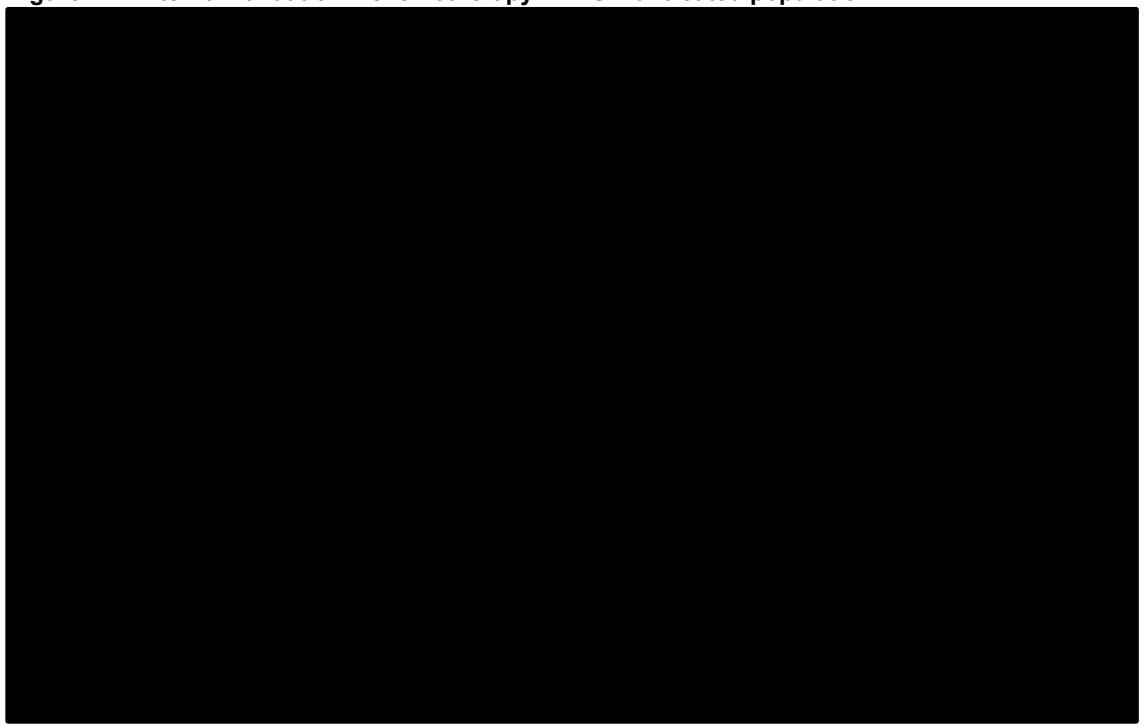
		Untreated population Figure 11 and Figure 12 presents the ERG's projected OS and PFS for the untreated population chemotherapy arm versus first-line published sources, respectively. **Figure 11: External validation – chemotherapy – OS – untreated population**  Abbreviations: 1L, first-line; OS, overall survival

Figure 12: External validation – chemotherapy – PFS – untreated population



Abbreviations: 1L, first-line; PFS, progression-free survival

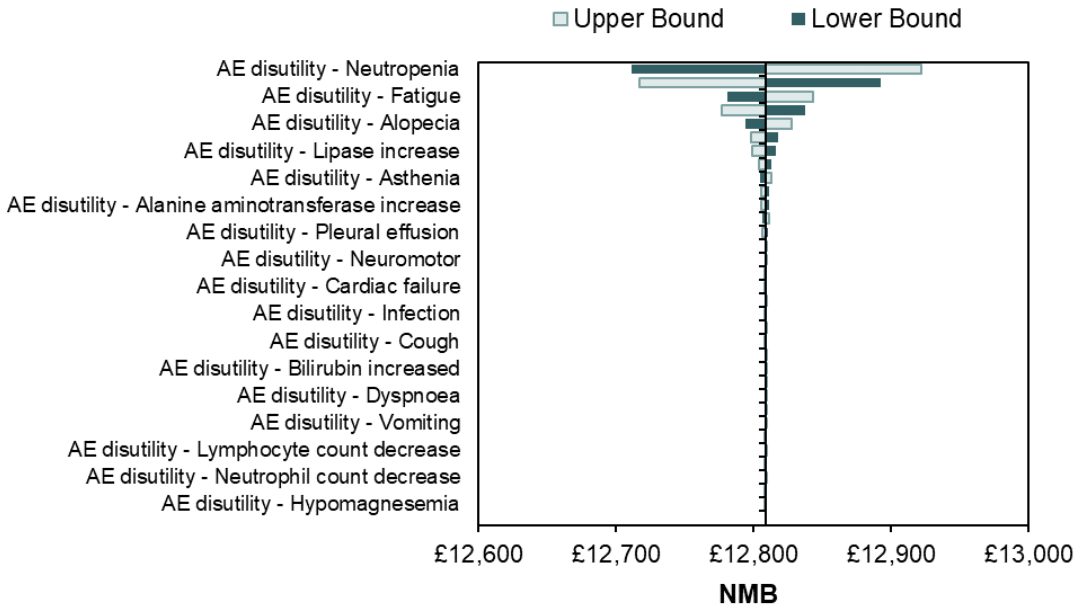
The ERG's OS chemotherapy model projections (Figure 11) look substantially optimistic in comparison to all of the external data sources and Merck's base case in the long-term. This suggests that the survival for chemotherapy is overestimated given the expectation of worse outcomes, in particular in comparison to the KEYNOTE studies which are a younger patient group. As with the overall population, the cause of these differences could be due to subsequent treatments which impact the OS of the real-world data. The PFS results seem more consistent with expectations in comparison to the external sources of validation, however the modelled curve does

		tail off after 1 year predicting higher PFS long term outcomes than expected based on the external data source and appearing to plateau in the long-term. As such, we do not consider the ERG's curves to be plausible alternatives to extrapolate chemotherapy PFS and OS outcomes. *Previously treated population* Figure 13 presents the ERG's projected OS for the previously treated population chemotherapy arm versus Merck's base case and previously treated published sources. **Figure 13: External validation – chemotherapy – OS – previously treated population**  Abbreviations: 2L+, second-line plus; OS, overall survival

		The ERG's OS chemotherapy model projections look drastically more optimistic in comparison to the KEYNOTE and CheckMate studies, particularly in the long-term survival estimates. A similar conclusion was reached for the Merck's base case using the most pessimistic curve for the chemotherapy arm. Therefore, given the ERG's choice is one of the most optimistic curves, we consider the ERG's choice to be highly implausible. ***External validation conclusion*** In conclusion Merck consider most of the ERG's base case curves to be implausible. This is particularly apparent for the chemotherapy OS curves, where the ERG have chosen the most optimistic curves out of the choices available for all populations, and seem to substantially overestimate survival with chemotherapy in the short and long-term, compared to external studies and clinical expert opinion. Merck chose curves in line with clinical plausibility, acknowledging that the modelled projections still appear over-estimated in comparison to external sources. As the ERG's curves project a much higher survival than Merck's, these are extremely unlikely to represent the long-term outcomes of patients treated with chemotherapy and thus severely underestimate the benefit versus tepotinib. Merck consider that the ERG curves here are not equally as plausible as the company's curve selections. **Overall conclusion** In conclusion, the curves selected for Merck's base case represent the most clinically plausible projections of OS and PFS for patients with NSCLC harbouring METex14 skipping alterations. With the exception of chemotherapy, the clinically validated curves are within an acceptable AIC and BIC range of the best statistically fitting curves and visually fit the data well. A limitation of the chemotherapy arm is that the real-world cohort (most from the US, but also Canada, Israel, Taiwan and the Netherlands) has better outcomes than would be expected in UK clinical practice notably due to the more aggressive subsequent treatments received. Therefore, the clinical plausibility of the long term projections was prioritised over the statistical and visual fit in the Merck's base case. Validation of these projections still highlighted the optimistic projections, therefore, considering the

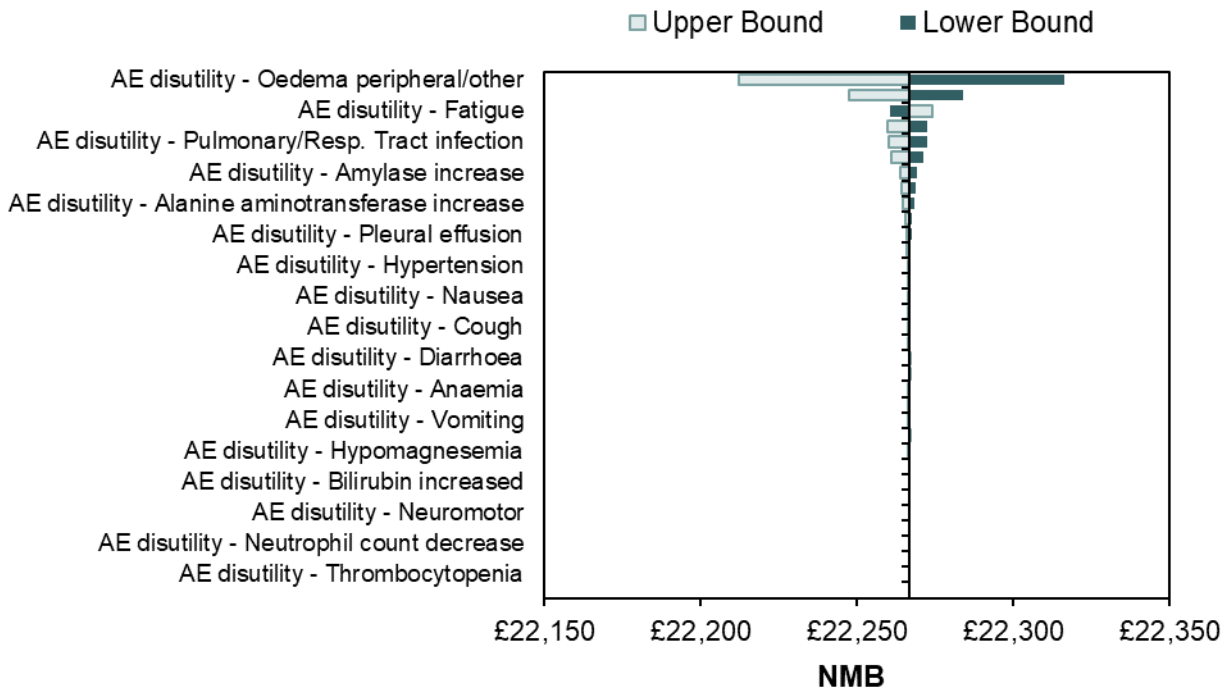
		ERG's curve choices are based solely on AIC and BIC and are more optimistic than Merck's choice, these are considered highly implausible and not reflective of outcomes expected in clinical practice.
Key issue 11: Representativeness of AE utility values for the UK population	**NO**	The ERG noted that several utility estimates for adverse events were not estimated using standard UK approved instruments or a relevant population. Merck accept the ERG's critique of the adverse event disutility values and acknowledge the limitation of available evidence as not being fully representative of the study population or the preferred measure of utility for the NICE reference case. However, as the ERG acknowledges in their report, these sources are the best available evidence and have been used in previous NSCLC appraisals. In addition, adverse event disutilities have very little impact on results as demonstrated from the one-way sensitivity analysis (OWSA) (see Figure 14 and Figure 15).

Figure 14: Tornado diagram showing OWSA results of the AE disutilities on the NMB versus chemotherapy (WTP=£50,000)



Abbreviations: AE, adverse event; OWSA, one-way sensitivity analysis; NMB, net monetary benefit

Figure 15: Tornado diagram showing OWSA results on the AE disutilities on the NMB versus immunotherapy (WTP=£30,000)



Abbreviations: AE, adverse event; NMB, net monetary benefit; OWSA, one-way sensitivity analysis

Conclusion

In conclusion, Merck do not consider alternative disutility values will impact the cost-effectiveness results and thus retained the original sources.

Key issue 12: It is possible there is better fitting model for ToT for tepotinib which was not fitted to the data by the company	**YES**	The ERG felt that as the best statistically fitting model for time on treatment (ToT) (log-logistic) possibly over-fits the tail-end of the data, more flexible models should have been produced. The range of parametric curves available to model ToT for tepotinib within the submission fit the KM estimates reasonably well, with the exception of the tail portion of the curve where an extended plateau is observed in the KM. This extended tail is likely an artifact of patient censoring, with clinical expert opinion indicating that while a couple of patients may receive treatment long-term, the vast majority would be off treatment by 5 years. Due to the nature of the extended KM tail, it is unlikely that any model extrapolation would be able to accurately capture the curve observed while remaining clinically plausible. As the parametric model extrapolations provided a wide range of long-term estimates of ToT, the parametric model options were considered sufficient to be used in sensitivity analysis (CS Doc B, Section B.3.8.3) and so more flexible models were not presented within the submission. For completeness, the spline model fits to tepotinib ToT are presented in Figure 16. The plot shows similar fits to the KM curve as seen with the parametric extrapolations, with a range of long-term ToT estimates available.

Figure 16: ToT spline model fits – tepotinib – overall population

Abbreviations: KM, Kaplan-Meier; ToT, time on treatment

Table 3 presents the AIC and BIC goodness-of-fit statistics for the ToT parametric and spline model extrapolations. The log-logistic and exponential models provide the best fit to the data according to AIC and BIC, respectively. By AIC, all models apart from the log-normal, 3-knot hazard and 3-knot normal are within 5 points of the smallest AIC, indicating a reasonable fit to the data. By BIC, of the nine spline options, only the 1-knot odds and 1-knot normal models provide a fit within 5 points of the smallest BIC.

Table 3: AIC and BIC – ToT – tepotinib, parametric and spline models

Model	Goodness-of-fit		Rank	
	AIC	BIC	AIC	BIC
Exponential	932.5	935.5	7	1
Weibull	934.3	940.4	12	6
Gompertz	933.0	939.1	9	3
Log-logistic	929.8	935.8	1	2
Log-normal	937.5	943.5	13	9
Generalised gamma	932.2	941.3	5	7
Spline – odds 1 knot	930.1	939.2	2	4
Spline – odds 2 knot	931.9	944.0	4	10
Spline – odds 3 knot	933.7	948.8	10	13
Spline – hazard 1 knot	933.0	942.1	8	8
Spline – hazard 2 knot	933.7	945.8	11	12
Spline – hazard 3 knot	939.6	954.7	14	14
Spline – normal 1 knot	930.7	939.8	3	5
Spline – normal 2 knot	932.4	944.5	6	11
Spline – normal 3 knot	944.1	959.2	15	15

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ToT, time on treatment

Table 4 presents the proportion of patients estimated to still be on treatment with tepotinib at 5 and 10 years. At 5 years, the parametric models range from [redacted]% on treatment with the Weibull model to [redacted]% with the log-logistic. The spline models range between [redacted]% with the 3-knot normal model to [redacted]% with the 1-knot odds model. At 10 years, the parametric models vary between [redacted]% and [redacted]% remaining on treatment with the spline models ranging from [redacted]% to [redacted]%.

Table 4: Proportion of patients estimated to be treated with tepotinib at 5 and 10 years

Model	Proportion on treatment	
	5 years	10 years
Exponential	[redacted]%	[redacted]%
Weibull	[redacted]%	[redacted]%
Gompertz	[redacted]%	[redacted]%
Log-logistic	[redacted]%	[redacted]%
Log-normal	[redacted]%	[redacted]%
Generalised gamma	[redacted]%	[redacted]%
Spline – odds 1 knot	[redacted]%	[redacted]%
Spline – odds 2 knot	[redacted]%	[redacted]%
Spline – odds 3 knot	[redacted]%	[redacted]%
Spline – hazard 1 knot	[redacted]%	[redacted]%
Spline - hazard 2 knot	[redacted]%	[redacted]%
Spline - hazard 3 knot	[redacted]%	[redacted]%
Spline - normal 1 knot	[redacted]%	[redacted]%
Spline - normal 2 knot	[redacted]%	[redacted]%
Spline - normal 3 knot	[redacted]%	[redacted]%

Conclusion

Given that the spline models do not provide a better fit in comparison to the parametric models and the range of long-term estimates produced from the splines are within that of the parametric models, these were considered appropriate to model tepotinib's ToT, providing a clinically plausible option for the base case and a reasonable range to explore as sensitivity analysis. As such, spline models have not been incorporated into the economic model.

<table>
<tr>
<td>Key issue 13:
Uncertainty in the cost estimates for immunotherapy and chemotherapy</td>
<td>YES</td>
<td>
The ERG were unable to reproduce the distribution of chemotherapies and immunotherapies used for the comparator arms in the model. Merck have provided some additional information below.
The distribution of immunotherapies and chemotherapies used for the comparator treatments are taken from the real-world cohort data. Treatments which were not considered part of UK clinical practice were either re-assigned to another similar treatment or re-distributed between the remaining treatments within the same class. Though within the immunotherapy group, most are aligned with UK practice (i.e., pembrolizumab, nivolumab, and atezolizumab), additionally, the majority of chemotherapy treatments are platinum doublets which are widely used in clinical practice.
The distribution taken forward for the model are based on the weighted patient numbers after application of the propensity score weighting from the ITC. This is done so that the distribution of treatments matches the weighted efficacy used to inform the comparator arms. Table 5 presents the treatments in the real-world cohort data with the unweighted and weighted incidence from the ITC and model category.
Table 5: Categorisation of the real-world treatments
<table>
<tr><th>Treatment</th><th>Model category</th><th>Unweighted n</th><th>Weighted n</th></tr>
<tr><td colspan="4">Chemotherapies</td></tr>
<tr><td>Carboplatin & pemetrexed</td><td>Pemetrexed/ platinum</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Platinum Doublet</td><td>Other</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Bevacizumab, carboplatin & pemetrexed</td><td>Pemetrexed/ platinum [a]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Carboplatin & paclitaxel</td><td>Paclitaxel/ platinum</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Docetaxel</td><td>Docetaxel monotherapy</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Pemetrexed</td><td>Pemetrexed/ platinum [a]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Cisplatin & pemetrexed</td><td>Pemetrexed/ platinum</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Pemetrexed & bevacizumab</td><td>Pemetrexed/ platinum [a]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Bevacizumab, cisplatin & pemetrexed</td><td>Pemetrexed/ platinum [a]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
</tr>
</table>

		Carboplatin	Other	[redacted]	[redacted]
		Carboplatin & gemcitabine	Gemcitabine/ platinum	[redacted]	[redacted]
		Cisplatin & etoposide	Docetaxel/ platinum [b]	[redacted]	[redacted]
		Cisplatin & gemcitabine	Gemcitabine/ platinum	[redacted]	[redacted]
		Cisplatin & vinorelbine	Vinorelbine/ platinum	[redacted]	[redacted]
		Everolimus	Other	[redacted]	[redacted]
		Gemcitabine & vinorelbine	Docetaxel/ gemcitabine [c]	[redacted]	[redacted]
		Vinorelbine	Vinorelbine monotherapy [d]	[redacted]	[redacted]
		Immunotherapies			
		Durvalumab	Other	[redacted]	[redacted]
		Immunotherapy	Other	[redacted]	[redacted]
		Ipilimumab & nivolumab	Nivolumab/ipilimumab	[redacted]	[redacted]
		Nivolumab	Nivolumab	[redacted]	[redacted]
		Pembrolizumab	Pembrolizumab	[redacted]	[redacted]
		Spartalizumab	Other	[redacted]	[redacted]

Note: [a] These pemetrexed based regimens were not considered part of UK practice therefore clinical opinion confirmed that pemetrexed + platinum would be an appropriate re-categorisation.
[b] Etoposide was not considered part of UK practice therefore alternative chemotherapy was considered an appropriate re-categorisation by clinical experts.
[c] Although various combinations of chemotherapies could be given in UK clinical practice (usually as a last resort when other treatments have failed), gemcitabine + vinorelbine was re-categorised as docetaxel + gemcitabine as this treatment was already included in the model and avoided the need to include multiple variations for small incidences. Considering the similar effectiveness and costs between these treatments and small incidence, this is not expected to have much impact on the distributions.
[d] Corrected during technical engagement

During the technical engagement process, it was noted that vinorelbine had been incorrectly categorised as vinorelbine + platinum in the 'overall' population. This has been subsequently corrected to be classed as vinorelbine monotherapy and updated results are presented in **Table**

15. Table 6 presents the original and corrected distributions used within the cost-effectiveness analysis.

Table 6: Distribution of comparator treatments in the model

Treatment	Original distribution	Corrected distribution
Immunotherapies		
Pembrolizumab	[redacted]%	[redacted]%
Atezolizumab	[redacted]%	[redacted]%
Nivolumab	[redacted]%	[redacted]%
Nivolumab/ipilimumab	[redacted]%	[redacted]%
Chemotherapies		
Docetaxel/ platinum	[redacted]%	[redacted]%
Gemcitabine/ platinum	[redacted]%	[redacted]%
Paclitaxel/ platinum	[redacted]%	[redacted]%
Vinorelbine/ platinum	[redacted]%	[redacted]%
Pemetrexed/ platinum	[redacted]%	[redacted]%
Docetaxel monotherapy	[redacted]%	[redacted]%
Docetaxel/ nintedanib	[redacted]%	[redacted]%
Docetaxel/ gemcitabine	[redacted]%	[redacted]%
Gemcitabine monotherapy	[redacted]%	[redacted]%
Vinorelbine monotherapy	[redacted]%	[redacted]%

Conclusion

The above information should be sufficient for the ERG to understand how the treatment distributions were derived. In addition, in response to clarification questions Merck provided the ERG with a spreadsheet which detailed the exact calculations using the ITC data to the model distributions.

Key issue 14: Uncertainty in the cost estimates for subsequent treatments	**NO**	The ERG noted that cost-effectiveness results were quite sensitive to the proportion of patients receiving subsequent treatment. Merck agree with the ERG and noted within the company submission that subsequent treatments are an area of uncertainty and influenced by countries included in the clinical trial and real-world cohorts. A randomised control trial in the UK with sufficient sample size and follow-up suggested by the ERG would be the gold standard in terms of evidence, however this evidence was not available for the submission and not possible to obtain. In the base case, the model uses the subsequent treatment distributions as per the clinical trial and real-world cohort, such that the efficacy is matched to the costs. Any treatments which were not licensed or available within the UK have been reclassified within a similar treatment class or re-distributed evenly such that costs are still reflective of the modelled efficacy. Scenario analyses using a UK based distributions were conducted to explore impacts of different costs. However, as discussed in the company submission, it is important to note that the modelled overall survival is based on the initial treatments and subsequent treatment distributions used in the base case, therefore the scenario considering UK based distributions only impacts the costs and not the difference in survival efficacy, and so is an unfair comparison. This was agreed by the ERG in the technical engagement call. It is unclear how the differences in these treatment distributions would impact the survival. Scenarios were considered where the comparator arm efficacy could be varied to explore the uncertainty, however it was not felt to be a valuable exercise as the degree of variation in efficacy could not be informed by any available data and therefore would have limited interpretability. **Conclusion** Merck reiterate that for the subsequent treatments in the immunotherapy and chemotherapy arms, it is more appropriate to use the treatment distribution based on the real-world data set in the economic model in order to maintain the relationship between the effectiveness and cost outcomes of which the ERG agrees with, as noted in their report and in the TE call.

<table>
<tr>
<td>Key issue 15: Insufficient reporting and clarity of reporting of the cost-effectiveness results</td>
<td>NO</td>
<td>
The ERG was unclear on which decision problem questions were addressed within the company's submission. Merck would like to clarify the reporting of cost-effectiveness results and which decision questions are being considered, in Table 7. The base case presents results for the overall population in line with the tepotinib license and clinical need. Subgroups are also presented by treatment line based on the available data.

Table 7: Decision problems in the Merck's cost-effectiveness analysis
<table>
<tr><th>Decision problem</th><th>Comparators</th><th>Model population</th></tr>
<tr><td>Overall (base case)</td><td>Immunotherapy,
Chemotherapy</td><td>Overall</td></tr>
<tr><td>Untreated</td><td>Immunotherapy,
Chemotherapy,
Immunotherapy + chemotherapy</td><td>Untreated</td></tr>
<tr><td>Previously treated</td><td>Immunotherapy,
Chemotherapy</td><td>Previously treated</td></tr>
</table>
As multiple comparators are available per population, fully incremental analysis was provided and is relevant to inform the decision problem. However, pair-wise results are also presented for completeness as these better reflect the clinical decision for patients who would receive chemotherapy or immunotherapy versus tepotinib (e.g., for patients who receive chemotherapy in practice, the comparison is between tepotinib and chemotherapy only). Merck have provided both sets of analyses (fully incremental and pairwise) and consider both informative for decision-making at this stage.

During the development of the submission, Merck received clinical feedback that there are a small number of patients for whom immunotherapies are contraindicated, therefore this was discussed in the original submission. However, given that this is expected to be a very small proportion of patients, this population does not necessarily need to be considered separately, and instead should be considered as part of the overall population, for the chemotherapy pairwise comparison, as per the base case.
</td>
</tr>
</table>

		Conclusion As per the response to Key Issue 8, we strongly prefer the results to be presented as per Table *7*, but acknowledge that the ERG's scenario analysis using clinical data by treatment line and amending the comparators by subgroup may be useful alongside these.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do not use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: End of life criteria	Section 7: End of life, page 119	NO	The ERG considered the end of life criteria and agreed that the ITC favoured the less than 24 month criteria for the overall population. However, there was some uncertainty based on the model results and incremental difference per subgroup. Therefore, Merck would like to re-affirm their arguments for the end-of life criteria in light of the comments from the ERG regarding decision problems within the cost-effectiveness analysis (outlined in Key Issue 15). As discussed in response to Key Issue 8, given the limited data available for NSCLC patients harbouring METex14 skipping mutations, evidence for the decision problem subgroups presented by the ERG (by histology and PD-l1 expression) is not available for the METex14 patient cohort. As such, we have evaluated end-of-life criteria using available evidence considering the overall population (company base case) and treatment line subpopulations (1L and 2L subgroups), in line with Merck's approach to the decision problem populations described in Key Issue 15. **Life expectancy in advanced NSCLC: external published sources**

Table 8 presents a summary of median OS for patients with advanced NSCLC available in the literature. Although evidence in the literature for patients treated with immunotherapy and chemotherapy is limited for METex14 skipping NSCLC patients (3 studies are presented), we also considered available studies in the wider advanced NSCLC population. Across all of these studies, median OS is under 24 months for all patients treated with chemotherapy, regardless of treatment line.

As discussed in Section 2.1.3.1 of the company submission, patients with METex14 skipping alterations have a poorer prognosis compared to wildtype NSCLC.[41;43-45] Studies reporting outcomes of METex14 patients shows a poorer response to treatment, with reported median OS ranging from 8.1 months to 18.2 months.[3;39;41] Patients harbouring METex14 skipping mutations tend to be older[46] and older patients with NSCLC tend to have a poorer prognosis.[47] One real-world study in older patients in advanced NSCLC reported a median OS of 7.7 months for patients treated with immunotherapy.[42]

Therefore, the evidence in the literature suggests that patients with advanced NSCLC harbouring METex14 have a life expectancy less than 24 months regardless of treatment line.

Table 8: Overview of median OS reported for advanced NSCLC in the literature

Source	Population	Median OS, months	
		Immunotherapy	Chemotherapy
Overall (mixed untreated/previously treated)			
Guisier et al[39]	Real-world study - METex14 skipping mutations	13.4 (9.4-NR)	-
Sabari et al[3]	Real-world study - METex14 skipping alterations	18.2 (12.9-NR)	-

			Awad et al[41]	Real-world study – METex14 skipping alterations	-	8.1 (5.3-NR)
			Untreated population			
			Cramer-van der Welle et al[40]	Real-world study – PD-L1 positive >50%	15.8 (9.4-22.1)	-
			Gajra et al[42]	Pooled clinical trials >=70 years	-	7.7 (6.0-8.9)
			KEYNOTE-189[48]	Phase III trial – non-squamous	-	10.7 (8.7-13.6)
			KEYNOTE-042[36]	Phase III trial – PD-L1 positive >1%	16.7 (13.9-19.7)	12.1 (11.3-13.3)
			KEYNOTE-024[35]	Phase III trial – PD-L1 positive >50%	26.3 (18.3-40.4)	13.4 (9.4-18.3)
			Previously treated			
			Cramer-van der Welle et al[40]	Real-world study – non-squamous PD-L1 positive <50%	8.2 (5.9-10.6)	-
			KEYNOTE-010[37]	Phase III trial – PD-L1 positive >1%	11.8 (10.4-13.1)	8.4 (7.6-9.5)
			CheckMate 017 & CheckMate 057[38]	Phase III trials	11.1 (9.2-13.1)	8.1 (7.2-9.2)

Key: OS, overall survival; NR, not reached

Life expectancy in advanced NSCLC: Merck data analysis (ITC and economic model)

The results of the ITC support the evidence in the literature, suggesting that regardless of treatment line, life expectancy is less than 24 months (median OS ranges from [redacted] to [redacted] months for immunotherapy and [redacted] to [redacted] months for chemotherapy- see Table ***9***). For chemotherapy-treated patients, modelled mean OS is [redacted]

			months in the overall cohort, and [redacted] months in the previously treated cohort. Table ***9*** presents the median survival from the ITC and mean survival from the cost-effectiveness model using the observed data from VISION and the weighted data from the real-world cohort, and extrapolating 30 years. The model predicts the mean survival to be under 24 months for chemotherapy and over 24 months for immunotherapy for the overall population. Though this seems more optimistic than what is reported in the literature, this provides evidence patients treated with chemotherapy have a life expectancy less than 24 months whilst immunotherapy is uncertain. Looking at the individual subgroups, the untreated population is estimated to have a greater life expectancy of over 24 months whereas patients who have been previously treated are expected to have a life expectancy less than 24 months regardless of treatment option. Life-expectancy in the chemotherapy arm looks relatively close to 24 months in the model for the overall and previously treated populations, however the chemotherapy survival from the real-world cohort has been noted to be overly optimistic compared to what would be expected in clinical practice and published sources (see Table 8) due to subsequent treatment patterns and use of subsequent MET inhibitors, even when using the most pessimistic curve (see response to Key Issue 10). Therefore, the mean OS for chemotherapy (overall and previously treated) is considered to be the most optimistic estimate, and the upper bound of what could be expected, accounting for uncertainty within the population. Nonetheless, these are still in line in line with the 24-month threshold.

Table 9: Mean and median survival

Evidence, months		Tepotinib	Immunotherapy	Chemotherapy
Overall population				
Observed data (ITC/VISION)	Median	[redacted]	[redacted]	[redacted]
Observed data (MAIC/VISION)	Median	[redacted]	13.4[39] – 18.2[3]	8.1[41]
CE model	Mean	[redacted]	[redacted]	[redacted]*
Untreated				
Observed data (ITC/VISION)	Median	[redacted]	[redacted]	[redacted]
CE model	Mean	[redacted]	[redacted]	[redacted]*
Previously treated				
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.

Based on the data presented in Table ***9***, tepotinib is expected to have a greater than 3 months gain in survival compared to patients treated with chemotherapy in the overall population and those treated with immunotherapy or chemotherapy in the previously treated population. For the previously treated chemotherapy patients, the mean OS from the model shows a difference of [redacted] months. As discussed in the company submission and in Key Issue 10, it is expected that the real-world cohort chemotherapy OS is overestimated, based on validation against external sources, as well clinical validation,

including for the previously treated group. This is possibly due to the high number and type of subsequent treatments (not seen in UK practice for METex14 skipping patients, such as crizotinib) in this cohort. The chemotherapy OS in this real-world cohort group showed a much larger mean and median OS in comparison to previously treated studies in the literature (see Table 8). Therefore, the OS benefit for tepotinib over chemotherapy (overall and previously treated) is considered to be the most conservative estimate, and the lower bound of the OS benefit that could be expected between tepotinib and chemotherapy, accounting for uncertainty within the population.

Conclusion

In conclusion, Merck consider tepotinib to meet end of life criteria:

- In the overall population for patients who would be treated with chemotherapy
- For all patients in the previously treated population regardless of treatment option.

This is supported by data in the literature showing poorer outcomes for patients with advanced NSCLC harbouring METex14 skipping mutations, data from the ITC, and extrapolated data from the cost-effectiveness model (see Table 10).

Table 10: Merck end of life criteria conclusion

Population	Evidence for EoL criteria
Overall	**<24 months** Chemotherapy: Literature sources show median OS ranging from 8.1 – 13.4 months (Table 8). ITC and model show expected survival <24 months (mean OS and median OS) (Table ***9***) for patients treated with chemotherapy

				>3 months benefit Chemotherapy: Mean benefit from model is [redacted] months, and median benefit from propensity score ITC is [redacted] months and MAIC ITC is [redacted] months (Table **9**) for chemotherapy compared to tepotinib Immunotherapy comparison is at the 30k threshold in the overall population.
			Untreated	All comparisons at the 30k threshold in the untreated population.
			Previously treated	**<24 months** Chemotherapy: Literature sources show median OS range from 8.1 to 8.4 months (Table 8). ITC and model show expected survival of [redacted] months (median) and [redacted] months (mean) at most (Table **9**), but this is likely to be overestimated as stated in Key issue 10 and Section B.3.2 of the company submission Immunotherapy: Literature sources show median OS ranges from 8.2 – 11.8 months (Table 8). ITC and model show expected survival to be < 24 months (Table **9**) **>3 months benefit** Chemotherapy: Mean benefit from model is [redacted] months, and median benefit from the ITC is [redacted] months (Table **9**). Given the overestimation of chemotherapy OS from the real-world data this benefit is likely to be underestimated. Immunotherapy: Mean benefit from model is [redacted] months, and median OS from the ITC is [redacted] months (Table **9**)
			Key: EOL, end of life; ITC, indirect treatment comparison; MAIC, match-adjusted indirect comparison; OS, overall survival	

Additional Issue 2: Additional clinical data availibility from VISION for Cohort A+C	Table 1.4: Key issue 3:	**No**	Recently published clinical data for Cohort A+C could help to address the uncertainty in the similarities and differences between Cohort A and Cohort A+C. The additional data published and provided includes: 1. More information on characteristics and outcomes in the different biopsy subgroups (standard of care tissue biopsy, and liquid biopsy) (Felip et al 2021) 2. More information on the efficacy of tepotinib in different age groups (Garassino et al 2021) **Felip E. et al. Tepotinib in patients with MET exon 14 (METex14) skipping NSCLC as identified by liquid (LBx) or tissue (TBx) biopsy. Presented at World Conference on Lung Cancer 2021, September 8–14. Abstract number 170.[49]** The efficacy analysis presented here includes all patients enrolled in Cohort A and patients enrolled in Cohort C with ≥3 months' follow-up (n=275). The data provided for this subgroup analysis (Cohort A and Cohort C) were recently published at WCLC 2021. A total of 159 patients with positive detection of MET exon 14 skipping by liquid biopsy, and 174 by tissue biopsy were enrolled (21% of patients had both a liquid and tissue biopsy). In the UK, tissue biopsy remains the standard of care and so these results can be considered appropriate when looking at tepotinib outcomes. Baseline demographics were broadly consistent between patients enrolled based on liquid (L+) (n=159) or tissue biopsy (T+) (n=174) (Table 11).

Table 11. Demographics and Baseline Characteristics, VISION Cohort A and Cohort C – 1 February 2021 cut-off

	L+			T+		
	Overall	**1L**	**2L+**	**Overall**	**1L**	**2L+**
	N=159	**N=81**	**N=78**	**N=174**	**N=86**	**N=88**
Sex, n (%)						
Male	74 (46.5)	39 (48.1)	45 (52.3)	91 (52.3)	35 (44.9)	46 (52.3)
Female	85 (53.5)	42 (51.9)	41 (47.7)	83 (47.7)	43 (55.1)	42 (47.7)
Age (years)						
Median (range)	71.3 (47-89)	72.0 (47-89)	75.4 (47-94)	73.0 (41-94)	70.8 (49-89)	71.0 (41-89)
Age groups, n (%)						
<65 years	36 (22.6)	16 (19.8)	10 (11.6)	30 (17.2)	20 (25.6)	20 (22.7)
65 to <75 years	59 (37.1)	31 (38.3)	30 (34.9)	70 (40.2)	28 (35.9)	40 (45.5)
75 to <85 years	53 (33.3)	26 (32.1)	35 (40.7)	57 (32.8)	27 (34.6)	22 (25)
≥85 years	11 (6.9)	8 (9.9)	11 (12.8)	17 (9.8)	3 (3.8)	6 (6.8)
Line of therapy for tepotinib n (%)						
1L	81 (50.9)	NA	NA	86 (49.4)	NA	NA
2L	45 (28.3)	NA	NA	61 (35.1)	NA	NA
3L	33 (20.8)	NA	NA	27 (15.5)	NA	NA
Smoking history[a] n (%)						
Yes	NR (50.9)	37 (45.7)	41 (47.7)	NR (48.9)	44 (56.4)	44 (50)
No	NR (46.5)	44 (54.3)	44 (51.2)	NR (45.4)	30 (38.5)	35 (39.8)

ECOG PS[b] n (%)								
0	NR (24.5)	21 (25.9)	28 (32.6)	NR (29.9)	18 (23.1)	24 (27.3)		
1	NR (75.5)	60 (74.1)	57 (66.3)	NR (69.5)	60 (76.9)	64 (72.7)		
Geographic region, n (%)								
Europe	85 (53.5)	19 (23.5)	16 (18.6)	33 (19.0)	18 (23.1)	17 (19.3)		
North America	37 (23.3)	50 (61.7)	45 (52.3)	80 (46.0)	35 (44.9)	35 (39.8)		
Asia	37 (23.3)	12 (14.8)	25 (29.1)	61 (35.1)	25 (32.1)	36 (40.9)		
Histology subtype,[c] n (%)								
Adenocarcinoma	NR (80.5)	67 (82.7)	70 (81.4)	NR (81.6)	61 (78.2)	72 (81.8)		
Squamous	NR (11.9)	8 (9.9)	5 (5.8)	NR (7.5)	11 (14.1)	8 (9.1)		
Sarcomatoid	NR (3.1)	4 (4.9)	1 (1.2)	NR (1.1)	1 (1.3)	1 (1.1)		
Other	NR (4.4)	2 (2.5)	9 (10.5)	NR (8.6)	5 (6.4)	6 (6.8)		

Abbreviations: 1L, first-line; 2L, second-line; 3L, third line; ECOG PS, Eastern Cooperative Oncology Group performance status; L+, positive detection of MET exon 14 skipping in liquid biopsy sample; MET, mesenchymal–epithelial transition factor; T+, positive detection of MET exon 14 skipping in tissue biopsy sample.
Notes:
a Smoking history data were missing for ten patients (3.6%);
b One patient (0.4%) had an ECOG PS of 2;
c Histology data were missing for two patients (0.7%)
Source: Felip, 2021[49]

Patients enrolled based on liquid biopsy had characteristics associated with a worse prognosis, such as high tumour load (median tumour load of target lesions, mm [range] 68.0 [11.6, 227.8] and 52.9 [10.2, 227.8] for liquid biopsy and tissue biopsy, respectively), and more brain metastases. This trend occurred in untreated (1L) and previously treated (2L+) patients.

			HRQoL scores at baseline indicate that patients with METex14 skipping detected by liquid biopsy entered the study with lower quality of life scores and worse symptom scores. Patients enrolled based on liquid biopsy (n=159) had an ORR of 49.1% (95% CI: 41.1, 57.1), with a median duration of response of 11.1 months (95% CI: 9.0, 18.5), median PFS of 8.5 months (95% CI: 6.9, 10.4), and median OS of 16.3 months (95% CI: 12.1, 20.4) (Table 12). Treatment-naïve patients (n=81) had an ORR of 54.3% (42.9, 65.4), a median duration of response of 13.8 months (7.2, NE), median PFS of 8.5 months (6.9, 11.3), and median OS of 15.1 months (9.5, 22.1) (Table 12). Previously treated patients (n=78) had an ORR of 43.6% (32.4, 55.3), a median duration of response of 11.1 months (8.4, 19.4), median PFS of 8.3 months (5.7, 11.0), and a median OS of 19.9 months (12.8, 22.3) (Table 12). Patients enrolled based on tissue biopsy (n=174) had an ORR of 51.1% (95% CI: 43.5, 58.8), with a median duration of response of 15.4 months (95% CI: 9.9, 32.7), median PFS of 12.4 months (95% CI: 10.3, 16.8), and **median OS of 22.3 months** (95% CI: 19.1, 29.8) (Table 12). Treatment-naïve patients (n=86) had an ORR of 54.7% (43.5, 65.4), an mDOR of 32.7 months (10.8, 32.7), median PFS of 15.3 months (9.6, NE), and **median OS of 29.7 months** (15.3, ne) (Table 12). Previously treated patients (n=88) had an ORR of 47.7% (37.0, 58.6), a median duration of response of 10.1 months (8.3, 15.7), median PFS of 11.1 months (8.2, 16.8), and **median OS of 22.3 months** (17.0, 27.2) (Table 12). The L+ patients had characteristics associated with a worse prognosis, such as higher tumour load and more brain metastases. These patients also had a higher incidence of AEs considered unrelated to tepotinib, which

is in line with a worse overall prognosis. The T+ group had a higher proportion of patients with ECOG PS 0.

Patients with MET exon 14 skipping NSCLC detected by liquid or tissue biopsy had similar tumour responses; however, time-dependent endpoints showed a trend for improvement in the tissue biopsy population, particularly in the treatment-naïve setting, and likely reflect that patients enrolled based on liquid biopsy had a worse prognosis. This is particularly relevant in the UK landscape, as tissue biopsy remains the standard of care, and the improved outcomes for tepotinib in this group, particularly for untreated patients, shows the high benefit of tepotinib for this group.

Table 12. Tumour responses with tepotinib based on liquid and tissue biopsy – VISION Cohort A and Cohort C – 1 February 2021 cut-off

	L+			T+		
	Overall	**1L**	**2L+**	**Overall**	**1L**	**2L+**
	N=159	**N=81**	**N=78**	**N=174**	**N=86**	**N=88**
Treatment duration months, median (range)	6.8 (0.4, 50.6)			6.6 (<0.1, 50.6)		
Objective response by IRC						
Best objective response, n (%)						
Complete response	0	0	0	0	0	0
Partial response	78 (49.1)	44 (54.3)	34 (43.6)	89 (51.1)	47 (54.7)	42 (47.7)
Stable disease	34 (21.4)	14 (17.3)	20 (25.6)	50 (28.7)	22 (25.6)	28 (31.8)
Progressive disease	22 (13.8)	11 (13.6)	11 (14.1)	19 (10.9)	7 (8.1)	12 (13.6)
Not evaluable	25 (15.7)	12 (14.8)	13 (16.7)	16 (9.2)	10 (11.6)	6 (6.8)
Objective response rate, % (95% CI)	49.1 (41.1, 57.1)	54.3 (42.9, 65.4)	43.6 (32.4, 55.3)	51.1 (43.5, 58.8)	54.7 (43.5, 65.4)	47.7 (37.0, 58.6)

Disease control rate, % (95% CI)	70.4 (62.7, 77.4)	71.6 (60.5, 81.1)	69.2 (57.8, 79.2)	79.9 (73.2, 85.6)	80.2 (70.2, 88.0)	79.5 (69.6, 87.4)
Duration of response by IRC						
N	79	44	34	89	47	42
Events n	36	18	18	31	10	21
Duration of response months, median (95% CI)	11.1 (9.0, 18.5)	13.8 (7.2, NE)	11.1 (8.4, 19.4)	15.4 (9.9, 32.7)	32.7 (10.8, 32.7)	10.1 (8.3, 15.7)
PFS by IRC						
N	159	81	78	174	86	88
Events n	95	45	50	71	30	41
Duration of response months, median (95% CI)	8.5 (6.9, 10.4)	8.5 (6.9, 11.3)	8.3 (5.7, 11.0)	12.4 (10.3, 16.8)	15.3 (9.6, NE)	11.1 (8.2, 16.8)
OS by IRC						
N	159	81	78	174	86	88
Events n	83	42	41	59	28	31
Duration of response months, median (95% CI)	16.3 (12.1, 20.4)	15.1 (9.5, 22.1)	19.9 (12.8, 22.3)	22.3 (19.1, 29.8)	29.7 (15.3, NE)	22.3 (17.0, 27.2)

Abbreviations: CI, confidence interval; IRC, independent review committee; L+, positive detection of MET exon 14 skipping in liquid biopsy sample; MET, mesenchymal–epithelial transition factor; OS, overall survival; PFS, progression free survival; T+, positive detection of MET exon 14 skipping in tissue biopsy sample

Garassino MC. Efficacy and safety of tepotinib in patients with advanced age: VISION subgroup analysis of patients with MET exon 14 (METex14) skipping NSCLC. Presented at ESMO 2021. Abstract 1254P.[50]

The efficacy analysis presented here includes all patients enrolled in Cohort A and patients enrolled in Cohort C with ≥3 months' follow-up (n=275). The data provided for this subgroup analysis (Cohort A and Cohort C) are recently published at ESMO 2021.

Overall, most patients in Cohorts A and C that were assessed for efficacy (N=275) were elderly (median age 72.4 years [range 41–94]), about half were male, half had smoking history, and most had adenocarcinoma. Baseline characteristics were similar in younger and older patients (Table 13).

ORR was 52.2% and 44.9%, median DOR was 12.4 and 13.8 months, and median PFS was 11.0 and 10.4 months in patients below and above 75 years of age, respectively (Table 14). Patient-reported outcomes indicated quality of life was maintained while on tepotinib treatment, in patients above and below 75 years of age. This is relevant as patients with METex14 skipping tend to be older, and so it is important to show that the efficacy of tepotinib is maintained in the older patient groups.

Table 13. Baseline characteristics – VISION Cohort A and Cohort C (1 February 2021 cut off)

Baseline characteristics	Overall
	N=275
Sex	
Male, n (%)	135 (49.1)
Female, n (%)	140 (50.9)
ECOG PS	

0, n (%)	76 (27.6)
1, n (%)	198 (72.0)
Smoking history	
Yes, n (%)	128 (46.5)
No, n (%)	147 (53.5)
Treatment	
Treatment-naïve, n (%)	137 (49.8)
Previously treated, n (%)	138 (50.2)
Age years	
<65, n (%)	56 (20.4)
≥65 to <75, n (%)	101 (36.7)
≥75 to <85, n (%)	94 (34.2)
≥85, n (%)	24 (8.7)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status
Source: Garassino 2021[50]

Table 14. Efficacy results – VISION Cohort A and Cohort C (1 February 2021 cut off)

Efficacy IRC	**<75 years**	**≥75 years**
	N=157	**N=118**
Best overall response, n (%)		
CR	0	0
PR	82 (52.2)	53 (44.9)
SD	35 (22.3)	36 (30.5)
PD	21 (13.4)	13 (11.0)
NE	19 (12.1)	16 (13.6)

			<table><tr><td>ORR, % (95% CI)</td><td>52.2 (44.1, 60.3)</td><td>44.9 (35.7, 54.3)</td></tr><tr><td>DCR, % (95% CI)</td><td>74.5 (67.0, 81.1)</td><td>75.4 (66.6, 82.9)</td></tr><tr><td>Median duration of response, % (95% CI)</td><td>12.4 (9.5, 32.7)</td><td>13.8 (9.0, NE)</td></tr><tr><td>Median progression free survival, % (95% CI)</td><td>11.0 (8.2, 13.7)</td><td>10.4 (8.2, 13.7)</td></tr></table> Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DCR, duration of complete response; NE, not evaluable; ORR, objective response rate; PD, progressed disease; PR, partial response; SD, stable disease
Additional issue 3: MHRA Conditional marketing authorisation	No specific location		Specific Obligations in the MHRA Conditional Marketing Authorisation for tepotinib The Specific Obligations in the MHRA Conditional Marketing Authorisation will provide more detailed information on the upcoming VISION data cuts and real-world studies planned by Merck. This will help to inform the upcoming data for tepotinib and other studies for patients with METex14 skipping alterations, which could potentially resolve areas of uncertainty in the submission. This is described below in detail: 1. **Specific Obligation 1:** The Marketing Authorisation Holder (MAH) should submit the final clinical study report of the VISION Study, including clinical efficacy data of NSCLC-METex14 patients enrolled in Cohort A and Cohort C. Due date December 2023. 2. **Specific Obligation 2:** In order to contextualise and strengthen efficacy and safety results from tepotinib assessed in VISION Cohorts A+C, the MAH should submit outcomes of the non-interventional study, Study MS200095-0048: External control study using ENSURE data to contextualize and strengthen efficacy and

			safety results of tepotinib as assessed in the VISION trial. Due date Q4 2025. 3. **Specific Obligation 3:** In order to compare the effectiveness and safety in patients treated with tepotinib and patients treated with other available therapies in the real-world clinical care setting, the MAH should submit outcomes of the non-intervention study, Study MS200095-0049, a registry-based study to compare the effectiveness and safety of tepotinib to other treatment options available in Europe for patients with non-small cell lung cancer (NSCLC) harbouring MET Exon 14 skipping alterations. Due date Q1 2028. The VISION study is ongoing, with expected primary completion date in December 2021. Subsequent data cuts are expected to provide additional PFS and OS data, for Cohort A + C, with ongoing follow-up expected post study completion to allow more mature OS data to be captured, with study completion expected in February 2023. Evidence will be provided by results from the: 1. VISION trial 2. Independent confirmation of Cohort A results by Cohort C results 3. Large and comprehensive dataset derived from Cohorts A + C to provide precise estimates of efficacy endpoints including OS for 1L advanced NSCLC patients. The clinical dataset that the VISION trial will provide at the time of final reporting will consist of at least 313 advanced NSCLC patients with tumours harbouring METex14 alterations. This includes 152 patients

			enrolled in Cohort A who will have a follow-up of at least 33 months from start of tepotinib treatment. Moreover, at least 150 patients enrolled by 31 March 2021 into the independent Cohort C are complementing the large clinical dataset of the VISION trial. These Cohort C patients will have a follow-up of at least 18 months from start of therapy. Merck will also prospectively collect data through a newly set-up multi-national disease registry (known as ENSURE), as part of the EU Conditional Marketing Authorisation (CMA) being assessed by the EMA. The data collected in the registry would include biomarker data, patient characteristics, clinical characteristics, treatment exposure, clinical outcomes and safety data, for patients with NSCLC harbouring METex14 skipping alterations. Using this disease registry, Merck will run two non-interventional studies: 1. Study MS200095-0048: Provide an external control to contextualise and strengthen efficacy and safety of tepotinib as assessed in VISION Cohort A+C. Final study report: Q4 2025. 2. Study MS200095-0049: Compare effectiveness and safety in patients treated with tepotinib and patients treated with other available therapies in the real-world clinical care setting. Final study report: Q1 2028.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Key Issue 13	Vinorelbine incorrectly classified as vinorelbine + platinum in the real-world cohort treatment distributions for the overall population	This has been corrected to 'vinorelbine monotherapy'. Please note that this only impacts the chemotherapy arm within the overall population. All other results presented within the ERG report are correct.	£19,781 (+£269)
Company's preferred base case following technical engagement	Incremental QALYs: [redacted]	Incremental costs: [redacted]	£19,781 (+£269)

Table 15: Corrected base case fully incremental analysis – overall population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)	Incremental ICER (extended dominance)
Chemotherapies	[redacted]	[redacted]				
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£19,781	£19,781
Immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Strictly dominated

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

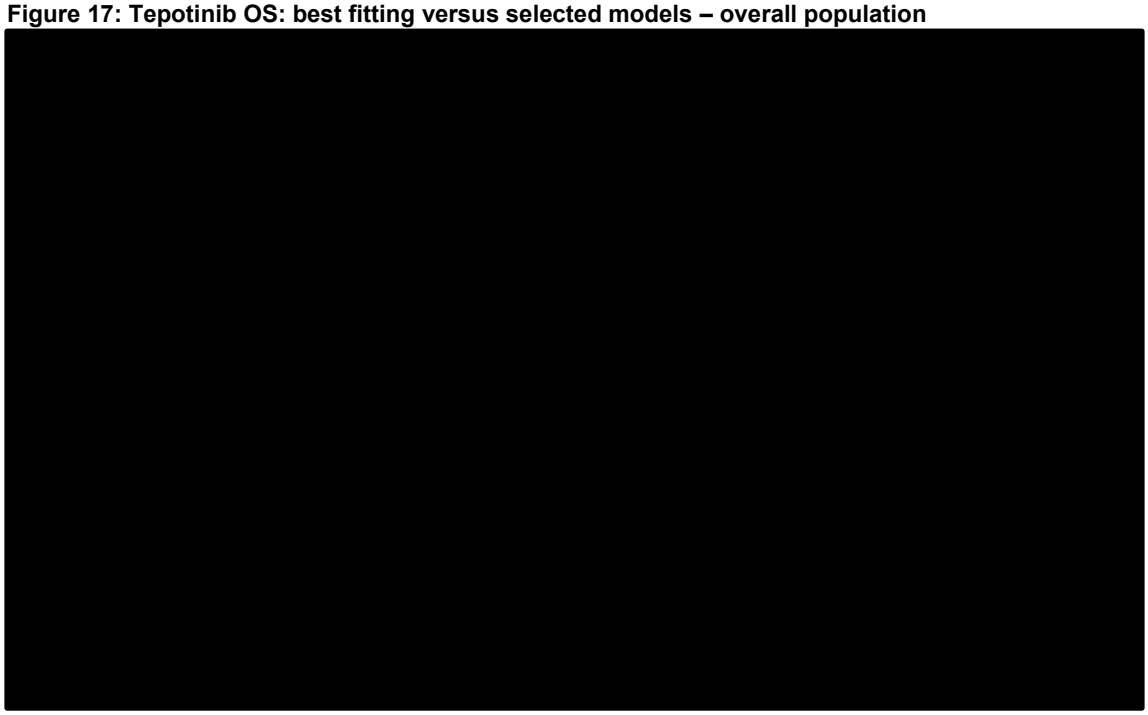
Table 16: Corrected base case pairwise results – overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NMB [a]
Tepotinib	[redacted]	2.85	[redacted]					
Chemotherapy	[redacted]	1.99	[redacted]	[redacted]	0.86	[redacted]	£19,781	£12,663
Immunotherapy	[redacted]	2.84	[redacted]	[redacted]	0.00	[redacted]	Dominant	£22,267

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years
Notes: [a] Willingness-to-pay threshold is £30,000 versus immunotherapy and £50,000 versus chemotherapy

Appendix: Comparison of best fitting models versus Merck selected model

Figure 17: Tepotinib OS: best fitting versus selected models – overall population



Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; KM, Kaplan-Meier; OS, overall survival

Figure 18: Chemotherapy OS: best fitting versus selected models – overall population

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; KM, Kaplan-Meier; OS, overall survival

Figure 19: Chemotherapy PFS: best fitting versus selected models – overall population

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

Figure 20: Immunotherapy OS: best fitting versus selected models – overall population

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; KM, Kaplan-Meier; OS, overall survival

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NICE National Institute for Health and Care Excellence

Clinical expert statement & technical engagement response form

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

Thank you for agreeing to comment on the ERG report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form:

- In **part 1** we are asking you to complete questions where we ask for your views on this technology. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.
- In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.
- The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a clinical perspective could help either:
- resolve any uncertainty that has been identified
  OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

Please return this form by **5pm** on **Monday 8 November 2021**.

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow.If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

NICE National Institute for Health and Care Excellence

PART 1 – Treating a patient with advanced non-small-cell lung cancer with MET gene alterations and current treatment options	
About you	
1. Your name	**Alastair Greystoke**
2. Name of organisation	**Newcastle upon Tyne Hospitals NHS Trust**
3. Job title or position	**Senior Lecturer and Honorary Consultant in Medical Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with advanced NSCLC with MET gene alterations? ☒ a specialist in the clinical evidence base for advanced NSCLC with MET gene alterations or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
The aim of treatment for advanced NSCLC with MET gene alterations	
8. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Maintain quality of life and prevent disability, improve survival, improve or prevent cancer related symptoms
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm,	An improvement in survival by 2 months. A response rate of over 30% maintained for over 2 months. A significant improvement in health related quality of life maintained for over two months.

or a reduction in disease activity by a certain amount.)	
10. In your view, is there an unmet need for patients and healthcare professionals in advanced NSCLC with MET gene alterations?	Yes once patients have been treated with chemotherapy and immunotherapy then further treatments. are limited and often poorly tolerated. In addition chemotherapy and immunotherapy combinations can be associated with significant side effects and difficult to deliver to a number of patients. Oral therapies that are easy to administer and have high efficacy and improved side effect profiles are needed
What is the expected place of the technology in current practice?	
11. How is advanced NSCLC with MET gene alterations currently treated in the NHS?	In most centres these patients will be treated as non small cell lung cancer without any known oncogenic driver; ie with chemotherapy and immunotherapy combinations in the frontline setting if fit enough followed by second line chemotherapy with docetaxel with or without nintedanib. There has been an early access to medicine scheme for tepotinib but uptake was variable due to issues with the testing.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Pathways are outlined in https://pathways.nice.org.uk/pathways/lung-cancer#path=view%3A/pathways/lung-cancer/advanced-non-squamous-stages-iiib-and-iv-non-small-cell-lung-cancer-systemic-anti-cancer-therapy.xml&content=view-index The Technology appraisal Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer [TA683] provides guidance for treatment. The European Society of Medical Oncology guidelines are commonly used https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer
• Is the pathway of care well defined? Does it vary or are there differences of opinion	The pathway of care is not well defined at present; In particular as testing for the oncogene is very variable. It was tested for as part of the Cancer Research UK stratified medicine panel but this closed to recruitment in August 2021. Some genomic laboratory hubs will test for it given the opening of the early access to medicines scheme, but despite

between professionals across the NHS? (Please state if your experience is from outside England.)	an application to include this on the national test directory at the start of 2021 it was not on the most recent update published in October 2021. In addition there is some differences in opinion as to the role of immunotherapy in this population. Some clinicians think that this is limited and would not include immunotherapy in the first line treatment; preferring to use chemotherapy alone which is also an approved treatment
• What impact would the technology have on the current pathway of care?	it would replace a line of treatment so that platinum doublet chemotherapy would move into the second line setting, or if patients had already received this teptonib would be used in the second line setting to replace docetaxel with or without nintedanib which would move into the third line setting for those patients who are fit enough.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	It will enable oral therapy through out-patient clinics. This will be a major benefit at present times when chemotherapy units are struggling to administer IV therapies with long wait times, and some units having to ration treatment
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist oncology clinics
• What investment is needed to introduce the technology? (For example,	Testing for MET Exon 14 will need to be introduced nationwide within the genomic laboratory hubs. Minimal training into the different side effect profiles compared to other tyrosine kinase inhibitors will be needed, in particular into the management of oedema.

for facilities, equipment, or training.)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes, although this may be difficult to formally quantify; the ability to receive an extra line of therapy should result in a longer life expectancy. In addition given the age group of this population some may choose to decline chemotherapy but would accept an oral targeted therapy.
• Do you expect the technology to increase health-related quality of life more than current care?	yes In general the quality of life of patients with lung cancer is driven by lung cancer related symptoms potentially added to by the adverse effects of any therapy given. Given the efficacy of this agent, and it's reduced side effects compared to chemotherapy it will likely be associated with an improvement in quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	

15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	this technology will be easier for doctors and patients to use given the oral nature. As described above this will have positive implications for the NH S in reduction in use of chemotherapy day units which are under intense strain at present time. Monitoring will be as through many other oral tyrosine kinase inhibitors for lung cancer, with treatment delivered in the outpatient setting. Most practices now have dedicated clinics for patients on oral therapies for lung cancer where care can be split between oncologists, nurse specialists and trained pharmacists with improvements in care for patients, and reduction in burden on oncologists for overbooked clinic slots.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing will be required. Patients will be monitored clinically and with CT/MRI scans until symptomatic progression
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in	No

the quality-adjusted life year (QALY) calculation?	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes this will be the first oral targeted therapy available for this population within NHS care. This is likely to lead to improvement in outcomes including quality of life and survival, and boost treatment rates.
• Does the use of the technology address any particular unmet need of the patient population?	yes this abnormality is commonly found in older patients with lung cancer who may not tolerate or accept treatment with chemotherapy with or without immunotherapy in combination.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most common side effect that may be problematic is oedema. This can normally be managed with supportive measures, use of dose modifications and treatment breaks.

Sources of evidence	
20. Do the clinical trials on the technology reflect current UK clinical practice?	yes although circulating free DNA testing is poorly integrated into the present healthcare system.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Tumour response, progression free and overall survival, health related quality of life. All were assessed in clinical trial
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
21. Are you aware of any relevant evidence that might not be found	No

by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatments since the publication of NICE technology appraisal guidance TA181, TA347, TA520, TA531 and TA655?	Long term outcome data has been presented for the immunotherapies and combinations For example on Pawel J, Bordoni R, Satouchi M, Fehrenbacher L, Cobo M, Han JY, Hida T, Moro-Sibilot D, Conkling P, Gandara DR, Rittmeyer A, Gandhi M, Yu W, Matheny C, Patel H, Sandler A, Ballinger M, Kowanetz M, Park K. Long-term survival in patients with advanced non-small-cell lung cancer treated with atezolizumab versus docetaxel: Results from the randomised phase III OAK study. Eur J Cancer. 2019 Jan;107:124-132. doi: 10.1016/j.ejca.2018.11.020. Epub 2018 Dec 17. PMID: 30562710. Rodríguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, Felip E, Speranza G, De Angelis F, Dómine M, Cheng SY, Bischoff HG, Peled N, Reck M, Hui R, Garon EB, Boyer M, Kurata T, Yang J, Pietanza MC, Souza F, Garassino MC. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. Ann Oncol. 2021 Jul;32(7):881-895. doi: 10.1016/j.annonc.2021.04.008. Epub 2021 Apr 22. PMID: 33894335. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50% Martin Reck, Delvys Rodríguez-Abreu, Andrew G. Robinson, Rina Hui, Tibor Csőszi, Andrea Fülöp, Maya Gottfried, Nir Peled, Ali Tafreshi, Sinead Cuffe, Mary O'Brien, Suman Rao, Katsuyuki Hotta, Ticiana A. Leal, Jonathan W. Riess, Erin Jensen, Bin Zhao, M. Catherine Pietanza, and Julie R. Brahmer Journal of Clinical Oncology 2021 39:21, 2339-2349

23. How do data on real-world experience compare with the trial data?	Real world data for immunotherapies/ immunotherapy seems to be similar in appropriate populations although adverse event rates may be higher
Equality	
24a. Are there any potential equality issues that should be taken into account when considering this treatment?	yes this patient group is older than other oncogene driven lung cancer. and may not tolerate previously approved combination therapies. However they may accept oral therapies.
24b. Consider whether these issues are different from issues with current care and why.	see above and in addition previous audits and studies have shown that older patients are less likely by clinicians to be offered treatments such as chemotherapy due to concerns about potential toxicity. Some of this under treatment may be justified but some of this is not and likely reflects underlying discrimination due to age.
Topic-specific questions	
25. Considering current standard care in the UK, what are the most relevant comparators for tepotinib	as above In the first line setting this would be carboplatin, pemetrexed, plus or minus pembrolizumab in the second line setting this would be docetaxel plus or minus nintedanib

in people with advanced NSCLC with MET gene alterations?	
26. What is currently known about the MET gene alteration population in advanced NSCLC in terms of patient characteristics and prognostic status?	these patients are likely to be older then patients with other oncogene driven lung cancers, and are more likely to have previously smoked. Prognosis is no better and maybe worse then with other forms of lung cancer. The UK experience was reported in our recent BTOG presentation. (https://www.researchgate.net/publication/351287498_Clinico-pathological_features_of_MET_exon_14_mutation_positive_NSCLC_in_the_UK) but will be potentially biassed by the testing environment.

PART 2 – Technical engagement questions for clinical experts	
Issues arising from technical engagement	
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting. For information: the professional organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
Key issue 1: Lack of clarity in the population	
Key issue 2: Lack of subgroup (line of therapy, histological status, PD-L1 status) analysis according to scope	The dominant histology will be non-squamous lung cancer and appropriate to restrict appraisal to that. NICE and clinical algorithms do split according to PDL1 status (either > or < than 50%) and this is appropriate
Key issue 3: Selection of analysis data set from VISION (cohort A instead of cohort A+C,	

and depending on length of follow-up)	
Key issue 4: Selection of studies to obtain data for the ITC	
Key issue 5: Source of AE frequencies not justified	
Key issue 6: Selection of method of adjustment for confounding in the ITC	
Key issue 7: Lack of justification for partitioned survival model vis-à-vis a state transition model	
Key issue 8: No analyses are considered for the subgroups stated in the decision problem	
Key issue 9: No analyses were considered using the individual	

treatment comparators for which there was enough evidence.	
Key issue 10: Potential bias from clinicians' selection of survival curves for the comparators, and lack of alternative scenario.	The clinical assumptions used in the company report seem reasonable in my opinion.
Key issue 11: Representativeness of AE utility values for the UK population	
Key issue 12: Insufficient reporting and clarity of reporting of the cost-effectiveness results	
Are there any important issues that have been missed in ERG report?	
PART 3 - Key messages	
27. In up to 5 sentences, please summarise the key messages of your statement:	

- This would be the first targeted therapy available for this population of patients with MET Exon14 skip lung cancer
- This will give an extra line of therapy for some patients which may be associated with improved overall outcomes
- Given the alternative is chemotherapy with or without immunotherapy the use of his agent is likely to be associated with improved quality of life.
- The use of an oral therapies in this population will have positive implications for the NHS reducing burden on chemotherapy units and oncology outpatients
- This patient group may be older and have more health problems then other oncogene driven lung cancer populations; this may mean they may particularly benefit from the availability of an oral therapy as they may not accept or be offered chemotherapy.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed document, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Monday 8 November 2021.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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

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

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**British Thoracic Oncology Group (BTOG)**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Lack of clarity in the population	**NO**	This is true, however it seems to be a minor point with little impact on the overall findings.
Key issue 2: Lack of subgroup (line of therapy, histological status, PD-L1 status) analysis according to scope	**NO**	Agree that analysis in terms of PD-L1 status is needed, because this impacts of appropriateness and efficacy of other lines of therapy. However, it is felt that it is unlikely that there is a meaningful difference in individual treatments in UK clinical practice.
Key issue 3: Selection of analysis data set from VISION (cohort A instead of cohort A+C, and depending on length of follow-up)	**NO**	Agree that due to similarity in cohorts, A+C should be used for the ITC.
Key issue 4: Selection of studies to obtain data for the ITC	**NO**	No comment
Key issue 5: Source of AE frequencies not justified	**NO**	Justification of AE source data is needed. However a systemic literature review is not essential, if instead the AE source data is clear and appropriate.
Key issue 6: Selection of method of adjustment for confounding in the ITC	**NO**	No comment

Key issue 7: Lack of justification for partitioned survival model vis-à-vis a state transition model	**NO**	Justification by the company of the choice of PSM is reasonable.
Key issue 8: No analyses are considered for the subgroups stated in the decision problem	**NO**	The proposed alternative approach by the ERG is reasonable. However the findings might be difficult to extrapolate to real-life clinical situations where the choice of one type of therapy over another is often complex and takes into account multiple factors. If Tepotinib were found to be theoretically cost effective compared to some current comparators, and not others, might this result in commissioning only for certain scenarios, and might this adversely affect clinical decision making?
Key issue 9: No analyses were considered using the individual treatment comparators for which there was enough evidence.	**NO**	No comment
Key issue 10: Potential bias from clinicians' selection of survival curves for the comparators, and lack of alternative scenario.	**NO**	Consideration of alternative survival models by the ERG is fair, given the difficulty there is for Clinical Experts to estimate survival probablilies, and the potential bias in this from a number of sources.
Key issue 11: Representativeness of AE utility values for the UK population	**NO**	Use of adverse event data from non-UK populations is entirely acceptable, and should not be seen as a Key Issue. EQ-5D Quality of Life scoring is not essential, so long as a different, validated and recognised, quality of life score is used.
Key issue 12: Insufficient reporting and clarity of reporting of the cost-effectiveness results	**NO**	The table constructed by the ERG is a useful addition.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	YES/NO	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER

Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER
..	..	..	[INSERT / DELETE ROWS AS REQUIRED]
Company's preferred base case following technical engagement	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide the revised company base-case ICER resulting from combining the changes described, and the change from the company's original base-case ICER

NICE National Institute for Health and Care Excellence

Technical engagement response form

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

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **Monday 8 November 2021.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted], and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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NICE National Institute for Health and Care Excellence

About you

Your name	[redacted]
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**

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	**Does this response contain new evidence, data or analyses ?**	Response	ERG response
Key issue 1: Lack of clarity in the population	**NO**	The MHRA licence for tepotinib states: "*TEPMETKO (tepotinib) is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring mesenchymal-epithelial transition factor gene (MET) exon 14 (METex14) skipping alterations.*" Therefore, Merck reflected the tepotinib license population in the decision problem as well as the population in the NICE scope. However, the ERG comments regarding the population in the ERG report are also correct: • The VISION trial included patients with stage IIIB to IV NSCLC, which is equivalent to 'advanced' disease • The VISION trial did exclude ALK+ and EGFR+ patients.	The company have not clarified that the decision problem population is more specific than in the NICE scope and, in particular should reflect that in the VISION trial. Instead, they have simply restated the nature of the population in the licence, the scope and the trial.

Key issue 2: Lack of subgroup (line of therapy, histological status, PD-L1 status) analysis according to scope	**NO**	Results by line of therapy (untreated and previously treated) were presented in Appendix N of the company submission. While the company recognises that comparison by PD-L1 status was part of the NICE scope, we informed the NICE team and the ERG team at draft scope, ERG clarification questions and at TE that such a comparison was not possible due to the following reasons: (1) PD-L1 status was not collected in the VISION clinical trial and (2) there is limited reporting of PD-L1 available in the real-world cohort. Therefore, it was not possible to perform subgrouping based on PD-L1 status. Based on feedback from clinical experts, METex14 skipping mutation is now a targetable oncogenic driver mutation. If METex14 skipping mutation was detected through testing methods, the patient would be offered a targeted treatment such as tepotinib, irrespective of their PD-L1 status. This is supported by multiple studies which show patients with METex14 skipping alterations tend to respond poorly to current treatments, including immunotherapies, regardless of PD-L1 expression.[1-3] In one study (Negrao *et al*. 2021),[2] which assessed outcomes for 34 METex14 skipping patients treated with immunotherapies, patients with METex14 skipping alterations were found to have high PD-L1 expression although with low tumour mutational burden (TMB). However, this did not translate to better clinical outcomes on immunotherapy as demonstrated by the short PFS and low response rates.[2] This suggests that oncogene-specific factors other than TMB and PD-L1 expression also impact clinical outcome from immunotherapy treatment. In other oncogenic driver mutation NSCLCs, such as EGFR-mutant NSCLC, PD-L1 expression was also unlikely to be a predictive biomarker for prognosis, based on a meta-analyses of 18 separate studies in 1,986 patients.[4] In other oncogenic-	The ERG acknowledges the limitations of the data. However, it is vital to point out that not differentiating analyses according to PD-L1 and histology subgroup implies potential loss of health benefit overall. This is because the comparator varies by subgroup and therefore the cost and effectiveness of tepotinib versus the relevant comparator in each subgroup might also vary such that whether tepotinib is cost effective might also vary by subgroup. In particular, it might be that, based on a comparison of tepotinib with a basket of comparators regardless of subgroup, tepotinib might be found to be cost effective. The result of this would be that patients' current treatment could be changed to tepotinib in any subgroup even though for

		driven NSCLCs such as EGFR, targeted treatments are recommended irrespective of PD-L1 expression.[5] With regards to histology, the majority of patients in VISION and the real-world cohort had adenocarcinoma ([redacted] tepotinib, [redacted] weighted chemotherapy and [redacted] weighted immunotherapy). The squamous histology subgroup includes [redacted] patients treated with tepotinib, [redacted] unweighted, chemotherapy patients and [redacted] immunotherapy patients, which we did not consider feasible for making a reasonable comparison between tepotinib and the comparators. A comparison in the adenocarcinoma group would be possible, however this was not felt to be relevant by clinical experts consulted throughout submission development, as it accounts for the vast majority of the overall METex14 population anyway, and so was not performed. Expert clinical opinion indicated that if a targeted therapy for METex14 skipping alterations was available, this would be the preferred treatment for patients irrespective of PD-L1 status and histology. Furthermore, experts confirmed that although squamous patients tend to not perform as well on treatments as adenocarcinoma patients, the overall costs and outcomes are considered generalisable between groups. In addition, the approach of analysing squamous and non-squamous patients together was recently accepted by the committee in the recent NICE submission of selpercatinib for RET fusion-positive advanced NSCLC.[6] The ACD noted: *"The marketing authorisation for selpercatinib did not differentiate between people with squamous and non-squamous advanced NSCLC. However, because of the rarity of RET gene fusions in squamous NSCLC, clinical advice, and the very small number of people with squamous*	some subgroups the tepotinib is not the best treatment. The ERG does see that there appear to be no data at all to inform a comparison according to PD-L1 status. However, it might still have been of some value to at least present outcomes analysed by histological status, specifically separately for adenocarcinoma and squamous histology. In the absence of any additional evidence by subgroup and given that most patients had adenocarcinoma, it might be reasonable to conclude that the evidence as presented is most appropriate to inform a decision regarding patients with adenocarcinoma. Standard care for these patients, as indicated in Table 1 of the ERG report, is pemetrexed in combination with a platinum drug (carboplatin or cisplatin),

		NSCLC in the LIBRETTO-001 trial, the company did not present any evidence on using selpercatinib to treat these tumours. The clinical expert said they might expect some difference in the effectiveness of selpercatinib in treating squamous advanced NSCLC. This is because people with squamous NSCLC may be older, have a higher chance of being smokers, and be less fit. However, they expected there would still be some level of response. The Cancer Drugs Fund clinical lead said that the NHS would expect to follow the same recommendation for people with squamous advanced NSCLC as for people with non-squamous advanced NSCLC. The committee agreed that the recommendations in this technology appraisal would apply to both squamous and non-squamous advanced NSCLC" In this respect there are similarities between selpercatinib and tepotinib, including that the marketing authorisation provides no differentiation between histology groups, and there is a small proportion of patients with squamous NSCLC in the relevant clinical trials. Therefore, we anticipate the same approach is applicable for tepotinib in advanced NSCLC with METex14 skipping mutations, i.e. the technology appraisal would apply to both squamous and non-squamous patients, despite no sub-group analysis being done for squamous patients. **Conclusion** Given that tepotinib targets a rare type of NSCLC and has a line-agnostic marketing authorisation irrespective histology and PD-L1 expression, we anticipate that the decision to use tepotinib will be based on the presence of METex14 skipping alterations, regardless of the subgroup and comparators based on histology and PD-L1. Whilst Merck acknowledges the limitations with regards to histology and PD-L1 expression in this rare	with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment.

		mutation with limited published data, the approach to modelling the population as a whole, irrespective of histology and PD-L1 expression, is considered appropriate and in line with previous NICE appraisals for targeted therapies as well as clinical expert feedback.	
Key issue 3: Selection of analysis data set from VISION (cohort A instead of cohort A+C, and depending on length of follow-up)	**YES**	For the ITC and economic analysis, Cohort A from VISION was used. However, VISION also included Cohort C which also recruited patients with METex14 skipping mutations. At the February 2021 data cut-off, 152 patients were available from Cohort A, and 123 patients were available from Cohort C with at least 3 months of follow-up available for the efficacy analysis. The reason only Cohort A was used for the analysis instead of Cohort A+C was that patient level data for Cohort C only became available for analysis shortly before the submission deadline. As a result, there was little time to update the submission with the data from this cohort, as the following analyses would need to be performed: • Update to the ITC • Analysis of treatments received in the real-world cohort • Fitting of survival curves to tepotinib, chemotherapy and immunotherapy for the three populations available in the economic model (line agnostic, untreated and previously treated) • Analysis of subsequent therapies received • Analysis of adverse events experienced in the VISION data • Utility analysis	The ERG agrees that the results for cohort A appear to be similar to those for cohort A+C. It also appears to be the case that OS is better for cohort A+C, which might therefore lead to a conclusion that use of cohort A+C would only make it more likely that tepotinib would be found to be cost effective. However, it is also possible, based on the current ITC evidence, which only uses data from cohort A, that tepotinib is found to be not cost effective, which might not be the case if data from cohort A+C were used. In conclusion, the ERG would still recommend the use of the data from cohort A+C for all analyses.

Merck have compared the patient characteristics and clinical outcomes between Cohort A and Cohort A+C, to demonstrate the similarities between the groups. As the ERG stated within their technical report, there is little difference in all outcomes between Cohort A and Cohort A+C.

Firstly, the patient characteristics of Cohort A and Cohort A+C are shown in Table 1. Cohort A+C is across a larger cohort, but there are very similar patient characteristics (within a few percentage points) between the cohorts, for the characteristics which were deemed by clinical experts to be prognostic of disease outcomes when developing the ITC. These comprised:

- Prior treatment experience
- Mean age
- Disease stage
- Sex
- Histology
- Presence of smoking history

Table 1: VISION patient characteristics - Cohort A versus Cohort A+C

Characteristic	Cohort A	Cohort A + C
n	[redacted]	[redacted]
Age (mean, (SD))	[redacted]	[redacted]
Age over 75 (%)	[redacted]	[redacted]
Prior treatment Untreated (%)	[redacted]	[redacted]

		Treatment Experienced (%)	[redacted]	[redacted]	[redacted]	
		Sex	[redacted]	[redacted]	[redacted]	
		Female (%)	[redacted]	[redacted]	[redacted]	
		Male (%)	[redacted]	[redacted]	[redacted]	
		Race	[redacted]	[redacted]	[redacted]	
		Asian	[redacted]	[redacted]	[redacted]	
		Black or African American	[redacted]	[redacted]	[redacted]	
		Other	[redacted]	[redacted]	[redacted]	
		White	[redacted]	[redacted]	[redacted]	
		Unknown	[redacted]	[redacted]	[redacted]	
		History of smoking (%)	[redacted]	[redacted]	[redacted]	
		No (%)	[redacted]	[redacted]	[redacted]	
		Yes (%)	[redacted]	[redacted]	[redacted]	
		ECOG	[redacted]	[redacted]	[redacted]	
		0	[redacted]	[redacted]	[redacted]	
		1	[redacted]	[redacted]	[redacted]	
		2	[redacted]	[redacted]	[redacted]	
		Stage (%)	[redacted]	[redacted]	[redacted]	
		IIIB/C	[redacted]	[redacted]	[redacted]	
		IIIB	[redacted]	[redacted]	[redacted]	
		IV	[redacted]	[redacted]	[redacted]	
		IVB	[redacted]	[redacted]	[redacted]	
		NA	[redacted]	[redacted]	[redacted]	
		Metastatic disease (%)	[redacted]	[redacted]	[redacted]	
		No (%)	[redacted]	[redacted]	[redacted]	
		Yes (%)	[redacted]	[redacted]	[redacted]	

Histology	[redacted]	[redacted]	[redacted]	[redacted]	
Adenocarcinoma	[redacted]	[redacted]	[redacted]	[redacted]	
Squamous	[redacted]	[redacted]	[redacted]	[redacted]	
Others	[redacted]	[redacted]	[redacted]	[redacted]	
Missing	[redacted]	[redacted]	[redacted]	[redacted]	

The observed outcomes are also similar as seen in **Figure *1*** - **Figure *3*** below. Greater censoring is observed earlier in Cohort A+C (compared to Cohort A alone) due to enrolment in Cohort C occurring later than enrolment into Cohort A.

Figure *1* presents the OS Kaplan-Meier curves for Cohorts A and A+C, where very similar curves are observed over time. Median OS was [redacted] months (95% CI: [redacted] months) in Cohort A compared to [redacted] months (95% CI: [redacted] months) in Cohort A+C with a non-significant p-value of [redacted].

Figure 1: VISION overall survival - Cohort A versus Cohort A+C

[redacted]

Similar to OS, the investigator PFS observed between Cohort A and Cohort A+C are closely aligned (Figure 2). Median PFS was [redacted] months

		(95% CI[redacted] months) in Cohort A compared to [redacted] months (95% CI: [redacted] months) in Cohort A+C with a non-significant p-value of [redacted]. **Figure 2: VISION progression-free survival - Cohort A versus Cohort A+C** [redacted] **Figure *3*** presents a comparison of time on treatment (ToT) from Cohort A and Cohort A+C showing similar curves between the two cohorts. Median ToT was [redacted] months (95% CI: [redacted] months) in Cohort A compared to [redacted] months (95% CI: [redacted] months) in Cohort A+C with a non-significant p-value of [redacted]. **Figure 3: VISION time on treatment - Cohort A versus Cohort A+C** [redacted]	

		Conclusion As the patient characteristics and outcomes between Cohort A and Cohort A+C are observed to be greatly similar, we do not anticipate the ITC or cost-effectiveness results would differ largely had the analysis been informed by Cohort A+C, compared to the results using Cohort A only. Despite this, there appears to be a minor improvement in median OS and lower median ToT for Cohort A+C compared to Cohort A, so if the ITC and economic model results were based on this analysis, we would expect that any direction of change would likely favour tepotinib.	
Key issue 4: Selection of studies to obtain data for the ITC	**NO**	The ERG claimed that further justification is required for the inclusion of studies used for the ITC using patient-level data, therefore Merck would like to confirm how and why these data were chosen. A feasibility analysis of all data available to Merck in the METex14 skipping population was performed in order to determine how to proceed with performing comparisons to the relevant comparators as detailed in the NICE scope. Conducting an ITC using patient level data was the preferred option (in line with NICE DSU TSD17[7]), therefore we proceeded with this approach for the primary ITC analysis and prioritised the sourcing of patient-level data in the METex14 skipping NSCLC population. The sources of real-world data in the METex14 skipping NSCLC population that Merck was able to obtain access to included: • Merck sponsored studies – NIS 0015, NIS 0035 • Databases – COTA • Data from academic centres – Wong et al.	The company seem to have exhausted all sources of evidence for the ITC, notwithstanding the dataset from French academic centres, analysis of which is not available until 2022.

		Further data sources were explored, but unfortunately access to patient level data was not available elsewhere. These further data sources included: • The Flatiron database. The database agreement with Merck did not allow access to patient level data, so was not useable for the purposes of the primary ITC (using patient-level data) as part of this submission. • Published studies in the METex14 skipping NSCLC population which were identified in an SLR (see Appendix D). Requests to obtain patient level data from three of the most relevant publications (Sabari et al., Awad et al. and Guisier et al.) were sent to the authors however, permissions were not granted. Therefore, we performed MAICs to compare between the published studies and the VISION data, which were presented as a supplementary ITC analysis in Appendix L of the submission. • A dataset from French academic centres with patient-level data available. This data set was deemed to be appropriate for consideration, but was not available in time for inclusion into the submission. Instead the ITC is being updated in Q1 2022 to include these new real-world data. The available patient-level data sources were assessed for suitability in the primary ITC based on the following criteria: • The correct population and comparators • The availability of data within the submission timelines • The characteristics and outcomes reported	

		Following this assessment, the NIS 0015, NIS 0035, COTA and Wong et al. data were included for the primary ITC which informed our base case analysis. Although Merck were not granted access to all patient-level data requested, this dataset is still the largest dataset for patients with NSCLC harbouring METex14 skipping mutations we are aware of, in this rare and relatively newly studied mutation. The availability of patient-level data allowed the use of more robust statistical techniques for matching patient cohorts, which is not always an option in other NICE submissions for treatments without a relevant head-to-head comparison.[8] Furthermore, the availability of METex14 skipping NSCLC patients for this comparator data is especially beneficial, allowing the characteristics and treatment effects of the specific decision problem population to be explored and accounted for. In previous NSCLC appraisals for targeted treatments, companies have been criticised for using data not in the specific mutation in the decision problem, resulting in high levels of uncertainty in the effectiveness analysis.[6;9] In this instance, patients used for the comparative efficacy are directly relevant to the licensed population, with patient-level data allowing them to be matched further to the VISION cohort. **Conclusion** Merck assessed all of the patient-level data available in the METex14 skipping population, against suitability criteria, and the relevant data sources were taken forward for the primary ITC. A SLR was also conducted to identify all published studies in the METEx14 skipping population, which were also assessed for suitability to take forward to the MAICs as part of the supplementary ITC. Therefore, systematic	

		approaches have been taken to identify all data sources which could be used, for both the patient-level ITC and published data MAIC.	
Key issue 5: Source of AE frequencies not justified	**NO**	The ERG was unclear how the sources of adverse event frequencies used in the economic model were obtained, and recommended a systematic approach to be taken to identify adverse event frequencies. Merck would like to clarify the approach taken to identify adverse event frequencies for the comparator treatments. Adverse event frequencies for the comparators were not available within the real-world data set and therefore needed to be sourced from the wider literature. A targeted literature approach was taken in order to source the most relevant adverse events for each comparator within the advanced and metastatic NSCLC setting. Firstly the NICE appraisal documents of the comparators were reviewed for adverse event frequencies, however in some cases these values were either redacted, unavailable or reported more substantially in the clinical trial publication. If that was the case, then either the clinical trial publication was used or an alternative source, such as the prescribing information, was used. Although the approach used to obtain the adverse event frequencies was not based on a systematic approach, the targeted review attempted to use the most up-to-date and relevant data for each comparator, and allowed us to obtain adverse event data from published pivotal clinical trial data in nearly all cases. Given the lack of adverse event information available from the METex14 specific population within the real-world data set, sourcing comparator adverse events from the literature is conservative, due to the limited reporting on certain adverse events in comparison to tepotinib, where all adverse events recorded in VISION can be included. This may have resulted in an underestimation of comparator adverse events compared to	The company have provided some clarification on the method used to obtain comparator adverse event frequencies. The ERG is not convinced that there has been underreporting of adverse events for the comparators or that adverse event frequency is likely to be higher in the METex14 skipping population. Therefore, a systematic review is probably still the better approach to obtaining these data.

		tepotinib. Another limitation is that the comparator adverse events are based on the wider NSCLC population, and it is unclear how comparator adverse events would differ in the METex14 skipping alteration patient group. Although there is limited evidence to draw conclusions, it could be expected the METex14 skipping NSCLC cohort might suffer from worse/more frequent severe adverse event burden from chemotherapy or immunotherapies, related to their older age compared to clinical trial cohorts in wildtype NSCLC. Again this could lead to an underestimation of comparator adverse events in the economic model. **Conclusion** Adverse events were derived from a targeted review of the wider literature and by choosing the most appropriate source. Despite not using a systematic approach, adverse events have very little impact on the overall cost-effectiveness results, therefore alternative sources for comparator adverse events are highly unlikely to impact decision making, despite potentially being underestimated for comparators.	
Key issue 6: Selection of method of adjustment for confounding in the ITC	**NO**	The ERG queried why we used the standardised mortality rate (SMR) approach instead of the inverse probability of treatment. However, the ERG also acknowledged that this approach facilitates the full incremental analysis in the cost-effectiveness analysis. The ERG are correct that there are a number of approaches that could have been taken to adjust for differences between the studies. These could range from including patient characteristics in survival regressions, through to different methods of propensity scoring (such as propensity score matching).	The company have provided the justification for use of the SMR approach that the ERG anticipated and which the ERG would agree is adequate for its choice.

		We consider the approach selected (reweighting comparator data to match tepotinib) to offer the following key advantages over these competing methods, as suggested by the ERG;
		• Interpretability
		  ○ All results can be compared, allowing the fully-incremental analysis preferred by the ERG to be performed
		• Consistency
		  ○ Tepotinib effectiveness remains consistent across comparisons meaning the long-term survival estimates do not change dependent on the selected comparator
		• Parametric curves
		  ○ Allows for the use of survival extrapolation using parametric curves, which may not otherwise have been possible depending on the method selected e.g., calculation of an effect size using doubly robust techniques.
		Had an Average Treatment Effect (ATE) or similar approach (i.e., standard Inverse Probability of Treatment Weighting [IPTW]) been used, consistent assumptions for tepotinib efficacy across comparisons would not apply, therefore losing that advantage, without gaining other advantages for such methods.
		Conclusion
		We acknowledge there are limitations to our selected approach, however these are far outweighed by the advantages described above. Therefore,	

		Merck are satisfied with the approach taken versus alternatives, and consider other options, which equally could be used, do not necessarily add additional value compared to the approach taken.	
Key issue 7: Lack of justification for partitioned survival model vis-à-vis a state transition model	**NO**	The ERG have requested more justification as to why a partitioned survival model was used to inform the economic analysis instead of a state-transition model. At model conceptualisation, both partitioned survival models and state-transition models were considered, acknowledging the limitations of both approaches. The main limitation of the state-transition model is the use of unclassified end points to model transitions such as post-progression survival. This is highly prone to bias due to the selection effects and informative censoring.[10] Moreover, post-progression outcomes are based on those patients who have progressed first (e.g., due to more severe disease or older age, etc.). Given that the data available for METex14 patients are based on small patient numbers, in addition to progressing early, the extrapolations of post-progression survival could be misleading. For the comparison with chemotherapies and immunotherapies the total number of patients is [redacted] and [redacted], respectively, thus the later model transitions (i.e., post-progression to death) would be based on even smaller patient numbers and subsequently small numbers of events, creating additional uncertainty in the extrapolated outcomes for later model transitions. This is not an issue when using OS directly from the start of the trial as required for a partitioned survival model, as all patients contribute to the function used to fit the curve. Therefore, selecting a state-transition model over a partitioned survival model would have likely resulted in greater uncertainty in OS, given the likely biased estimates these analyses will produce. Moreover, as the comparator data is based on real-world	The company has provided their justification for the use of a partitioned survival model (PSM) instead of a state-transition model (STM). The justification does not mention any relative benefits of STMs. The ERG considers that a STM could have been conducted and may have improved extrapolation of survival, but acknowledges that PSMs are commonplace in technology appraisals. The ERG comments on the following 5 issues are stated below: (1) individual patient data, (2) selection bias and censoring, (3) prediction precision, (4) model complexity.

		evidence, patients are not assessed for progression as routinely as in the VISION trial nor collected as routinely, if at all (see company submission Section B.2.9.8). Therefore, independent transitions between the different health states may not be comparable versus tepotinib. Another limitation of the state-transition model is that it does not negate the need to extrapolate data, therefore extrapolating more immature data (such as post-progression survival) produces more uncertain estimates for those particular transition probabilities and hence creating uncertain OS projections from the final model outputs. In addition to the above, further limitations to a state-transition model involve underlying data availability and complexity of the approach to allow for all possible transitions within the CE model itself. For a state-transition model, the development of a three-health state model using time-dependencies in event rates for each possible transition would add significant complexity based on the number of tunnel states that would be required to accurately model the transitions (i.e., tunnel state per cycle). This would create unnecessary computational complexity that would potentially make the model burdensome to run. **Conclusion** Based on the above points, the partitioned survival model structure was considered the most appropriate for this appraisal compared to a state-transition model. This is also consistent with the structure used in the majority of previous NSCLC NICE appraisals, which were considered appropriate by the committees of each appraisal.[11-19] Moreover, as stated in Section B.3.2.2, the partitioned survival model structure revolves	(1) Individual patient data (IPD) The ERG notes that the company selected real world studies with IPD for evidence for the effectiveness of comparators. This makes it more feasible to estimate the transition probabilities necessary to appropriately implement a STM. (2) Selection bias and censoring The ERG agrees that there is the possibility of selection bias and censoring effects in the estimation of the transition probability to death for patients in the post-progression state (PPS). Time to disease progression was shorter for chemotherapy and immunotherapy compared to Tepotinib. However, the use of a STM would allow scenario analysis around the bias to be explored.

		around the key secondary endpoints from VISION (OS and PFS) and available outcomes for the comparator data using the real-world cohort.	(3) Prediction precision The company is correct to note that both mortality risk for progression-free (PFS) patients and PPS patients need to be estimated for a STM instead of just overall survival (OS) in a PSM. There will be fewer data available to estimate each of PFS and PPS mortality risk than would be available to estimate OS, and consequently there is likely to be more uncertainty in the estimates. The company has not reported the numbers that died before progression for chemotherapy and immunotherapy populations. 21% of patients died before progression in VISION (Table 15, Cohort A, ITT-02 Oct 2019). Assuming similar percentages for chemotherapy and immunotherapy, this would result in greater uncertainty in particular for PFS patients. However, as stated in TSD 19, a STM has the potential to more accurately extrapolate

			survival as it does not assume that OS and PFS are independent. (4) Model complexity The company argues that a STM is more complex and takes more time to run the analysis. The ERG agrees with this. The model construction and the estimation of transition probabilities will be more time consuming. The model would also take longer to run either using tunnel states for a cohort analysis or running an individual patient simulation. But this type of model should not need to take a prohibitively long time to run. The probabilistic sensitivity analysis would also be more meaningful as the STM correctly does not assume that OS and PFS are independent.

Key issue 8: No analyses are considered for the subgroups stated in the decision problem	**NO**	Merck acknowledge the ERG's critique relating to the decision problem populations and comparators, and see value in the ERG's suggested approach to this. However, we would like to highlight that the ERG's decision problem 'subgroups' relating to treatment line (untreated/previously treated), histology (squamous/non-squamous) and PD-L1 expression (< 50%/ ≥50%) are not true subgroups as the underlying clinical data does not align with the subgroup defined, and in fact is the same data across all subgroups for each line of therapy group. The data used in the ERG's results are not split by histology or PD-L1 (as this is not available, as discussed in Key Issue 2 response) and instead uses the same data from the treatment line subgroups available in the model and just amends the comparator for each decision problem group to reflect the treatments relevant to that subgroup. For example, the efficacy data used to inform the 'untreated, non-squamous PD-L1≥50%' population are also used to inform the following other ERG subgroups, with just the comparators adjusted: • Untreated, non-squamous, PD-L1<50% • Untreated, adenocarcinoma/large cell carcinoma, PD-L1 <50% • Untreated, squamous, PD-L1 ≥50% population • Untreated, squamous, PD-L1 <50% population. As the comparators vary in each of the decision problem subgroups, we value the ERG's attempt to address this issue however, do not consider this to be a true subgroups analysis due to the lack of clinical subgroup data informing each separate subgroup analysis. As such, we request that these analyses are referred as 'subgroup scenario analyses'.	The ERG acknowledges that effectiveness evidence specific to the subgroup was not available. Furthermore, the cost of treatment may vary across subgroups and this evidence is not available. However, these subgroups were identified as relevant decision populations in the NICE scope with different comparators and decisions need to be made for these subgroups using the best available evidence using the relevant comparator. This is the reason that the ERG used the untreated or treated effectiveness data as appropriate as the best effectiveness evidence available. As the ERG has stated and the company notes, it is just the comparators that change across the untreated subgroups and across the treated subgroups. As stated

		The company did not present the cost-effectiveness results by the subgroups specified in the NICE scope for several reasons. Firstly, as discussed, data were not available to split patients by PD-L1 expression and not enough patients were in the squamous group to split by histology (see response to Key Issue 2). Thus, it was not possible to perform subgroup analysis as specified in the final scope. We were only able to split patients by treatment history (untreated or previously treated) but acknowledge that this analysis is still limited due to the small patient numbers for each group. Therefore, the line-agnostic population was presented as the base case analysis, and by line of therapy as sub-groups. Furthermore, tepotinib is licensed for all advanced NSCLC patients harbouring METex14 skipping alterations regardless of treatment line, histology and PD-L1 status. Therefore we consider it more appropriate to consider the 'all comers' approach in line with the label as the base case and not split results by decision problem subgroups where data is limited, and clinical input suggests it is not appropriate for decision making. This is in line with the latest NSCLC appraisals for targeted treatments, where the final scope outlines comparators for different groups of patients, but results are not split by these subgroups, based on their licence.[9;20;21] Moreover, clinical experts consulted at the advisory board and in separate validation calls agreed they would like the flexibility to use tepotinib at any treatment line and that if a patient is tested positive for METex14 then the targeted treatment (i.e., tepotinib) would be used over currently available therapies, regardless of histology and PD-L1 expression.[22] Therefore, this approach as the base case aligns with clinical need as well as the licence for tepotinib.	for Key Issue 2, the different comparators imply different decision problems and if decisions are not based on the best available evidence using the relevant comparators for those subgroups, then health benefit may not be optimised.

		Assessment by these subgroups causes further issues when considering the end of life criteria, as the data specifically for these subgroups within the METex14 NSCLC population are not available. METex14 skipping is a rare mutation within NSCLC, with limited available data, and so outcomes within the different subgroups proposed by the ERG are not currently available in the literature or in any real-world data known to Merck. Outcomes for patients in the larger wildtype NSCLC are available for these subgroups, however it is unknown how well METex14 skipping patients respond in comparison, although it is known that patients with METex14 skipping mutations generally have poorer outcomes compared to other types of NSCLC, including wildtype NSCLC.[1;3] Unfortunately, how much this differs by histology or PD-L1 status is currently not clear due to the lack of data (see response to Key Issue 2), and decision making using these sub groups would run into additional challenges when assessing end of life criteria. **<u>Conclusion</u>** Merck acknowledge that the ERG's attempt to address the decision problem by amending the comparator per subgroup could be a useful scenario analysis for consideration, and see value in the approach taken. However, for the reasons stated above, we continue to present our base case results using the overall population considering both chemotherapy and immunotherapy as comparators. Subgroup analysis by treatment line is also presented for completeness. Merck consider this approach sufficient to support decision making as it is reflective of how clinicians will choose tepotinib over the current comparators.	
Key issue 9: No analyses were	**NO**	The comparators in the ITC were grouped by treatment class due to the limited number of patients receiving each individual treatment. The ERG	The ERG agree that an individual treatment

considered using the individual treatment comparators for which there was enough evidence.		noted that within the immunotherapy group, [redacted] patients received pembrolizumab and within the chemotherapy group, [redacted] patients received pemetrexed plus carboplatin. Based on these numbers, the ERG felt it is possible to conduct the ITC using these individual treatments in comparison to tepotinib. Although it would have been desirable to conduct comparisons against individual comparators, in what is a rare sub-population in NSCLC, Merck considers that insufficient data were available for any individual comparator. The largest group within the chemotherapy and immunotherapy categories is pembrolizumab, where [redacted] patients had PFS information available. These [redacted] patients were split between treatment naïve (n=[redacted]) and experienced (n=[redacted]) groups (thus preventing an analysis by line) and include a range of clinical characteristics which would confound any comparison. These numbers are even smaller for chemotherapy due to the number of possible regimens, with [redacted] naïve and [redacted] experienced patients receiving carboplatin + pemetrexed, and no other individual named treatment/combination having more than [redacted] patients ([redacted] patients received docetaxel monotherapy, and pemetrexed monotherapy). Based on these patient numbers, although it may be technically possible to perform comparisons against these two individual treatments, these would be extremely uncertain, and unlikely to meaningfully inform the decision problem. Furthermore, analysis by line of therapy would not be possible. As the comparators were weighted to match the tepotinib population, this would mean weighting [redacted] pembrolizumab patients and [redacted] pemetrexed plus carboplatin patients to 151 tepotinib patients to form a comparison. For this reason, the Merck considers that there was not enough evidence to perform such comparisons within the immunotherapy	comparison could only feasibly be done for pembrolizumab and carboplatin + pemetrexed. The value of doing the analysis, if these are the most common treatments in the UK, is that the cost-effectiveness of tepotinib compared to commonly used UK treatments could be evaluated. The company clinical experts did not identify carboplatin + pemetrexed as a commonly used treatment in the UK. They did identify pembrolizumab as a commonly used treatment in the UK. The ERG agrees that such an analysis could only be conducted in a line-agnostic population. The company states that there may be confounding in effectiveness estimates when considering only the patients receiving the specific treatments. Population

		and chemotherapy classes and that these would not provide meaningful results for decision making. Even if just comparing in the line agnostic population, only pembrolizumab and pemetrexed + carboplatin comparisons would be technically possible, and all of the other comparators in the decision problem missed. Grouping the immunotherapies and chemotherapy treatments allowed for larger datasets to be used, and therefore increasing the robustness of the comparisons. These approaches were also considered appropriate by health economic experts and clinical experts at the advisory board.[22] The clinical experts considered that the treatments within each class have similar outcomes, and where appropriate, they tend to consider products by treatment class.[23-27] In addition, the grouping of treatments approach has been used in previous NICE submissions where the comparators are a mix of different treatments.[15;28-30] Conclusion Merck stand by their original approach and do not agree that comparisons against the individual treatments would be informative. These comparisons also would not allow for comparisons by line of therapy. The grouping approach mean that all treatment classes in the decision group can be compared to, and this approach has been supported by clinical experts and previous NICE appraisals.	matching would need to be done for the specific treatments, and the smaller sample sizes is likely to make the matching harder. Whether the populations are comparable would only be know after attempting to match the populations.
Key issue 10: Potential bias from clinicians' selection of survival curves for the comparators, and	**NO**	**Comments on ERG's approach to best fitting curves** The ERG made several comments within their report regarding the approach to selecting the most appropriate curves, and noted that the clinical experts did not think the best fitting models represented the long term projections of OS and PFS. Merck disagree with the ERG's	The ERG does not think that AIC and BIC assessment are the only relevant criteria to use in the selection of statistical models. The ERG

lack of alternative scenario.		assessment of best fitting curves, noting that the only criteria the ERG appear to use are based on AIC and BIC assessment. Although AIC and BIC are a good statistical measure of how well the curves fit the observed data, NICE DSU TSD 14[31] specifies the need to also account for visual assessment and clinical plausibility as well as AIC and BIC to identify the most plausible curves. AIC and BIC provide a useful statistical test of the relative fit of alternative parametric models ordered by smallest value (best fitting) to largest value (worst fitting). While NICE DSU TSD 14 does not specify any fixed rules related to either AIC or BIC scores to compare specific models, a general 'rule of thumb' is proposed by Burnham & Anderson (2004)[32] regarding AIC scores. Based on the difference in the AIC scores for the 'best-fitting' model (i.e., the lowest AIC) and an alternative model, Burnham & Anderson suggest: • If the difference is ≤2, the models are essentially equivalent • If the difference is >2 but <10, the alternative model has less support, but may still provide a reasonable fit • If the difference is >10, the alternative model has essentially no support and should not be selected For BIC, a similar rule of thumb is proposed by Raftery (1995),[33] wherein differences in the BIC score of 0–2, 2–6, 6–10, and ≥10 are referred to as a means of justifying additional model complexity. **Comments on Merck's approach to best fitting curves** Merck considered the best fitting curves according to AIC and BIC alongside visual fit and clinical plausibility, obtained at an advisory board where clinicians validated the long term projections. In some cases the clinicians did not feel the curves identified as the statistically best fitting	does agree that visual assessment and clinical plausibility are relevant. The company appears to have misunderstood the points made by the ERG. Indeed, the ERG stated that the models selected by the company are plausible. The company also makes statements here such as "we strongly disagree with the ERG's view here. The real-world cohort was adequately matched to the VISION trial…" In section 4.2.6 the ERG presented possible scenarios in which the clinical expert opinion may or may not be right; the ERG did not claim it knew what the actual situation was. The key issue here concerns appropriately investigating uncertainty associated with the selection of statistical models with a view to

(according to AIC, BIC) were the most plausible and chose alternative curves. However, with the exception of chemotherapy the chosen curves are within a difference of 10 of the best statistical fitting, and visual fit was reasonable for all (see Table *2* and **Figure *17*** - **Figure *20***). Therefore, for tepotinib and immunotherapy the base case choices obtained by clinical validation do not penalise the plausibility of the data or suggest potential bias in the selection of curve fits. For chemotherapy, we acknowledge that the data from the real-world cohort may overestimate the survival projections compared to what would be expected in clinical practice and when compared to published data for chemotherapy, either in the METex14 skipping population and in wildtype NSCLC (see Section B.3.10 of company submission). This is possibly due to the high number of subsequent treatments given to these patients, including subsequent immunotherapies and MET inhibitors, some of which do not reflect UK practice and would not be available to UK patients (as the real-world cohort patients were primarily from the US). Therefore, for the chemotherapy base case, we selected curves which best represent expected long-term projections (as dictated by clinical expert opinion) over statistical and visual fit. However, despite the statistical fits not abiding the 'rule of thumb' (see Table 2), we consider that the visual fit of the selected curves versus the observed data are within reason (see **Figure *18*** and **Figure *19*** in the Appendix).

Table 2: AIC and BIC – best fitting versus selected models – overall population

Models	**OS**		**PFS**
	AIC	**BIC**	**AIC**
Tepotinib			
Best fitting	Log-logistic (743.5)	Exponential (748.8)	Log-normal (776.5)

estimating the relative effectiveness of tepotinib compared to chemotherapy and immunotherapy. The company switched statistical models one at a time in scenario analyses. The ERG selected combinations of models for both OS and PFS. These were presented as an alternative base case, not a preferred base case.

Survival curves are fitted *independently* to the single-arm trial tepotinib and comparator data in the company submission due to the single-arm trial data, and the clinical experts naturally have more information about long-term survival for chemotherapy and immunotherapy than for tepotinib. This contrasts with estimating the hazard functions jointly for the intervention and comparator in a randomised controlled

Selected	Log-logistic (743.5)	Log-logistic (749.6)	Log-normal (776.5)	Log-normal (782.5)	
Assessment	Best fitting selected	Within 1 score	Best fitting selected	Best fitting selected	
Chemotherapy					
Best fitting	Generalised gamma (827.9)	Log-normal (832.61)	Odds 3 knot spline (726.2)	Odds 3 knot spline (737.2)	
Selected	Weibull (842.1)	Weibull (846.5)	Odds 1 knot spline (739.2)	Odds 1 knot spline (745.7)	
Assessment	>10 score difference	>10 score difference	> 10 score difference	> 10 score difference	
Immunotherapy					
Best fitting	Normal 2 knot spline (748.6)	Generalised gamma (754.4)	Piece-wise log-logistic (376.3)	Piece-wise log-logistic (378.6)	
Selected	Normal 1 knot spline (756.5)	Normal 1 knot spline (762.3)	Piece-wise log-logistic (376.3)	Piece-wise log-logistic (378.6)	
Assessment	Within 8 score difference	Within 8 score difference	Best fitting selected	Best fitting selected	

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

In conclusion, Merck consider the choice of base case curves for immunotherapy and tepotinib to be appropriate based on statistical fit, visual fit and clinical validation. The chosen curves for chemotherapy, did not pass the acceptability in terms of statistical fit, but still have a good visual fit and are substantially more clinically plausible than the statistically best fitting. Despite the chemotherapy curves being the most clinically plausible, they are still considered to overestimate the expected benefit of chemotherapy (see validation section of this response), thus the efficacy comparison between tepotinib and chemotherapy, and resulting

trial using the same model type, and then testing alternative types of models. The ERG considers that there is uncertainty in the relative effectiveness associated with the approach taken in the company submission, where the relative effectiveness of Tepotinib over time is described by the difference in survival curves, and that it is useful to estimate the cost-effectiveness of Tepotinib where the use of clinical expert opinion is minimised as a plausible alternative scenario. There is uncertainty in the relative effectiveness of Tepotinib compared to chemotherapy and immunotherapy. The issue is about the selection of models for estimation of relative effectiveness, not about specific procedure for selecting any one survival model.

		benefit for tepotinib, is likely to be under-estimated resulting in a more conservative ICER. **<u>Comments on the ERG's assessment</u>** Merck would also like to address the three possible reasons the ERG provided for the statistically best-fitting survival models not aligning with the clinical experts selections, specifically that: 1. The sample population in VISION is not representative of the overall population 2. The real-world data was inadequately matched to VISION 3. Another more flexible model is required but there is not enough data to model Regarding the first reason, the patient characteristics of the VISION trial and real-world cohorts were considered representative of the METex14 skipping alterations NSCLC population based on the literature, which was agreed by the clinical experts at the advisory board (see Section B.2.3.1.2). Therefore, we do not believe this is a large issue. Regarding the second argument, we strongly disagree with the ERG's view here. The real-world cohort was adequately matched to the VISION trial using robust statistical techniques with the availability of patient-level data in line with the NICE DSU 17 guidance.[7] Regarding the final point, when selecting curves, Merck considered an array of options available give a good range of extrapolations to choose from based on both fitting to the observed data and long-term projections. In cases deemed necessary, more flexible models were included in line with NICE DSU 21.[34] Considering the chemotherapy OS, only parametric	The discussion presented here by the company comparing the ERG survival curves to those in published studies is useful. However, the issue here concerns the adoption of an appropriate method to estimate the relative effectiveness of tepotinib. If an adjustment is made to the comparator survival curve but that same adjustment is not made to the intervention survival curve, there is uncertainty around whether the estimated relative effectiveness is accurate. The ERG approached this by producing alternative scenarios where clinical expert input in the selection of models was minimised in order to investigate the impact on the results of making these alternative assumptions.

		models were fit to the data after assessment concluded that further flexible models were not required (see Section B.3.3.1 of the company submission). Given that the issue with chemotherapy projected survival came from the observed real-world data itself, more flexible models would not resolve this. We do acknowledge that subsequent treatment use is one area where the real-world data differs from VISION and clinical practice in the UK and this is a limitation. However as stated earlier, the impact of this would be to underestimate the benefit of tepotinib vs. chemotherapy, and hence would represent a conversative assumption in the economic analysis. Overall, Merck disagree with the ERG's concerns regarding our approach to extrapolating OS and PFS. As discussed previously, the curves for tepotinib and immunotherapy in the base case analysis were selected based on clinical plausibility and were within the acceptable AIC and BIC score difference with reasonable visual fit to the data. For chemotherapy, clinicians noted that the subsequent treatments in the chemotherapy arm appeared more aggressive than what would be used in the UK which may have impacted OS. As such, the most plausible curve was selected for the chemotherapy arm, acknowledging that this may still overestimate the survival of the chemotherapy patients. Merck do not consider any bias to have been introduced by seeking clinical expert opinion for the validation of survival estimates. Clinicians used their experience of treating patients in the wider NSCLC population and knowledge of patients harbouring METex14 skipping alterations. Therefore, the experts were able to make informed estimates of survival for patients treated with immunotherapy, chemotherapy and targeted therapies, which have been used to inform Merck's base case. We	

		acknowledge the ERG's conclusion that the set of curves we presented in our base case can be considered plausible, and below, share our comments on the alternative set of PFS and OS extrapolations presented by the ERG, and why we think these are not as plausible. **<u>Comments on ERG's base case</u>** The ERG chose another set of curves for their base case, based on AIC and BIC choice alone. As previously discussed, curves chosen based on AIC and BIC alone are not recommended by NICE DSU TSD 14. This suggests that where there is a need to extrapolate outcomes and a significant amount of censoring, then external data, clinical plausibility and external judgement should be all used to assess the suitability and external validity of the alternative models.[31] Therefore, our critique and validation of the ERG's choices are discussed below. ***Tepotinib*** For the overall population and previously treated subgroup, the ERG chose the same curves as Merck's base case. For the untreated population, the ERG chose log-logistic for both PFS and OS instead of log-normal. The company chose log-normal for the base case as this appeared to have the better visual fit over the log-logistic distribution and was within 1 AIC and BIC score difference. Therefore, we stand by our choice of log-normal as our base. ***Immunotherapy*** The ERG chose alternative immunotherapy curves for OS in the overall and previously treated populations, and PFS in the untreated population.	

		These choices have been compared against external sources as per Section B.3.10 of the company submission. *Overall population* Figure 4 and **Figure 5** presents the ERG's projected OS for the overall population immunotherapy arm versus Merck's projected OS and published sources. **Figure 4: External validation – immunotherapy – OS – overall population versus clinical trials**  Abbreviations: 1L, first-line; 2L, second-line; OS, overall survival	

		Figure 5: External validation – immunotherapy – OS – overall population versus real-world data  Abbreviations: 1L, first-line; 2L, second-line; OS, overall survival Similar to Merck's base case curve, in comparison to the clinical studies (Figure 4), the ERG's OS for the immunotherapy group projects lower survival compared to the pembrolizumab arm in KEYNOTE-024[35] and more in line with KEYNOTE-042.[36] Given that the KEYNOTE-024[35] and 042[36] populations are in first-line PD-L1 positive NSCLC without METex14 skipping alterations or other oncogenic driver mutations and are younger (median age 64.5 years and 63.0 years respectively compared to 72 years in the METex14 immunotherapy cohort), the survival for the METex14 skipping alterations immunotherapy group is expected to be lower. In comparison to the previously treated clinical trials (KEYNOTE-010[37] and CheckMate 057/017[38]), the ERG's immunotherapy group survival projects better outcomes until around 3 to 4 years, after which the curve projects worse outcomes. Given the expectation of poorer outcomes for METex14 skipping alterations patients, and an older cohort, the survival would be expected to be either in line or lower than the	

		immunotherapy arms from the published clinical trials in the previously treated group. Compared to published real-world data (**Figure 5**), the ERG's projected OS for the METex14 skipping alterations immunotherapy group appears in line with the two METex14 skipping alterations population sources (Guisier *et al.*[39] and Sabari et al.[3]), although underestimated compared to Sabari et al.[3] for the first two years and overestimated from one year compared to Guisier *et al.*[39] The ERG's immunotherapy OS curve sits consistently on the first-line real-world outcomes presented in Cramer-van der Welle *et al.*[40], however, compared to a wildtype NSCLC population, outcomes for a METex14 skipping alterations population are expected to be closer to the second-line projections. A similar conclusion was drawn from Merck's external validation of the base case choice, however the ERG's choice seems somewhat pessimistic compared to the feedback we received from clinicians at the advisory board who expected more of a plateau between five and eight years.	

		Untreated population **Figure *6*** presents the ERG's projected PFS for the untreated population immunotherapy arm versus Merck's base case and first-line published sources. **Figure 6: External validation – immunotherapy – PFS – untreated population**  Abbreviations: 1L, first-line; PFS, progression-free survival The ERG's model projections are in line with the real-world outcomes in Cramer-van der Welle et al[40] and KEYNOTE-042. However the expectation would be that for the METex14 population, projections would be worse than those in the wider NSCLC group. In addition, the modelled PFS curve would be expected to be lower than KEYNOTE-042 given the age of the study populations and PD-L1 status. Therefore, this suggests that the ERG's PFS projections could be more optimistic than expected. This was also the conclusion of the Merck's base case curve (see Appendix N.1.1.8), therefore given the ERG's curve choice is slightly more optimistic than our base case, we consider the ERG's choice to be an implausible alternative.	

		Figure 7 presents the ERG's projected OS for the previously treated population immunotherapy arm versus second-line published sources. **Figure 7: External validation – immunotherapy – OS – previously treated population**  Abbreviations: 2L+, second-line plus; OS, overall survival Similarly to Merck's base case, the ERG's model survival projection looks to be as expected compared to KEYNOTE-010[37] although predicting lower OS from two years. Compared to the second-line data from Cramer-van der Welle,[40] the survival looks to be overestimated and more in line with the immunotherapy trial studies. This is slightly higher than would be expected given the poorer response associated with METex14 skipping alterations patients in comparison to wildtype NSCLC. Given the similarities to our base case curve, we consider the ERG's choice to be a plausible alternative but note that the underlying assumptions of the exponential distribution (i.e., constant hazards) may not be appropriate for long term projections of immunotherapy as per the diagnostic plots (see Appendix N.1.1.8). ***Chemotherapy***	

		The ERG chose alternative curves for the OS and PFS in the overall and untreated population, and OS in the previously treated population. These choices have been validated against external sources as per Section B.3.10 of the company submission. *Overall population* **Figure *8*** and **Figure *9*** presents the ERG's projected OS for the overall population chemotherapy arm versus Merck's base case and published sources, respectively. **Figure 8: External validation – chemotherapy – OS – overall population – versus clinical studies**  Abbreviations: 1L, first-line; 2L+, second-line plus; OS, overall survival	

		Figure 9: External validation – chemotherapy – OS – overall population – versus real-world data  Abbreviations: 1L, first-line; 2L+, second-line plus; OS, overall survival Compared to clinical studies (**Figure *8***) the ERG's OS curve from the model projects greater survival compared to any of the chemotherapy clinical trials, although close to KEYNOTE-189.[41] At around three years the survival then projects lower estimates in comparison to KEYNOTE-189, but remains higher than any other study.[41] Based on the mix of untreated and previously treated patients, and a generally older cohort, the modelled chemotherapy OS would be expected to sit more closely with the previously treated published data (i.e., KEYNOTE-010[37] and CheckMate 057/017[38]). Additionally, compared to real-world studies (**Figure *9***), the ERG's modelled OS looks overestimated when compared to the real-world study Awad *et al*,[41] which is a mix of both untreated and previously patients and the study from Gajra *et al*.[42] of older patients. In conclusion, the ERG's OS looks substantially overestimated when comparing against external sources for chemotherapy (clinical trials in wildtype NSCLC and published real-world studies in METex14 skipping alterations patients), particularly in the long term. As discussed in Section	

		B.3.10 the high estimates of survival are mainly driven by the real-world data as opposed to the curve selected. This could be largely due to subsequent treatments which will differ by study and will be dependent on the time period of the studies. Clinical experts at the advisory board noted the aggressive subsequent treatment usage in the real-world data sets which is not in line with UK clinical practice (e.g., high use of targeted MET inhibitors) which is likely having an impact on the survival. Subsequent treatments from the published METex14 skipping alterations studies are not available therefore it is not possible to compare appropriately what impact subsequent treatments may be having. Similar conclusions were reached for Merck's base case using the most pessimistic curve for the chemotherapy arm, and that even these could be overstated. Therefore, given the ERG's curve is one of the most optimistic options, we consider the ERG's choice to be highly implausible and also does not align with clinical advice that expected survival at 5 years is around 5% (log-normal estimates 12% 5-year survival). The higher long term survival estimates in the ERG curve are particularly implausible based on clinical expert feedback. **Figure *10*** presents the ERG's projected chemotherapy PFS curve versus Merck's base case and published sources.	

Figure 10: External validation – chemotherapy – PFS – overall population

Abbreviations: 1L, first-line; 2L+, second-line plus; PFS, progression-free survival

Similar to Merck's base case, the ERG's PFS looks mostly in line with the external sources as they all project similar outcomes when naively compared in the first year. However the ERG's curve looks largely overestimated than would be expected after one year and into the long-term in comparison.

Untreated population

Figure 11 and Figure 12 presents the ERG's projected OS and PFS for the untreated population chemotherapy arm versus first-line published sources, respectively.

Figure 11: External validation – chemotherapy – OS – untreated population Abbreviations: 1L, first-line; OS, overall survival

Figure 12: External validation – chemotherapy – PFS – untreated population

Abbreviations: 1L, first-line; PFS, progression-free survival

		The ERG's OS chemotherapy model projections (Figure 11) look substantially optimistic in comparison to all of the external data sources and Merck's base case in the long-term. This suggests that the survival for chemotherapy is overestimated given the expectation of worse outcomes, in particular in comparison to the KEYNOTE studies which are a younger patient group. As with the overall population, the cause of these differences could be due to subsequent treatments which impact the OS of the real-world data. The PFS results seem more consistent with expectations in comparison to the external sources of validation, however the modelled curve does tail off after 1 year predicting higher PFS long term outcomes than expected based on the external data source and appearing to plateau in the long-term. As such, we do not consider the ERG's curves to be plausible alternatives to extrapolate chemotherapy PFS and OS outcomes. *Previously treated population* Figure 13 presents the ERG's projected OS for the previously treated population chemotherapy arm versus Merck's base case and previously treated published sources. **Figure 13: External validation – chemotherapy – OS – previously treated population**	

		 Abbreviations: 2L+, second-line plus; OS, overall survival The ERG's OS chemotherapy model projections look drastically more optimistic in comparison to the KEYNOTE and CheckMate studies, particularly in the long-term survival estimates. A similar conclusion was reached for the Merck's base case using the most pessimistic curve for the chemotherapy arm. Therefore, given the ERG's choice is one of the most optimistic curves, we consider the ERG's choice to be highly implausible. ***External validation conclusion*** In conclusion Merck consider most of the ERG's base case curves to be implausible. This is particularly apparent for the chemotherapy OS curves, where the ERG have chosen the most optimistic curves out of the choices available for all populations, and seem to substantially overestimate survival with chemotherapy in the short and long-term, compared to external studies and clinical expert opinion. Merck chose curves in line with clinical plausibility, acknowledging that the modelled projections still appear over-estimated in comparison to external sources. As the ERG's	

		curves project a much higher survival than Merck's, these are extremely unlikely to represent the long-term outcomes of patients treated with chemotherapy and thus severely underestimate the benefit versus tepotinib. Merck consider that the ERG curves here are not equally as plausible as the company's curve selections. **Overall conclusion** In conclusion, the curves selected for Merck's base case represent the most clinically plausible projections of OS and PFS for patients with NSCLC harbouring METex14 skipping alterations. With the exception of chemotherapy, the clinically validated curves are within an acceptable AIC and BIC range of the best statistically fitting curves and visually fit the data well. A limitation of the chemotherapy arm is that the real-world cohort (most from the US, but also Canada, Israel, Taiwan and the Netherlands) has better outcomes than would be expected in UK clinical practice notably due to the more aggressive subsequent treatments received. Therefore, the clinical plausibility of the long term projections was prioritised over the statistical and visual fit in the Merck's base case. Validation of these projections still highlighted the optimistic projections, therefore, considering the ERG's curve choices are based solely on AIC and BIC and are more optimistic than Merck's choice, these are considered highly implausible and not reflective of outcomes expected in clinical practice.	
Key issue 11: Representativeness of AE utility	**NO**	The ERG noted that several utility estimates for adverse events were not estimated using standard UK approved instruments or a relevant population. Merck accept the ERG's critique of the adverse event disutility values and acknowledge the limitation of available evidence as not being	The company response is consistent with the ERG critique. And as shown there

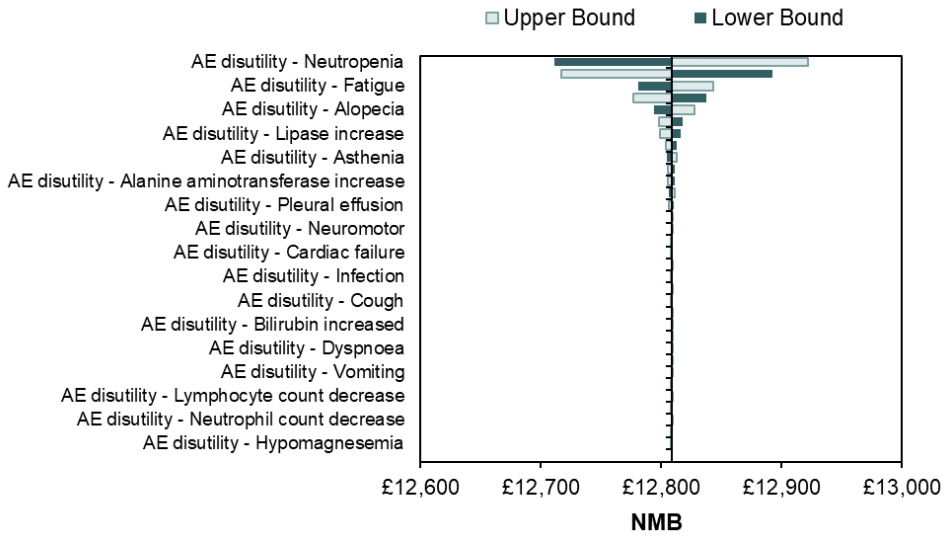
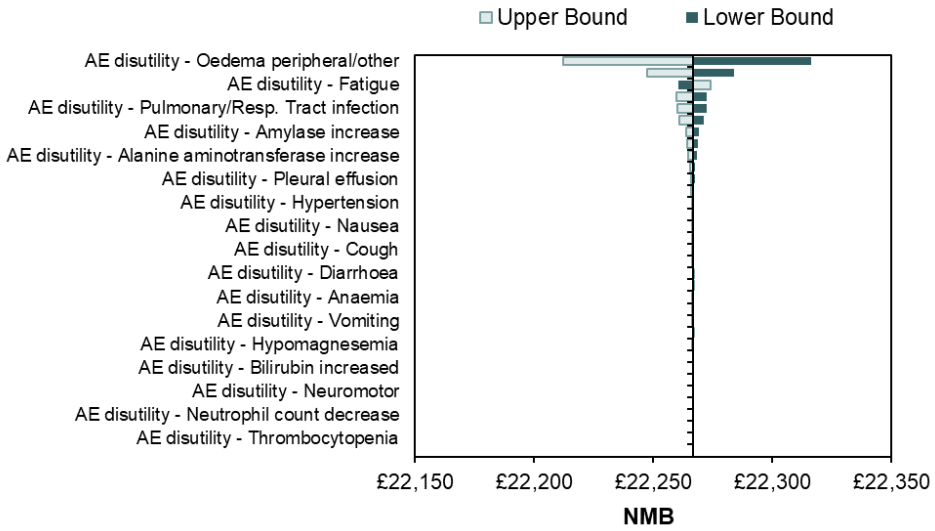
values for the UK population		fully representative of the study population or the preferred measure of utility for the NICE reference case. However, as the ERG acknowledges in their report, these sources are the best available evidence and have been used in previous NSCLC appraisals. In addition, adverse event disutilities have very little impact on results as demonstrated from the one-way sensitivity analysis (OWSA) (see Figure 14 and Figure 15). **Figure 14: Tornado diagram showing OWSA results of the AE disutilities on the NMB versus chemotherapy (WTP=£50,000)**  Abbreviations: AE, adverse event; OWSA, one-way sensitivity analysis; NMB, net monetary benefit	is very little impact on the cost-effectiveness estimates.

Figure 15: Tornado diagram showing OWSA results on the AE disutilities on the NMB versus immunotherapy (WTP=£30,000)



Abbreviations: AE, adverse event; NMB, net monetary benefit; OWSA, one-way sensitivity analysis

Conclusion

In conclusion, Merck do not consider alternative disutility values will impact the cost-effectiveness results and thus retained the original sources.

Key issue 12: It is possible there is better fitting model for ToT for tepotinib which was not fitted to the data by the company	**YES**	The ERG felt that as the best statistically fitting model for time on treatment (ToT) (log-logistic) possibly over-fits the tail-end of the data, more flexible models should have been produced. The range of parametric curves available to model ToT for tepotinib within the submission fit the KM estimates reasonably well, with the exception of the tail portion of the curve where an extended plateau is observed in the KM. This extended tail is likely an artifact of patient censoring, with clinical expert opinion indicating that while a couple of patients may receive treatment long-term, the vast majority would be off treatment by 5 years. Due to the nature of the extended KM tail, it is unlikely that any model extrapolation would be able to accurately capture the curve observed while remaining clinically plausible. As the parametric model extrapolations provided a wide range of long-term estimates of ToT, the parametric model options were considered sufficient to be used in sensitivity analysis (CS Doc B, Section B.3.8.3) and so more flexible models were not presented within the submission. For completeness, the spline model fits to tepotinib ToT are presented in Figure 16. The plot shows similar fits to the KM curve as seen with the parametric extrapolations, with a range of long-term ToT estimates available.	The company has presented additional spline statistical models for ToT. None of these are better fitting according to AIC or BIC statistics than the parametric models already presented. It is not known which curve in Figure 16 represents each model. Based on this information, there is no reason to prefer an alternative statistical model for ToT to use in the economic analysis. The discussion around the tail end of the KM curve suggests the base case model selection may be the most appropriate.

Figure 16: ToT spline model fits – tepotinib – overall population

Abbreviations: KM, Kaplan-Meier; ToT, time on treatment

Table 3 presents the AIC and BIC goodness-of-fit statistics for the ToT parametric and spline model extrapolations. The log-logistic and exponential models provide the best fit to the data according to AIC and BIC, respectively. By AIC, all models apart from the log-normal, 3-knot hazard and 3-knot normal are within 5 points of the smallest AIC, indicating a reasonable fit to the data. By BIC, of the nine spline options, only the 1-knot odds and 1-knot normal models provide a fit within 5 points of the smallest BIC.

Table 3: AIC and BIC – ToT – tepotinib, parametric and spline models

Model	Goodness-of-fit		Rank	
	AIC	BIC	AIC	BIC
Exponential	932.5	935.5	7	1
Weibull	934.3	940.4	12	6
Gompertz	933.0	939.1	9	3

Log-logistic	929.8	935.8	1	2
Log-normal	937.5	943.5	13	9
Generalised gamma	932.2	941.3	5	7
Spline – odds 1 knot	930.1	939.2	2	4
Spline – odds 2 knot	931.9	944.0	4	10
Spline – odds 3 knot	933.7	948.8	10	13
Spline – hazard 1 knot	933.0	942.1	8	8
Spline – hazard 2 knot	933.7	945.8	11	12
Spline – hazard 3 knot	939.6	954.7	14	14
Spline – normal 1 knot	930.7	939.8	3	5
Spline – normal 2 knot	932.4	944.5	6	11
Spline – normal 3 knot	944.1	959.2	15	15

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; ToT, time on treatment

Table 4 presents the proportion of patients estimated to still be on treatment with tepotinib at 5 and 10 years. At 5 years, the parametric models range from [redacted] on treatment with the Weibull model to [redacted] with the log-logistic. The spline models range between [redacted] with the 3-knot

normal model to [redacted] with the 1-knot odds model. At 10 years, the parametric models vary between [redacted] remaining on treatment with the spline models ranging from [redacted]

Table 4: Proportion of patients estimated to be treated with tepotinib at 5 and 10 years

Model	Proportion on treatment	
	5 years	10 years
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]
Spline – odds 1 knot	[redacted]	[redacted]
Spline – odds 2 knot	[redacted]	[redacted]
Spline – odds 3 knot	[redacted]	[redacted]
Spline – hazard 1 knot	[redacted]	[redacted]
Spline - hazard 2 knot	[redacted]	[redacted]
Spline - hazard 3 knot	[redacted]	[redacted]
Spline - normal 1 knot	[redacted]	[redacted]

		<table><tr><td>Spline - normal 2 knot</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>Spline - normal 3 knot</td><td>[redacted]</td><td>[redacted]</td></tr></table> **Conclusion** Given that the spline models do not provide a better fit in comparison to the parametric models and the range of long-term estimates produced from the splines are within that of the parametric models, these were considered appropriate to model tepotinib's ToT, providing a clinically plausible option for the base case and a reasonable range to explore as sensitivity analysis. As such, spline models have not been incorporated into the economic model.	
Key issue 13: Uncertainty in the cost estimates for immunotherapy and chemotherapy	**YES**	The ERG were unable to reproduce the distribution of chemotherapies and immunotherapies used for the comparator arms in the model. Merck have provided some additional information below. The distribution of immunotherapies and chemotherapies used for the comparator treatments are taken from the real-world cohort data. Treatments which were not considered part of UK clinical practice were either re-assigned to another similar treatment or re-distributed between the remaining treatments within the same class. Though within the immunotherapy group, most are aligned with UK practice (i.e., pembrolizumab, nivolumab, and atezolizumab), additionally, the majority of chemotherapy treatments are platinum doublets which are widely used in clinical practice.	The company has provided further details for the calculation of treatment distributions, both for the proportion of treatments used in the calculation and for the reason why pemetrexed was reclassified as pemetrexed + platinum (notes in Table 5). The calculation is now clear. The ERG considers the alternative treatment distribution analysis presented

The distribution taken forward for the model are based on the weighted patient numbers after application of the propensity score weighting from the ITC. This is done so that the distribution of treatments matches the weighted efficacy used to inform the comparator arms. Table 5 presents the treatments in the real-world cohort data with the unweighted and weighted incidence from the ITC and model category.

Table 5: Categorisation of the real-world treatments

Treatment	Model category	Unweighted n	Weighted n
Chemotherapies			
Carboplatin & pemetrexed	Pemetrexed/ platinum	[redacted]	[redacted]
Platinum Doublet	Other	[redacted]	[redacted]
Bevacizumab, carboplatin & pemetrexed	Pemetrexed/ platinum [a]	[redacted]	[redacted]
Carboplatin & paclitaxel	Paclitaxel/ platinum	[redacted]	[redacted]
Docetaxel	Docetaxel monotherapy	[redacted]	[redacted]
Pemetrexed	Pemetrexed/ platinum [a]	[redacted]	[redacted]
Cisplatin & pemetrexed	Pemetrexed/ platinum	[redacted]	[redacted]
Pemetrexed & bevacizumab	Pemetrexed/ platinum [a]	[redacted]	[redacted]
Bevacizumab, cisplatin & pemetrexed	Pemetrexed/ platinum [a]	[redacted]	[redacted]
Carboplatin	Other	[redacted]	[redacted]
Carboplatin & gemcitabine	Gemcitabine/ platinum	[redacted]	[redacted]

in Table 6.13, P110 of the ERG report to now be redundant.

The results presented in the appendix to this document in Tables 14, 15 and 16 show that the revised treatment distribution has a negligible effect of the cost-effectiveness results.

		Cisplatin & etoposide	Docetaxel/ platinum [b]	[redacted]	[redacted]	
		Cisplatin & gemcitabine	Gemcitabine/ platinum	[redacted]	[redacted]	
		Cisplatin & vinorelbine	Vinorelbine/ platinum	[redacted]	[redacted]	
		Everolimus	Other	[redacted]	[redacted]	
		Gemcitabine & vinorelbine	Docetaxel/ gemcitabine [c]	[redacted]	[redacted]	
		Vinorelbine	Vinorelbine monotherapy [d]	[redacted]	[redacted]	
		Immunotherapies				
		Durvalumab	Other	[redacted]	[redacted]	
		Immunotherapy	Other	[redacted]	[redacted]	
		Ipilimumab & nivolumab	Nivolumab/ipilimumab	[redacted]	[redacted]	
		Nivolumab	Nivolumab	[redacted]	[redacted]	
		Pembrolizumab	Pembrolizumab	[redacted]	[redacted]	
		Spartalizumab	Other	[redacted]	[redacted]	

Note: [a] These pemetrexed based regimens were not considered part of UK practice therefore clinical opinion confirmed that pemetrexed + platinum would be an appropriate re-categorisation.
[b] Etoposide was not considered part of UK practice therefore alternative chemotherapy was considered an appropriate re-categorisation by clinical experts.
[c] Although various combinations of chemotherapies could be given in UK clinical practice (usually as a last resort when other treatments have failed), gemcitabine + vinorelbine was re-categorised as docetaxel + gemcitabine as this treatment was already included in the model and avoided the need to include multiple variations for small incidences. Considering the similar effectiveness and costs between these treatments and small incidence, this is not expected to have much impact on the distributions.
[d] Corrected during technical engagement

During the technical engagement process, it was noted that vinorelbine had been incorrectly categorised as vinorelbine + platinum in the 'overall' population. This has been subsequently corrected to be classed as vinorelbine monotherapy and updated results are presented in **Table *15***. Table 6 presents the original and corrected distributions used within the cost-effectiveness analysis.

Table 6: Distribution of comparator treatments in the model

Treatment	Original distribution	Corrected distribution
Immunotherapies		
Pembrolizumab	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]
Nivolumab/ipilimumab	[redacted]	[redacted]
Chemotherapies		
Docetaxel/ platinum	[redacted]	[redacted]
Gemcitabine/ platinum	[redacted]	[redacted]
Paclitaxel/ platinum	[redacted]	[redacted]
Vinorelbine/ platinum	[redacted]	[redacted]
Pemetrexed/ platinum	[redacted]	[redacted]
Docetaxel monotherapy	[redacted]	[redacted]
Docetaxel/ nintedanib	[redacted]	[redacted]
Docetaxel/ gemcitabine	[redacted]	[redacted]
Gemcitabine monotherapy	[redacted]	[redacted]
Vinorelbine monotherapy	[redacted]	[redacted]

Conclusion

		The above information should be sufficient for the ERG to understand how the treatment distributions were derived. In addition, in response to clarification questions Merck provided the ERG with a spreadsheet which detailed the exact calculations using the ITC data to the model distributions.	
Key issue 14: Uncertainty in the cost estimates for subsequent treatments	**NO**	The ERG noted that cost-effectiveness results were quite sensitive to the proportion of patients receiving subsequent treatment. Merck agree with the ERG and noted within the company submission that subsequent treatments are an area of uncertainty and influenced by countries included in the clinical trial and real-world cohorts. A randomised control trial in the UK with sufficient sample size and follow-up suggested by the ERG would be the gold standard in terms of evidence, however this evidence was not available for the submission and not possible to obtain. In the base case, the model uses the subsequent treatment distributions as per the clinical trial and real-world cohort, such that the efficacy is matched to the costs. Any treatments which were not licensed or available within the UK have been reclassified within a similar treatment class or re-distributed evenly such that costs are still reflective of the modelled efficacy. Scenario analyses using a UK based distributions were conducted to explore impacts of different costs. However, as discussed in the company submission, it is important to note that the modelled overall survival is based on the initial treatments and subsequent treatment distributions used in the base case, therefore the scenario considering UK based distributions only impacts the costs and not the difference in survival efficacy, and so is an unfair comparison. This was agreed by the ERG in the technical engagement call. It is unclear how the differences in these treatment distributions would impact the survival. Scenarios were	The company agrees with the critique of the ERG, but a randomised controlled trial has not been conducted and so there is no further evidence to inform this issue.

<table>
<tr>
<td></td>
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<td>considered where the comparator arm efficacy could be varied to explore the uncertainty, however it was not felt to be a valuable exercise as the degree of variation in efficacy could not be informed by any available data and therefore would have limited interpretability.

<u>Conclusion</u>

Merck reiterate that for the subsequent treatments in the immunotherapy and chemotherapy arms, it is more appropriate to use the treatment distribution based on the real-world data set in the economic model in order to maintain the relationship between the effectiveness and cost outcomes of which the ERG agrees with, as noted in their report and in the TE call.</td>
<td></td>
</tr>
<tr>
<td>Key issue 15: Insufficient reporting and clarity of reporting of the cost-effectiveness results</td>
<td>NO</td>
<td>The ERG was unclear on which decision problem questions were addressed within the company’s submission. Merck would like to clarify the reporting of cost-effectiveness results and which decision questions are being considered, in Table 7. The base case presents results for the overall population in line with the tepotinib license and clinical need. Subgroups are also presented by treatment line based on the available data.

Table 7: Decision problems in the Merck’s cost-effectiveness analysis
<table>
<tr><th>Decision problem</th><th>Comparators</th><th>Model population</th></tr>
<tr><td>Overall (base case)</td><td>Immunotherapy, Chemotherapy</td><td>Overall</td></tr>
<tr><td>Untreated</td><td>Immunotherapy, Chemotherapy, Immunotherapy + chemotherapy</td><td>Untreated</td></tr>
<tr><td>Previously treated</td><td>Immunotherapy, Chemotherapy</td><td>Previously treated</td></tr>
</table>
</td>
<td>The company has clarified here that a subgroup mentioned in the company submission of patients contra-indicated to immunotherapy is not a relevant subgroup for this submission.

The company has presented 3 decision problems in Table 7 that are consistent with those in the company submission.

The company mentions in the text pairwise comparisons with either chemotherapy or</td>
</tr>
</table>

		As multiple comparators are available per population, fully incremental analysis was provided and is relevant to inform the decision problem. However, pair-wise results are also presented for completeness as these better reflect the clinical decision for patients who would receive chemotherapy or immunotherapy versus tepotinib (e.g., for patients who receive chemotherapy in practice, the comparison is between tepotinib and chemotherapy only). Merck have provided both sets of analyses (fully incremental and pairwise) and consider both informative for decision-making at this stage. During the development of the submission, Merck received clinical feedback that there are a small number of patients for whom immunotherapies are contraindicated, therefore this was discussed in the original submission. However, given that this is expected to be a very small proportion of patients, this population does not necessarily need to be considered separately, and instead should be considered as part of the overall population, for the chemotherapy pairwise comparison, as per the base case. **Conclusion** As per the response to Key Issue 8, we strongly prefer the results to be presented as per Table 7, but acknowledge that the ERG's scenario analysis using clinical data by treatment line and amending the comparators by subgroup may be useful alongside these.	immunotherapy as appropriate depending on what patients receive in practice. The ERG considers that the relevant list of comparators should not be defined by what a patient actually receives in practice, but by the relevant list of comparators specified in the NICE scope.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do not use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	ERG response
Additional issue 1: End of life criteria	Section 7: End of life, page 119	NO	The ERG considered the end of life criteria and agreed that the ITC favoured the less than 24 month criteria for the overall population. However, there was some uncertainty based on the model results and incremental difference per subgroup. Therefore, Merck would like to re-affirm their arguments for the end-of life criteria in light of the comments from the ERG regarding decision problems within the cost-effectiveness analysis (outlined in Key Issue 15). As discussed in response to Key Issue 8, given the limited data available for NSCLC patients harbouring METex14 skipping mutations, evidence for the decision problem subgroups presented by the ERG (by histology and PD-l1 expression) is not available for the METex14 patient cohort. As such, we have evaluated end-of-life criteria using available evidence considering the overall population (company base case) and treatment line subpopulations (1L and 2L subgroups), in line with Merck's approach to the decision problem populations described in Key Issue 15. Life expectancy in advanced NSCLC: external published sources	The company has provided information on end-of-life criteria for the untreated and treated populations as well as the overall population. The company submission only considered the

Table 8 presents a summary of median OS for patients with advanced NSCLC available in the literature. Although evidence in the literature for patients treated with immunotherapy and chemotherapy is limited for METex14 skipping NSCLC patients (3 studies are presented), we also considered available studies in the wider advanced NSCLC population. Across all of these studies, median OS is under 24 months for all patients treated with chemotherapy, regardless of treatment line.

As discussed in Section 2.1.3.1 of the company submission, patients with METex14 skipping alterations have a poorer prognosis compared to wildtype NSCLC.[41;43-45] Studies reporting outcomes of METex14 patients shows a poorer response to treatment, with reported median OS ranging from 8.1 months to 18.2 months.[3;39;41] Patients harbouring METex14 skipping mutations tend to be older[46] and older patients with NSCLC tend to have a poorer prognosis.[47] One real-world study in older patients in advanced NSCLC reported a median OS of 7.7 months for patients treated with immunotherapy.[42]

Therefore, the evidence in the literature suggests that patients with advanced NSCLC harbouring METex14 have a life expectancy less than 24 months regardless of treatment line.

Table 8: Overview of median OS reported for advanced NSCLC in the literature

Source	Population	Median OS, months	
		Immunotherapy	Chemotherapy
Overall (mixed untreated/previously treated)			
Guisier et al[39]	Real-world study - METex14 skipping mutations	13.4 (9.4-NR)	-
Sabari et al[3]	Real-world study - METex14 skipping alterations	18.2 (12.9-NR)	-

overall population.

The data presented here suggests that the end-of-life criteria are met when compared to chemotherapy in the overall population and when compared to either chemotherapy or immunotherapy in the treated population, although a survival benefit greater than 3 months is only found from the economic model survival predictions for

			Awad et al[41]	Real-world study – METex14 skipping alterations	-	8.1 (5.3-NR)
			Untreated population			
			Cramer-van der Welle et al[40]	Real-world study – PD-L1 positive >50%	15.8 (9.4-22.1)	-
			Gajra et al[42]	Pooled clinical trials >=70 years	-	7.7 (6.0-8.9)
			KEYNOTE-189[48]	Phase III trial – non-squamous	-	10.7 (8.7-13.6)
			KEYNOTE-042[36]	Phase III trial – PD-L1 positive >1%	16.7 (13.9-19.7)	12.1 (11.3-13.3)
			KEYNOTE-024[35]	Phase III trial – PD-L1 positive >50%	26.3 (18.3-40.4)	13.4 (9.4-18.3)
			Previously treated			
			Cramer-van der Welle et al[40]	Real-world study – non-squamous PD-L1 positive <50%	8.2 (5.9-10.6)	-
			KEYNOTE-010[37]	Phase III trial – PD-L1 positive >1%	11.8 (10.4-13.1)	8.4 (7.6-9.5)
			CheckMate 017 & CheckMate 057[38]	Phase III trials	11.1 (9.2-13.1)	8.1 (7.2-9.2)

Key: OS, overall survival; NR, not reached

Life expectancy in advanced NSCLC: Merck data analysis (ITC and economic model)

The results of the ITC support the evidence in the literature, suggesting that regardless of treatment line, life expectancy is less than 24 months (median OS ranges from [redacted] to [redacted] months for immunotherapy and [redacted] to [redacted] months for chemotherapy- see

chemotherapy and not from the ITC results.

The ERG agrees with the company that the end-of-life criteria are probably not met in the untreated population.

			Table ***9***). For chemotherapy-treated patients, modelled mean OS is [redacted] months in the overall cohort, and [redacted] months in the previously treated cohort. Table ***9*** presents the median survival from the ITC and mean survival from the cost-effectiveness model using the observed data from VISION and the weighted data from the real-world cohort, and extrapolating 30 years. The model predicts the mean survival to be under 24 months for chemotherapy and over 24 months for immunotherapy for the overall population. Though this seems more optimistic than what is reported in the literature, this provides evidence patients treated with chemotherapy have a life expectancy less than 24 months whilst immunotherapy is uncertain. Looking at the individual subgroups, the untreated population is estimated to have a greater life expectancy of over 24 months whereas patients who have been previously treated are expected to have a life expectancy less than 24 months regardless of treatment option. Life-expectancy in the chemotherapy arm looks relatively close to 24 months in the model for the overall and previously treated populations, however the chemotherapy survival from the real-world cohort has been noted to be overly optimistic compared to what would be expected in clinical practice and published sources (see Table 8) due to subsequent treatment patterns and use of subsequent MET inhibitors, even when using the most pessimistic curve (see response to Key Issue 10). Therefore, the mean OS for chemotherapy (overall and previously treated) is considered to be the most optimistic estimate, and the upper bound of what could be expected, accounting for uncertainty within the population. Nonetheless, these are still in line with the 24-month threshold. **Table 9: Mean and median survival**	

Evidence, months		Tepotinib	Immunotherapy	Chemotherapy
Overall population				
Observed data (ITC/VISION)	Median	[redacted]	[redacted]	[redacted]
Observed data (MAIC/VISION)	Median	[redacted]	13.4[39] – 18.2[3]	8.1[41]
CE model	Mean	[redacted]	[redacted]	[redacted]
Untreated				
Observed data (ITC/VISION)	Median	[redacted]	[redacted]	[redacted]
CE model	Mean	[redacted]	[redacted]	[redacted]
Previously treated				
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.

Based on the data presented in Table ***9***, tepotinib is expected to have a greater than 3 months gain in survival compared to patients treated with chemotherapy in the overall population and those treated with immunotherapy or chemotherapy in the previously treated population. For the previously treated chemotherapy patients, the mean OS from the model shows a difference of [redacted] months. As discussed in the company submission and in Key Issue 10, it is expected that the real-world cohort chemotherapy OS is overestimated, based on validation against external sources, as well clinical validation, including for the previously treated group. This is possibly due to the high number and type of

subsequent treatments (not seen in UK practice for METex14 skipping patients, such as crizotinib) in this cohort. The chemotherapy OS in this real-world cohort group showed a much larger mean and median OS in comparison to previously treated studies in the literature (see Table 8). Therefore, the OS benefit for tepotinib over chemotherapy (overall and previously treated) is considered to be the most conservative estimate, and the lower bound of the OS benefit that could be expected between tepotinib and chemotherapy, accounting for uncertainty within the population.

Conclusion

In conclusion, Merck consider tepotinib to meet end of life criteria:

- In the overall population for patients who would be treated with chemotherapy
- For all patients in the previously treated population regardless of treatment option.

This is supported by data in the literature showing poorer outcomes for patients with advanced NSCLC harbouring METex14 skipping mutations, data from the ITC, and extrapolated data from the cost-effectiveness model (see Table 10).

Table 10: Merck end of life criteria conclusion

Population	Evidence for EoL criteria
Overall	**<24 months** Chemotherapy: Literature sources show median OS ranging from 8.1 – 13.4 months (Table 8). ITC and model show expected survival <24 months (mean OS and median OS) (Table ***9***) for patients treated with chemotherapy **>3 months benefit** Chemotherapy: Mean benefit from model is [redacted] months, and median benefit from propensity score ITC is [redacted] months and MAIC ITC is [redacted]

				months (Table ***9***) for chemotherapy compared to tepotinib Immunotherapy comparison is at the 30k threshold in the overall population.	
				Untreated	All comparisons at the 30k threshold in the untreated population.	
				Previously treated	**<24 months** Chemotherapy: Literature sources show median OS range from 8.1 to 8.4 months (Table 8). ITC and model show expected survival of [redacted] months (median) and [redacted] months (mean) at most (Table ***9***), but this is likely to be overestimated as stated in Key issue 10 and Section B.3.2 of the company submission Immunotherapy: Literature sources show median OS ranges from 8.2 – 11.8 months (Table 8). ITC and model show expected survival to be < 24 months (Table ***9***) **>3 months benefit** Chemotherapy: Mean benefit from model is [redacted] months, and median benefit from the ITC is [redacted] months (Table ***9***). Given the overestimation of chemotherapy OS from the real-world data this benefit is likely to be underestimated. Immunotherapy: Mean benefit from model is [redacted] months, and median OS from the ITC is [redacted] months (Table ***9***)	
				Key: EOL, end of life; ITC, indirect treatment comparison; MAIC, match-adjusted indirect comparison; OS, overall survival	

Additional Issue 2: Additional clinical data availibility from VISION for Cohort A+C	Table 1.4: Key issue 3:	**No**	Recently published clinical data for Cohort A+C could help to address the uncertainty in the similarities and differences between Cohort A and Cohort A+C. The additional data published and provided includes: 1. More information on characteristics and outcomes in the different biopsy subgroups (standard of care tissue biopsy, and liquid biopsy) (Felip et al 2021) 2. More information on the efficacy of tepotinib in different age groups (Garassino et al 2021) **Felip E. et al. Tepotinib in patients with MET exon 14 (METex14) skipping NSCLC as identified by liquid (LBx) or tissue (TBx) biopsy. Presented at World Conference on Lung Cancer 2021, September 8–14. Abstract number 170.[49]** The efficacy analysis presented here includes all patients enrolled in Cohort A and patients enrolled in Cohort C with ≥3 months' follow-up (n=275). The data provided for this subgroup analysis (Cohort A and Cohort C) were recently published at WCLC 2021. A total of 159 patients with positive detection of MET exon 14 skipping by liquid biopsy, and 174 by tissue biopsy were enrolled (21% of patients had both a liquid and tissue biopsy). In the UK, tissue biopsy remains the	The ERG have nothing further to add.

standard of care and so these results can be considered appropriate when looking at tepotinib outcomes.

Baseline demographics were broadly consistent between patients enrolled based on liquid (L+) (n=159) or tissue biopsy (T+) (n=174) (Table 11).

Table 11. Demographics and Baseline Characteristics, VISION Cohort A and Cohort C – 1 February 2021 cut-off

	L+			T+		
	Overall	**1L**	**2L+**	**Overall**	**1L**	**2L+**
	N=159	**N=81**	**N=78**	**N=174**	**N=86**	**N=88**
Sex, n (%)						
Male	74 (46.5)	39 (48.1)	45 (52.3)	91 (52.3)	35 (44.9)	46 (52.3)
Female	85 (53.5)	42 (51.9)	41 (47.7)	83 (47.7)	43 (55.1)	42 (47.7)
Age (years)						
Median (range)	71.3 (47-89)	72.0 (47-89)	75.4 (47-94)	73.0 (41-94)	70.8 (49-89)	71.0 (41-89)
Age groups, n (%)						
<65 years	36 (22.6)	16 (19.8)	10 (11.6)	30 (17.2)	20 (25.6)	20 (22.7)
65 to <75 years	59 (37.1)	31 (38.3)	30 (34.9)	70 (40.2)	28 (35.9)	40 (45.5)
75 to <85 years	53 (33.3)	26 (32.1)	35 (40.7)	57 (32.8)	27 (34.6)	22 (25)
≥85 years	11 (6.9)	8 (9.9)	11 (12.8)	17 (9.8)	3 (3.8)	6 (6.8)
Line of therapy for tepotinib n (%)						

			1L	81 (50.9)	NA	NA	86 (49.4)	NA	NA	
			2L	45 (28.3)	NA	NA	61 (35.1)	NA	NA	
			3L	33 (20.8)	NA	NA	27 (15.5)	NA	NA	
			Smoking history[a] n (%)							
			Yes	NR (50.9)	37 (45.7)	41 (47.7)	NR (48.9)	44 (56.4)	44 (50)	
			No	NR (46.5)	44 (54.3)	44 (51.2)	NR (45.4)	30 (38.5)	35 (39.8)	
			ECOG PS[b] n (%)							
			0	NR (24.5)	21 (25.9)	28 (32.6)	NR (29.9)	18 (23.1)	24 (27.3)	
			1	NR (75.5)	60 (74.1)	57 (66.3)	NR (69.5)	60 (76.9)	64 (72.7)	
			Geographic region, n (%)							
			Europe	85 (53.5)	19 (23.5)	16 (18.6)	33 (19.0)	18 (23.1)	17 (19.3)	
			North America	37 (23.3)	50 (61.7)	45 (52.3)	80 (46.0)	35 (44.9)	35 (39.8)	
			Asia	37 (23.3)	12 (14.8)	25 (29.1)	61 (35.1)	25 (32.1)	36 (40.9)	
			Histology subtype,[c] n (%)							
			Adenocarcinoma	NR (80.5)	67 (82.7)	70 (81.4)	NR (81.6)	61 (78.2)	72 (81.8)	
			Squamous	NR (11.9)	8 (9.9)	5 (5.8)	NR (7.5)	11 (14.1)	8 (9.1)	
			Sarcomatoid	NR (3.1)	4 (4.9)	1 (1.2)	NR (1.1)	1 (1.3)	1 (1.1)	
			Other	NR (4.4)	2 (2.5)	9 (10.5)	NR (8.6)	5 (6.4)	6 (6.8)	

			Abbreviations: 1L, first-line; 2L, second-line; 3L, third line; ECOG PS, Eastern Cooperative Oncology Group performance status; L+, positive detection of MET exon 14 skipping in liquid biopsy sample; MET, mesenchymal–epithelial transition factor; T+, positive detection of MET exon 14 skipping in tissue biopsy sample. Notes: a Smoking history data were missing for ten patients (3.6%); b One patient (0.4%) had an ECOG PS of 2; c Histology data were missing for two patients (0.7%) Source: Felip, 2021[49] Patients enrolled based on liquid biopsy had characteristics associated with a worse prognosis, such as high tumour load (median tumour load of target lesions, mm [range] 68.0 [11.6, 227.8] and 52.9 [10.2, 227.8] for liquid biopsy and tissue biopsy, respectively), and more brain metastases. This trend occurred in untreated (1L) and previously treated (2L+) patients. HRQoL scores at baseline indicate that patients with METex14 skipping detected by liquid biopsy entered the study with lower quality of life scores and worse symptom scores. Patients enrolled based on liquid biopsy (n=159) had an ORR of 49.1% (95% CI: 41.1, 57.1), with a median duration of response of 11.1 months (95% CI: 9.0, 18.5), median PFS of 8.5 months (95% CI: 6.9, 10.4), and median OS of 16.3 months (95% CI: 12.1, 20.4) (Table 12). Treatment-naïve patients (n=81) had an ORR of 54.3% (42.9, 65.4), a median duration of response of 13.8 months (7.2, NE), median PFS of 8.5 months (6.9, 11.3), and median OS of 15.1 months (9.5, 22.1) (Table	

			12). Previously treated patients (n=78) had an ORR of 43.6% (32.4, 55.3), a median duration of response of 11.1 months (8.4, 19.4), median PFS of 8.3 months (5.7, 11.0), and a median OS of 19.9 months (12.8, 22.3) (Table 12). Patients enrolled based on tissue biopsy (n=174) had an ORR of 51.1% (95% CI: 43.5, 58.8), with a median duration of response of 15.4 months (95% CI: 9.9, 32.7), median PFS of 12.4 months (95% CI: 10.3, 16.8), and **median OS of 22.3 months** (95% CI: 19.1, 29.8) (Table 12). Treatment-naïve patients (n=86) had an ORR of 54.7% (43.5, 65.4), an mDOR of 32.7 months (10.8, 32.7), median PFS of 15.3 months (9.6, NE), and **median OS of 29.7 months** (15.3, ne) (Table 12). Previously treated patients (n=88) had an ORR of 47.7% (37.0, 58.6), a median duration of response of 10.1 months (8.3, 15.7), median PFS of 11.1 months (8.2, 16.8), and **median OS of 22.3 months** (17.0, 27.2) (Table 12). The L+ patients had characteristics associated with a worse prognosis, such as higher tumour load and more brain metastases. These patients also had a higher incidence of AEs considered unrelated to tepotinib, which is in line with a worse overall prognosis. The T+ group had a higher proportion of patients with ECOG PS 0. Patients with MET exon 14 skipping NSCLC detected by liquid or tissue biopsy had similar tumour responses; however, time-dependent endpoints showed a trend for	

improvement in the tissue biopsy population, particularly in the treatment-naïve setting, and likely reflect that patients enrolled based on liquid biopsy had a worse prognosis. This is particularly relevant in the UK landscape, as tissue biopsy remains the standard of care, and the improved outcomes for tepotinib in this group, particularly for untreated patients, shows the high benefit of tepotinib for this group.

Table 12. Tumour responses with tepotinib based on liquid and tissue biopsy – VISION Cohort A and Cohort C – 1 February 2021 cut-off

	L+			T+		
	Overall	**1L**	**2L+**	**Overall**	**1L**	**2L+**
	N=159	**N=81**	**N=78**	**N=174**	**N=86**	**N=88**
Treatment duration months, median (range)	6.8 (0.4, 50.6)			6.6 (<0.1, 50.6)		
Objective response by IRC						
Best objective response, n (%)						
Complete response	0	0	0	0	0	0
Partial response	78 (49.1)	44 (54.3)	34 (43.6)	89 (51.1)	47 (54.7)	42 (47.7)
Stable disease	34 (21.4)	14 (17.3)	20 (25.6)	50 (28.7)	22 (25.6)	28 (31.8)
Progressive disease	22 (13.8)	11 (13.6)	11 (14.1)	19 (10.9)	7 (8.1)	12 (13.6)
Not evaluable	25 (15.7)	12 (14.8)	13 (16.7)	16 (9.2)	10 (11.6)	6 (6.8)
Objective response rate, % (95% CI)	49.1 (41.1, 57.1)	54.3 (42.9, 65.4)	43.6 (32.4, 55.3)	51.1 (43.5, 58.8)	54.7 (43.5, 65.4)	47.7 (37.0, 58.6)

Disease control rate, % (95% CI)	70.4 (62.7, 77.4)	71.6 (60.5, 81.1)	69.2 (57.8, 79.2)	79.9 (73.2, 85.6)	80.2 (70.2, 88.0)	79.5 (69.6, 87.4)			
Duration of response by IRC									
N	79	44	34	89	47	42			
Events n	36	18	18	31	10	21			
Duration of response months, median (95% CI)	11.1 (9.0, 18.5)	13.8 (7.2, NE)	11.1 (8.4, 19.4)	15.4 (9.9, 32.7)	32.7 (10.8, 32.7)	10.1 (8.3, 15.7)			
PFS by IRC									
N	159	81	78	174	86	88			
Events n	95	45	50	71	30	41			
Duration of response months, median (95% CI)	8.5 (6.9, 10.4)	8.5 (6.9, 11.3)	8.3 (5.7, 11.0)	12.4 (10.3, 16.8)	15.3 (9.6, NE)	11.1 (8.2, 16.8)			
OS by IRC									
N	159	81	78	174	86	88			
Events n	83	42	41	59	28	31			
Duration of response months, median (95% CI)	16.3 (12.1, 20.4)	15.1 (9.5, 22.1)	19.9 (12.8, 22.3)	22.3 (19.1, 29.8)	29.7 (15.3, NE)	22.3 (17.0, 27.2)			

Abbreviations: CI, confidence interval; IRC, independent review committee; L+, positive detection of MET exon 14 skipping in liquid biopsy sample; MET, mesenchymal–epithelial transition factor; OS, overall survival; PFS, progression free survival; T+, positive detection of MET exon 14 skipping in tissue biopsy sample

			Garassino MC. Efficacy and safety of tepotinib in patients with advanced age: VISION subgroup analysis of patients with MET exon 14 (METex14) skipping NSCLC. Presented at ESMO 2021. Abstract 1254P.[50] The efficacy analysis presented here includes all patients enrolled in Cohort A and patients enrolled in Cohort C with ≥3 months' follow-up (n=275). The data provided for this subgroup analysis (Cohort A and Cohort C) are recently published at ESMO 2021. Overall, most patients in Cohorts A and C that were assessed for efficacy (N=275) were elderly (median age 72.4 years [range 41–94]), about half were male, half had smoking history, and most had adenocarcinoma. Baseline characteristics were similar in younger and older patients (Table 13). ORR was 52.2% and 44.9%, median DOR was 12.4 and 13.8 months, and median PFS was 11.0 and 10.4 months in patients below and above 75 years of age, respectively (Table 14). Patient-reported outcomes indicated quality of life was maintained while on tepotinib treatment, in patients above and below 75 years of age. This is relevant as patients with METex14 skipping tend to be	

older, and so it is important to show that the efficacy of tepotinib is maintained in the older patient groups.

Table 13. Baseline characteristics – VISION Cohort A and Cohort C (1 February 2021 cut off)

Baseline characteristics	Overall
	N=275
Sex	
Male, n (%)	135 (49.1)
Female, n (%)	140 (50.9)
ECOG PS	
0, n (%)	76 (27.6)
1, n (%)	198 (72.0)
Smoking history	
Yes, n (%)	128 (46.5)
No, n (%)	147 (53.5)
Treatment	
Treatment-naïve, n (%)	137 (49.8)
Previously treated, n (%)	138 (50.2)
Age years	
<65, n (%)	56 (20.4)
≥65 to <75, n (%)	101 (36.7)
≥75 to <85, n (%)	94 (34.2)
≥85, n (%)	24 (8.7)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status

<table>
<tr>
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<td>Source: Garassino 2021[50]
Table 14. Efficacy results – VISION Cohort A and Cohort C (1 February 2021 cut off)
<table>
<tr><th>Efficacy IRC</th><th><75 years</th><th>≥75 years</th></tr>
<tr><th></th><th>N=157</th><th>N=118</th></tr>
<tr><td>Best overall response, n (%)</td><td></td><td></td></tr>
<tr><td>CR</td><td>0</td><td>0</td></tr>
<tr><td>PR</td><td>82 (52.2)</td><td>53 (44.9)</td></tr>
<tr><td>SD</td><td>35 (22.3)</td><td>36 (30.5)</td></tr>
<tr><td>PD</td><td>21 (13.4)</td><td>13 (11.0)</td></tr>
<tr><td>NE</td><td>19 (12.1)</td><td>16 (13.6)</td></tr>
<tr><td>ORR, % (95% CI)</td><td>52.2 (44.1, 60.3)</td><td>44.9 (35.7, 54.3)</td></tr>
<tr><td>DCR, % (95% CI)</td><td>74.5 (67.0, 81.1)</td><td>75.4 (66.6, 82.9)</td></tr>
<tr><td>Median duration of response, % (95% CI)</td><td>12.4 (9.5, 32.7)</td><td>13.8 (9.0, NE)</td></tr>
<tr><td>Median progression free survival, % (95% CI)</td><td>11.0 (8.2, 13.7)</td><td>10.4 (8.2, 13.7)</td></tr>
</table>
Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DCR, duration of complete response; NE, not evaluable; ORR, objective response rate; PD, progressed disease; PR, partial response; SD, stable disease</td>
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<tr>
<td>Additional issue 3: MHRA Conditional</td>
<td>No specific location</td>
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<td>Specific Obligations in the MHRA Conditional Marketing Authorisation for tepotinib

The Specific Obligations in the MHRA Conditional Marketing Authorisation will provide more detailed</td>
<td>The ERG have nothing further to add.</td>
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marketing authorisation			information on the upcoming VISION data cuts and real-world studies planned by Merck. This will help to inform the upcoming data for tepotinib and other studies for patients with METex14 skipping alterations, which could potentially resolve areas of uncertainty in the submission. This is described below in detail: 1. **Specific Obligation 1:** The Marketing Authorisation Holder (MAH) should submit the final clinical study report of the VISION Study, including clinical efficacy data of NSCLC-METex14 patients enrolled in Cohort A and Cohort C. Due date December 2023. 2. **Specific Obligation 2:** In order to contextualise and strengthen efficacy and safety results from tepotinib assessed in VISION Cohorts A+C, the MAH should submit outcomes of the non-interventional study, Study MS200095-0048: External control study using ENSURE data to contextualize and strengthen efficacy and safety results of tepotinib as assessed in the VISION trial. Due date Q4 2025. 3. **Specific Obligation 3:** In order to compare the effectiveness and safety in patients treated with tepotinib and patients treated with other available therapies in the real-world clinical care setting, the MAH should submit outcomes of the non-intervention study, Study MS200095-0049, a	

			registry-based study to compare the effectiveness and safety of tepotinib to other treatment options available in Europe for patients with non-small cell lung cancer (NSCLC) harbouring MET Exon 14 skipping alterations. Due date Q1 2028. The VISION study is ongoing, with expected primary completion date in December 2021. Subsequent data cuts are expected to provide additional PFS and OS data, for Cohort A + C, with ongoing follow-up expected post study completion to allow more mature OS data to be captured, with study completion expected in February 2023. Evidence will be provided by results from the: 1. VISION trial 2. Independent confirmation of Cohort A results by Cohort C results 3. Large and comprehensive dataset derived from Cohorts A + C to provide precise estimates of efficacy endpoints including OS for 1L advanced NSCLC patients. The clinical dataset that the VISION trial will provide at the time of final reporting will consist of at least 313 advanced NSCLC patients with tumours harbouring METex14 alterations. This includes 152 patients enrolled in Cohort A who will have a follow-up of at least 33 months from start of tepotinib treatment. Moreover, at least 150 patients enrolled by 31 March 2021 into the	

			independent Cohort C are complementing the large clinical dataset of the VISION trial. These Cohort C patients will have a follow-up of at least 18 months from start of therapy. Merck will also prospectively collect data through a newly set-up multi-national disease registry (known as ENSURE), as part of the EU Conditional Marketing Authorisation (CMA) being assessed by the EMA. The data collected in the registry would include biomarker data, patient characteristics, clinical characteristics, treatment exposure, clinical outcomes and safety data, for patients with NSCLC harbouring METex14 skipping alterations. Using this disease registry, Merck will run two non-interventional studies: 1. Study MS200095-0048: Provide an external control to contextualise and strengthen efficacy and safety of tepotinib as assessed in VISION Cohort A+C. Final study report: Q4 2025. 2. Study MS200095-0049: Compare effectiveness and safety in patients treated with tepotinib and patients treated with other available therapies in the real-world clinical care setting. Final study report: Q1 2028.	

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Key Issue 13	Vinorelbine incorrectly classified as vinorelbine + platinum in the real-world cohort treatment distributions for the overall population	This has been corrected to 'vinorelbine monotherapy'. Please note that this only impacts the chemotherapy arm within the overall population. All other results presented within the ERG report are correct.	£19,781 (+£269)
Company's preferred base case following technical engagement	Incremental QALYs: [redacted]	Incremental costs: [redacted]	£19,781 (+£269)

Table 15: Corrected base case fully incremental analysis – overall population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)	Incremental ICER (extended dominance)
Chemotherapies	[redacted]	[redacted]				
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£19,781	£19,781
Immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	Strictly dominated

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

Table 16: Corrected base case pairwise results – overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NMB [a]
Tepotinib	[redacted]	2.85	[redacted]					
Chemotherapy	[redacted]	1.99	[redacted]	[redacted]	0.86	[redacted]	£19,781	£12,663
Immunotherapy	[redacted]	2.84	[redacted]	[redacted]	0.00	[redacted]	Dominant	£22,267

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMB, net monetary benefit; QALYs, quality-adjusted life years
Notes: [a] Willingness-to-pay threshold is £30,000 versus immunotherapy and £50,000 versus chemotherapy

Appendix: Comparison of best fitting models versus Merck selected model

Figure 17: Tepotinib OS: best fitting versus selected models – overall population

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; KM, Kaplan-Meier; OS, overall survival

Figure 18: Chemotherapy OS: best fitting versus selected models – overall population

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; KM, Kaplan-Meier; OS, overall survival

Figure 19: Chemotherapy PFS: best fitting versus selected models – overall population

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

Figure 20: Immunotherapy OS: best fitting versus selected models – overall population

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; KM, Kaplan-Meier; OS, overall survival

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in collaboration with:

Newcastle University

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

Additional Commentary on Subsequent Treatment

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

Authors
Jeremy Howick, Reviews Manager, KSR Ltd, United Kingdom (UK)
Bram Ramaekers, Health Economist, Maastricht University Medical Center+ (UMC+), the Netherlands
Thomas Otten, Health Economist, Maastricht UMC+, the Netherlands
Edyta Ryczek, Systematic Reviewer, KSR Ltd, UK
Debra Fayter, Systematic Reviewer, KSR Ltd, UK
Sean Harrison, Statistician, KSR Ltd, UK
Charlotte Ahmadu, Health Economist, KSR Ltd, UK
Lisa Stirk, Information Specialist, KSR Ltd, UK
Robert Wolff, Managing Director, Kleijnen Systematic Reviews Ltd, UK
Manuela Joore, Health Economist, Maastricht UMC+, the Netherlands
Jos Kleijnen, Director, KSR Ltd, UK

Correspondence to Robert Wolff, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, United Kingdom
YO19 6FD

Date completed 13/12/2021

This document provides additional commentary on subsequent treatment and how it is used in the company model. The total undiscounted cost associated with subsequent treatment in the model was [redacted] for tepotinib and [redacted] for chemotherapy. The total discounted cost associated with subsequent treatment in the model was [redacted] for tepotinib and [redacted] for chemotherapy.

The distribution of subsequent treatments was different across the comparators, and the percentage of patients who had at least one subsequent treatment differed. There was significantly higher use of subsequent treatment for chemotherapy ([redacted]) than for tepotinib ([redacted]), and greater use of subsequent treatment for tepotinib than immunotherapy ([redacted]).

The issues associated with subsequent treatment include: (1) generalisability to UK setting, (2) data quality, (3) plausibility of increased use of subsequent treatment for chemotherapy, (4) implementation in model, (5) the effect on the ICER.

1. Generalisability to UK setting

The single-arm trials were not conducted in the UK. The company clinical experts estimated different distributions of treatments that may be used in the UK.

2. Data quality

The company reported in the CS that it was not clear in the real world data sets if the subsequent treatments listed were combination treatments, or second or third-line treatments. The company costed one instance of every drug listed as an individual treatment. Time on treatment assumptions were made for each of these.

3. Possible explanations for greater use of subsequent treatment for chemotherapy

Four possible explanations for increased use of subsequent treatment for chemotherapy include: (a) differences in clinical practice across trials, (b) possible greater percentage of patients with progressed disease with chemotherapy, (c) lower use of subsequent treatment following disease progression for tepotinib, (d) different treatment stopping rules. The relative contribution of these possible explanations to the differences in subsequent treatment cost is not clear to the ERG.

(a) The single-arm trials were conducted in different countries. Differences in the use and distribution of subsequent treatments may be related to different clinical practice in the different settings of the trials.

(b) The NICE treatment pathways suggest that most subsequent treatment is delivered after progression. If we can assume that is the case then higher use of subsequent treatment for chemotherapy than tepotinib could possibly be partly explained by a greater proportion of patients that may enter the progressed state following chemotherapy than following tepotinib: time to progression or death is significantly less for chemotherapy than tepotinib, yet the time to death is not significantly different between the two. Greater progression with chemotherapy than tepotinib would require a greater proportion of patients dying while progression-free for tepotinib than for chemotherapy. Equal mortality hazard rate curves while progression-free across comparators would

result in a greater number of deaths while progression-free for the treatment with a longer average time to progression (and by extension, time to progression or death), and tepotinib has a longer average time to progression or death. No evidence specifically on the hazard rates of progression (or % progressed) or specifically on the hazard rates of mortality while progression-free (or % died while progression-free) was provided in the CS as the company only estimated progression-free survival (PFS) and overall survival (OS). The company developed a partitioned survival model rather than a Markov model. Note that all but 1% of tepotinib patients had progressed or died after 11 years and every patient had progressed or died after 28 years.

(c) An increased time to progression or death with tepotinib compared to chemotherapy but little difference in overall survival may mean that patients at disease progression are less fit for subsequent treatment for tepotinb than for chemotherapy.

(d) If in fact some subsequent treatment may be given prior to progression then some of the difference could be explained by the different stopping rules. Except for disease progression and adjustments for adverse effects, there is no time limit for stopping tepotinib, the time limit is long (2 years) for immunotherapy, and a maximum of 6 3-week cycles in assumed for chemotherapy.

4. Implementation in model

A single cost of subsequent treatment is assigned to the patients that leave the PFS state every cycle. Over the duration of the running period of the model, effectively every patient is assigned the cost. This is equivalent to assigning the cost at the point that a patient either progresses or dies. This is consistent with the estimate of subsequent treatment use from the trials which are an average across all patients in the trials, adjusted using propensity score matching.

5. Effect on ICER

The company conducted a scenario analysis incorporating the UK practice treatment distribution in order to address the generalisability to the UK issue. The results from the company analysis and from the ERG analysis using the ERG survival model assumptions without comparator PAS/CMU prices for comparators are presented in Table 1.

The degree to which differences in stopping rules, differences in progression/mortality risk while progression-free and differences in patient characteristics at progression explain greater use of subsequent treatment in the chemotherapy evidence than in the tepotinib evidence is unknown. It is possible that differences in clinical practice across single-arm trials may partly explain the differences. The ERG has now conducted for this document an analysis making a strong assumption that subsequent treatment would be equal across first-line treatment groups. This was done assuming the subsequent treatment distribution from the chemotherapy trial data, and also assuming the UK practice subsequent treatment distribution. The results without comparator PAS/CMU prices for comparators are presented in Table 1. The results with comparator PAS/CMU prices for comparators are presented in Table 1.

Making the assumption of equal subsequent treatment across first-line treatment has roughly the same effect on the ICER as making the assumption of specific UK practice subsequent treatment distributions following chemotherapy and immunotherapy.

Table 1Error! No text of specified style in document.1: Pairwise ICERs for tepotinib versus immunotherapy and chemotherapy (without PAS/CMU comparator prices) Error! No text of specified style in document.

Analysis	Technologies	ICER (tepotinib vs comparator)	
		ERG	Company
Base-case	Immunotherapy	[redacted]	[redacted]
	Chemotherapy	[redacted]	[redacted]
Subsequent Treatment has a UK based distribution	Immunotherapy	[redacted]	[redacted]
	Chemotherapy	[redacted]	[redacted]
Equal subsequent treatment distribution using the chemotherapy trial data	Immunotherapy	[redacted]	[redacted]
	Chemotherapy	[redacted]	[redacted]
Equal subsequent treatment distribution using the chemotherapy UK expert opinion data	Immunotherapy	[redacted]	[redacted]
	Chemotherapy	[redacted]	[redacted]
Source: ERG calculated from company model			

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Addendum to ERG Report

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

Authors
Jeremy Howick, Reviews Manager, KSR Ltd, United Kingdom (UK)
Bram Ramaekers, Health Economist, Maastricht University Medical Center+ (UMC+), the Netherlands
Thomas Otten, Health Economist, Maastricht UMC+, the Netherlands
Edyta Ryczek, Systematic Reviewer, KSR Ltd, UK
Debra Fayter, Systematic Reviewer, KSR Ltd, UK
Sean Harrison, Statistician, KSR Ltd, UK
Charlotte Ahmadu, Health Economist, KSR Ltd, UK
Lisa Stirk, Information Specialist, KSR Ltd, UK
Robert Wolff, Managing Director, Kleijnen Systematic Reviews Ltd, UK
Manuela Joore, Health Economist, Maastricht UMC+, the Netherlands
Jos Kleijnen, Director, KSR Ltd, UK

Correspondence to Robert Wolff, Kleijnen Systematic Reviews
Unit 6, Escrick Business Park
Riccall Road, Escrick
York, United Kingdom
YO19 6FD

Date completed 22/12/2021

The company provided an updated economic model as part of the technical engagement response (TE model). This model differed from the model provided as part of the company response to the Letter of Points for Clarification (PfC model) in that the initial treatment distribution for chemotherapy for the Overall population was slightly different due to misclassification of Vinorelbine as vinorelbine + platinum. The results in the ERG report were obtained using the PfC model. The results for the base case company and ERG analyses using the TE model are presented in Table 1.

In addition, this document provides both the deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) for three analyses included in the ERG report. The deterministic ICERs for these analyses were close to either a £30,000 or a £50,000 threshold. The results are presented in Table 2.

The CS model was designed with a maximum of 1000 iterations that could be used in the probabilistic sensitivity analyses (PSA). When the ERG first tested the PSA results the company base case model was used and the sampling error did not appear too large. However, when running the model using the ERG survival model selections, the sampling error appeared to be much greater. Consequently, the ERG edited a CS model to run 8000 iterations. This was done by changing the numbers in the 'inc_PSA' macro and editing the formulae in row 49 in the PSA sheet. Note that there will still be some sampling error with 8000 iterations. With 8000 iterations the model took more than an hour to run. The model edited was the model provided by the company in response to the PfCs which enabled probabilistic sensitivity analysis with incremental cost-effectiveness analysis: ID3761 Tepotinib alterations CE Model additional updates 27082021KM (ACIC).

Table 1: ERG base-case full incremental results for overall population and the company base-case ICER (corresponds to Table 6.9 in the ERG report)

Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)	Company base-case ICER (£/QALY)
Chemotherapy	[redacted]		2.45		[redacted]			
Tepotinib	[redacted]	[redacted]	2.85	0.40	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	2.02	-0.83	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Table 2: Deterministic and probabilistic ICERs for three scenario analyses with deterministic results close to either the £30,000/QALY or £50,000/QALY thresholds

Analysis	Population	Next best (not dominated) comparator	ICER (£/QALY)	
			Deterministic	Probabilistic
ERG model	Overall	Chemotherapy	[redacted]	[redacted]
CS model	Untreated	Chemotherapy	[redacted]	[redacted]
CS model	Treated	Immunotherapy	[redacted]	[redacted]
ERG: Evidence Review Group; CS: company submission; CMU: Commercial Medicines Unit Source: calculated from company model				