NICE National Institute for Health and Care Excellence

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

Lead team presentation

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Company: Merck

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Key issues

Model driver

Unknown impact

Small/Moderate impact

Issue	ICER impact	Resolved?
1. Appropriateness of subgroup analysis (ERG issues 2, 8 & 15)		No
2. Analysis by treatment class rather than individual comparators (ERG issue 9)		No
3. Selection of survival curves (ERG issue 10)		No
4. Selection of time on treatment model for tepotinib (ERG issue 12)		No
5. Subsequent treatment distribution and costs (ERG issue 14)		No
6. Cohort A versus Cohort A + C (ERG issue 3)		No

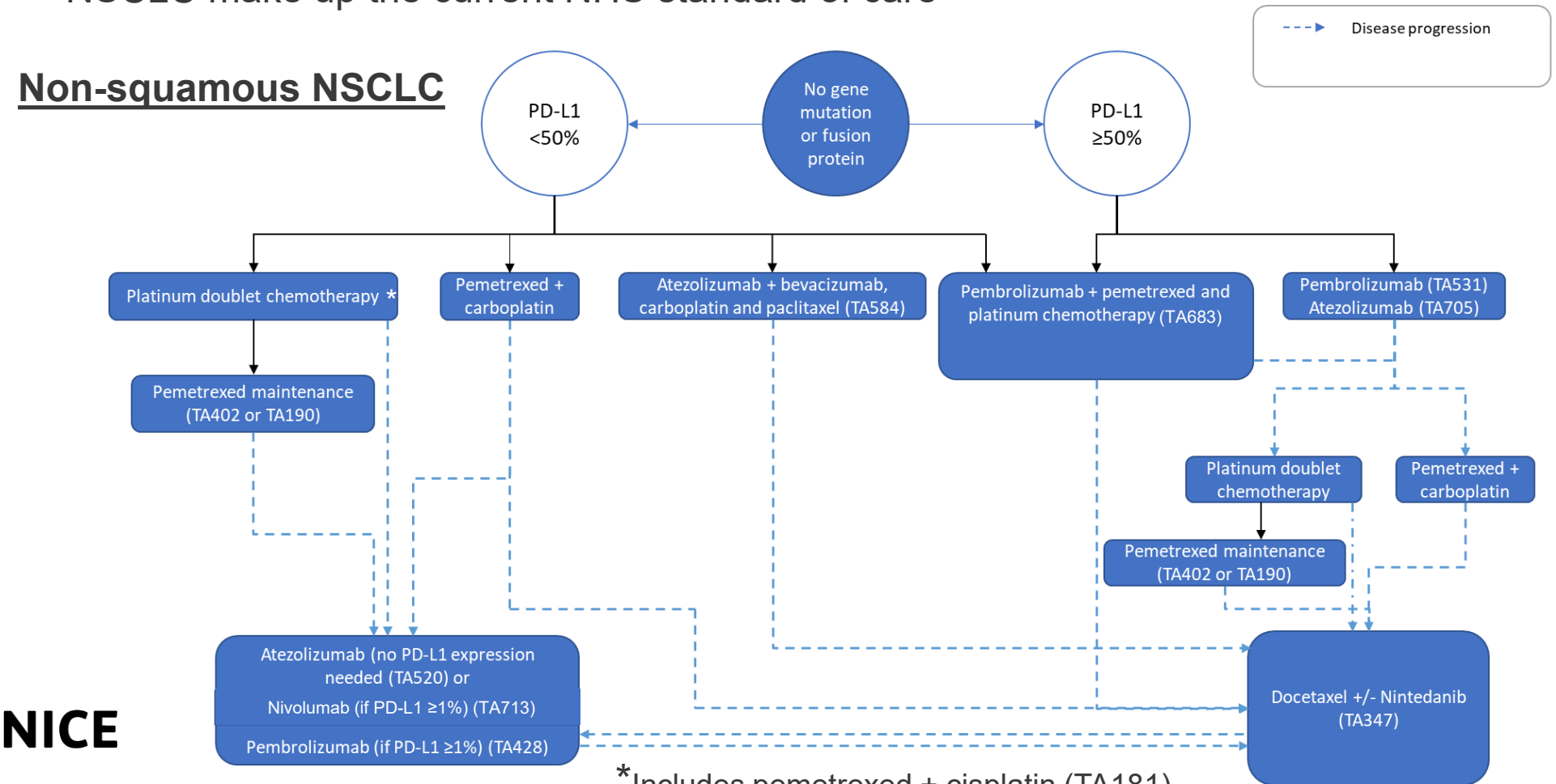
NSCLC: Disease overview

- More than 47,000 people are diagnosed with lung cancer each year in the UK, and there are over 35,000 deaths
- 48% of lung cancers in England are stage 4 (metastatic) at diagnosis. 5-year survival at stage 4 is around 3%
- 80 to 85% of lung cancer cases are non-small cell lung cancer (NSCLC). There are 2 major histological subtypes of NSCLC:
  - Squamous cell carcinoma (25 to 30% of cases)
  - Non-squamous cell carcinoma: comprises adenocarcinoma (40% of cases) and large cell carcinoma (10 to 15% of cases)
- Several biomarkers used in the NHS, including PD-L1, EGFR, ALK and ROS1
- METex14 skipping is an oncogenic driver by activating MET, a receptor tyrosine kinase. These alterations account for around 3% of NSCLC cases. 79% of METex14 skipping is in adenocarcinomas; 3% in squamous histology
- METex14 skipping NSCLC more likely to be PD-L1 positive. METex14 skipping alterations mutually exclusive to other oncogenic drivers (e.g., EGFR, ALK, ROS1)
- People with METex14 skipping NSCLC tend to have a poorer prognosis than people without this biomarker. They tend to be older than other oncogenic driven NSCLC subpopulations. Treating this population is challenging, further impacted by comorbidities and overall frailty

Key: ALK = Anaplastic lymphoma kinase; EGFR = Epidermal growth factor receptor; METex14 = Mesenchymal-epithelial transition gene exon 14; PD-L1 = Programmed death-ligand 1; ROS1 = C-ros oncogene 1

Current treatment pathway: non-squamous advanced NSCLC (no driver mutations)

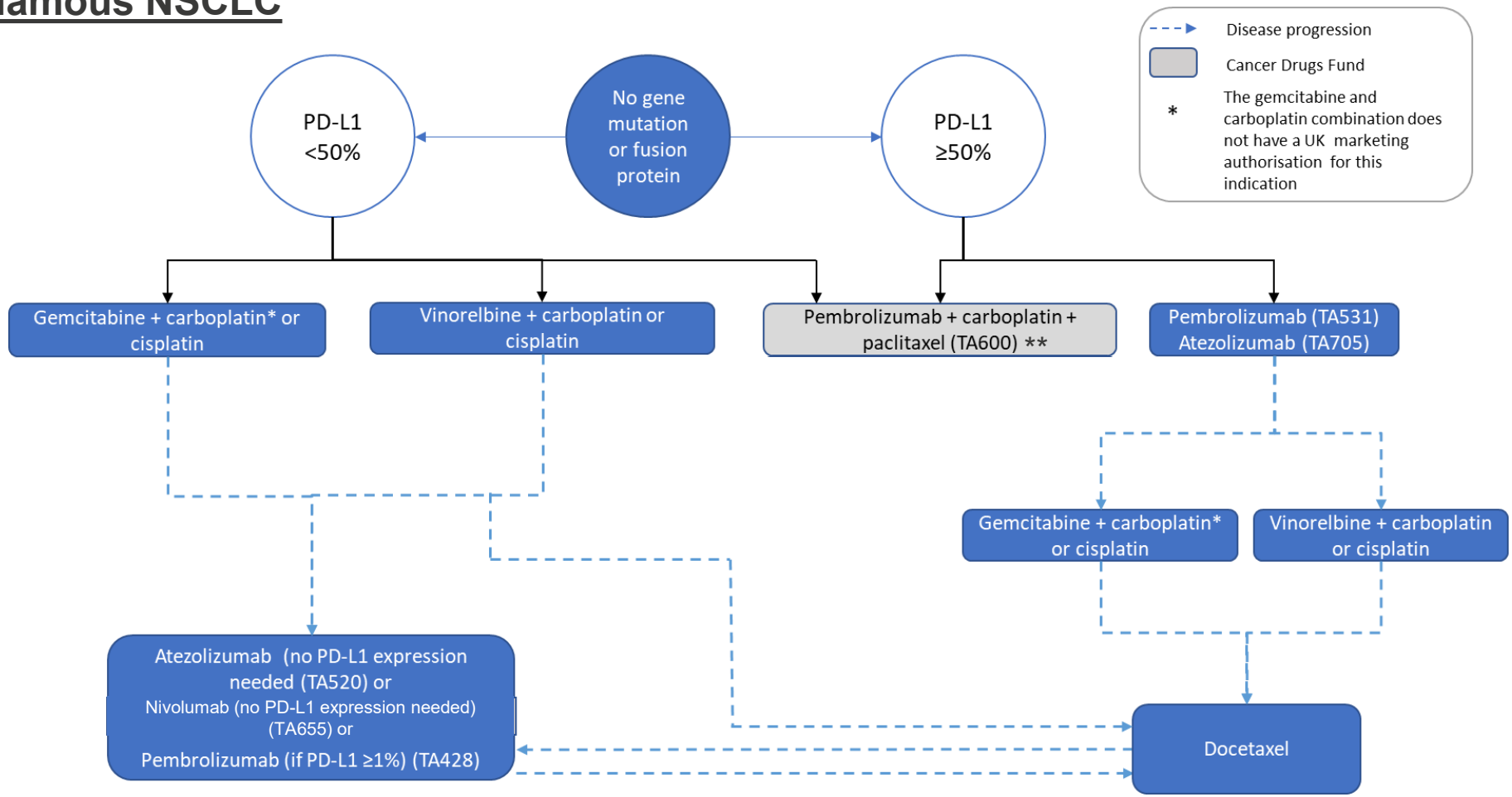
- There is no defined pathway specific for METex14 skipping NSCLC, reflecting that there are no agents licensed and routinely commissioned in the UK
- Treatments currently used for patients without any identifiable biomarkers in advanced NSCLC make up the current NHS standard of care



*Includes pemetrexed + cisplatin (TA181)

Current treatment pathway: squamous advanced NSCLC (no driver mutations)

Squamous NSCLC



** TA600 has recently been removed from CDF and is now recommended.

Clinical and patient perspectives

British Thoracic Oncology Group; Newcastle upon Tyne Hospitals NHS Foundation Trust, Roy Castle Lung Cancer Foundation

- Unmet need: no treatments in UK specific for METex14 skipping mutation
- People with oncogene driven lung cancers tend to have a lower response rate to immunotherapy
- People with METex14 skipping mutations are characterised by being older, with more aggressive disease and a worse prognosis: median overall survival is 6.7 months compared to 11.2 months for those without METex14 (Gow et al. 2017)
- Tepotinib would become a fundamental part of the treatment paradigm for patients with METex14 NSCLC
- Tepotinib ideally used as a first-line therapy, in place of current chemotherapy and immunotherapy options
- Reduced burden on both patients and oncology clinics: oral therapy so would not require day-unit attendance. Tepotinib would be given in 4-weekly cycles, compared with 3-weekly for intravenous chemotherapy or chemo-immunotherapy
- Older population (comorbidities and frailty) would benefit from an oral therapy
- Favourable side effect profile of tepotinib compared to chemo-immunotherapy. Peripheral oedema is the most commonly reported serious side effect

Tepotinib (Tepmetko, Merck)

Description of technology	Selective, potent, reversible small-molecule inhibitor of MET tyrosine kinase (the receptor of hepatocyte growth factor), which is encoded by the MET proto-oncogene. It has antitumour activity in tumours with oncogenic alterations of MET, such as METex14 skipping alterations and MET amplification
Marketing authorisation (granted September 2021)	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
Administration	• Each tablet contains 225 mg tepotinib • The recommended dose is 450 mg tepotinib (2 tablets) taken once daily (equivalent to 500 mg tepotinib hydrochloride hydrate) • Tepotinib is taken until disease progression or undue toxicity
Price (list price)	List price: £[redacted] for 60 x 250 mg tablets (equivalent to a 1-month dose) Annual cost of treatment = £[redacted] A confidential Patient Access Scheme (PAS) has been agreed

Decision problem

	NICE scope	Company submission	ERG comment
Population	Adults with advanced METex14 skipping NSCLC	As per scope	Should be clarified that population is stage 3b-4 excluding ALK+ and EGFR+
Intervention	Tepotinib	As per scope	In line with scope
Comparators	Chemo-immunotherapies, split by: • Untreated or treated • Histology (squamous or non-squamous) • PD-L1 tumour proportion score (TPS) (above or below 50%)	2 grouped comparators: • Chemotherapy • Immunotherapy Omitted comparators: • Pembrolizumab + carbopac, as in CDF • Nivolumab + ipilimumab • Best supportive care Subgroup analysis presented for untreated and treated	• Agrees with omitted comparators • Unclear why atezolizumab monotherapy not included as a comparator for squamous NSCLC with PD-L1 above 50%; likely a typo • Lack of appropriate subgroup analysis is serious issue
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects • HRQoL	As per scope	In line with scope

Issue 1: Lack of subgroup analyses (1)

Background:

- NICE scope splits comparators into untreated and treated subgroups, further divided by histology (squamous and non-squamous) and PD-L1 tumour proportion score (above or below 50%)

Company

- Comparison by PD-L1 status not possible because PD-L1 status not collected in VISION, and limited reporting of PD-L1 in real-world cohort
- Base case is line-agnostic population regardless of histology
- Subgroup analyses presented for untreated and previously treated groups
- If MET alteration, would be offered tepotinib regardless of PD-L1 status and histology
- Subgroup analyses by histology not done because:
  1. patient numbers to provide effectiveness evidence would be too small
  2. clinical experts stated results should be generalisable across histology groups
- ERG's suggested subgroups are not true subgroups, same patient data used for each, only comparators change in economic model
- Majority in VISION trial and the real-world cohort had adenocarcinoma. Subgroup analysis would be possible, but not considered relevant by clinical experts
- Analysing squamous and non-squamous patients together accepted in recent NICE submission of selpercatinib for RET fusion-positive advanced NSCLC

Issue 1: Lack of subgroup analyses (2)

ERG

- Recognises limitations of the data, but not differentiating according to subgroups might disguise a variation in treatment effect and cost effectiveness
- Could be reasonable to conclude that the evidence as currently presented is most appropriate to inform a decision regarding patients with adenocarcinoma only
- Relevant comparators differ according to untreated or treated status, and by PD-L1 tumour proportion score
- Agree effectiveness evidence relevant to subgroups in decision problem not available
- Decisions need to be made for these subgroups using the best available evidence for the relevant comparator

Clinical experts:

- Dominant histology will be non-squamous lung cancer and appropriate to restrict appraisal to that
- Advocate presenting results by PD-L1 status
- Unlikely to be a meaningful difference in individual treatments in UK clinical practice

Q. Are the subgroup analyses presented appropriate for decision making?

VISION trial design

An ongoing open-label, single-arm, non-randomised trial

Population	• Adults with locally advanced or metastatic NSCLC (all histological types) with MET alterations • ECOG PS 0 or 1 • Either untreated or previously treated (up to 2 lines of prior therapy) • EGFR activating mutations and ALK rearrangements excluded
Cohorts	• **Cohort A**: METex14 skipping alterations (n=152) • Cohort B: MET amplification (not relevant to decision problem) • **Cohort C**: confirmatory cohort for METex14 skipping alterations (n=123)
Intervention	Tepotinib
Comparator	N/A (single-arm trial)
Outcomes (bold indicates those used in the economic model, from Cohort A)	• Objective response rate (ORR, primary outcome) • Duration of response (DOR) • Objective disease control • **Progression-free survival (PFS)** • **Overall survival (OS)** • **EQ-5D-5L** • EORTC QLQ-C30 • EORTC QLQ-LC13 • **Safety**
Study locations	Europe (51%), North America (26%) and Asia (23%). No UK centres

VISION – Key results

Cohort A: used in economic model (February 2021 cut off):

	Overall	First line	Second line +
N	[redacted]	[redacted]	[redacted]
ORR, % (95% CI)	[redacted]	[redacted]	[redacted]
Median DOR, months (95% CI)	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]
People with OS event, n (%)	[redacted]	[redacted]	[redacted]

Cohorts A + C (February 2021 cut off):

	Overall	First line	Second line +
N	[redacted]	[redacted]	[redacted]
ORR, % (95% CI)	[redacted]	[redacted]	[redacted]
Median DOR, months (95% CI)	[redacted]	[redacted]	[redacted]
Median PFS, months (95% CI)	[redacted]	[redacted]	[redacted]
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]
People with OS event, n (%)	[redacted]	[redacted]	[redacted]

Key: NE = not estimable, DOR = duration of response, ORR = objective response rate, PFS = progression-free survival, OS = overall survival, CI = confidence interval

Issue 6: Selection of VISION analysis dataset

Company:

- Used Cohort A for analysis instead of Cohort A+C because patient-level data for Cohort C only available shortly before submission
- Patient characteristics and outcomes very similar between Cohort A and Cohort A+C
- Does not anticipate indirect treatment comparison (ITC) or cost-effectiveness results would differ much if Cohort A+C used in analysis
- Minor improvement in median OS and lower median time on treatment for Cohort A+C, but expect any change in ITC results would likely favour tepotinib

ERG:

- Agrees that the results for Cohort A are similar to those for Cohort A+C
- Also that OS is better for Cohort A+C, so more likely that tepotinib cost effective
- Would still recommend the use of the data from Cohort A+C for all analyses because could be deciding factor in whether cost effective or not

Clinical experts:

- Agree that due to similarity in cohorts, A+C should be used for the ITC

Q. Are results based on Cohort A acceptable for decision making?

PFS and OS KM curves: Cohort A vs Cohorts A+C

Progression-free survival
(February 2021 cut off)

Overall survival
(February 2021 cut off)

Comparator real-world cohort – 4 data sources

- No head-to-head data available for tepotinib versus scope comparators. No comparator clinical trial data specifically in METex14 NSCLC
- Patient-level data for METex14 NSCLC available from:
  - 3 non-interventional studies done by Merck: NIS-0015, NIS-0035 and COTA
  - British Columbia, Canada, made available by authors Wong et al. (2021)

Study	Description
NIS-0015	Electronic Medical Records (US database). Complete data on 39 patients with MET alterations. Large number of patient characteristics captured. Outcomes include PFS, OS, and response rate
NIS-0035	Electronic Medical Records (multiple countries, not UK). Data on 86 patients harbouring a MET alteration. Large number of patient characteristics captured. Outcomes did not include response rates or PFS (Time to Next Treatment or Death used as proxy for PFS)
COTA	Real-World Evidence (RWE) database (US and Canada). 202 complete patient records were available with at least 1 data point. OS available, PFS calculated from information available in the dataset
Wong et al. (2021)	Based on retrospective review of treatments and outcomes for 41 people with METex14 skipping alterations in Canada. OS available, PFS calculated from duration of treatment

Indirect treatment comparison - method

- Company did an ITC for OS and PFS from its real-world cohort. Patient-level data was preferred option, for more robust matching of patient cohorts. Patient numbers too small to compare tepotinib with individual comparators, so company did 2 main comparisons:
    1. VISION versus immunotherapy
    2. VISION versus chemotherapy
- This approach accepted in NICE TA531 (NSCLC) and other oncology submissions
- Inclusion/exclusion criteria as per the VISION trial were applied to the real-world patient data to form a comparable dataset
- Base-case ITC assumes line-agnostic population, regardless of histology
- Some patients had multiple lines of treatment – only 1 randomly selected line used per patient within each analysis
- To adjust for possible confounding, propensity scoring used to achieve balance of patient characteristics between tepotinib and comparators
- Only 5 patients had immunotherapy with chemotherapy in real-world cohort, so OS & PFS derived by applying a hazard ratio (from KEYNOTE-189) to each of the curves with chemotherapy only estimated using the ITC
- Unanchored matching-adjusted indirect comparison (MAIC) analyses also done using 3 published studies in the METex14 skipping population. ERG and company agreed that propensity scoring method more robust

Comparator real-world cohort – treatment mix

- 66 chemotherapy-treated patients and 51 immunotherapy-treated patients were available to conduct the primary indirect treatment comparison with the tepotinib VISION data
- Treatment mix scenario analysis informed by clinical opinion based on UK clinical practice

Category	Treatment	Real-world data (base case)	Clinical opinion (scenario)
Immunotherapy (n=51)	Pembrolizumab	[redacted]	66.3%
	Atezolizumab	[redacted]	21.7%
	Nivolumab	[redacted]	12.0%
	Nivolumab + ipilimumab	[redacted]	0.0%
Chemotherapy (n=66)	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%

a Treatments not listed within NICE final scope but incorporated within efficacy and so costed for

ITC results – all patients

	Tepotinib (n=151)	Immunotherapy (n=51, ESS=150)	Chemotherapy (n=66, ESS=152)
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]

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)

ITC results – untreated versus treated

Untreated

	Outcomes	Tepotinib (n=69)	Immunotherapy (n=20, ESS=69)	Chemotherapy (n=49, ESS=68)
OS	Median, months (95% CI)	[redacted]	[redacted]	[redacted]
	RMST, months	[redacted]	[redacted]	[redacted]
	HR versus tepotinib (95% CI)	[redacted]	[redacted]	[redacted]
	p-value	[redacted]	[redacted]	[redacted]
PFS	Median, months (95% CI)	[redacted]	[redacted]	[redacted]
	RMST, months	[redacted]	[redacted]	[redacted]
	HR versus tepotinib (95% CI)	[redacted]	[redacted]	[redacted]
	p-value	[redacted]	[redacted]	[redacted]

Previously treated

	Outcomes	Tepotinib (n=82)	Immunotherapy (n=32, ESS=80)	Chemotherapy (n=34, ESS=80)
OS	Median, months (95% CI)	[redacted]	[redacted]	[redacted]
	RMST, months	[redacted]	[redacted]	[redacted]
	HR versus tepotinib (95% CI)	[redacted]	[redacted]	[redacted]
	p-value	[redacted]	[redacted]	[redacted]
PFS	Median, months (95% CI)	[redacted]	[redacted]	[redacted]
	RMST, months	[redacted]	[redacted]	[redacted]
	HR versus tepotinib (95% CI)	[redacted]	[redacted]	[redacted]
	p-value	[redacted]	[redacted]	[redacted]

Key: CI = confidence interval; RMST = restricted mean survival time; HR = hazard ratio; ESS = effective sample size

Progression-free survival – comparators (all patients)

Chemotherapy

Immunotherapy

Overall survival – comparators (all patients)

Chemotherapy

Immunotherapy

Issue 2: No analyses considered using individual treatment comparators

Company:

- Because of limited data available to model specific treatments, chosen comparators were immunotherapy, chemotherapy, and combined immuno-chemotherapy
- Grouped comparators have been used in previous appraisals, and advisory board experts considered that treatments within class have similar outcomes
- Assumptions of treatment distributions within each class to calculate treatment costs
- Largest group is pembrolizumab, but still too small for meaningful comparison
- Any individual comparison would be extremely uncertain, and unlikely to meaningfully inform the decision problem. Analysis by line of therapy would not be possible
- Grouping the immunotherapies and chemotherapy treatments allowed for larger datasets to be used, and therefore increasing the robustness of the comparisons

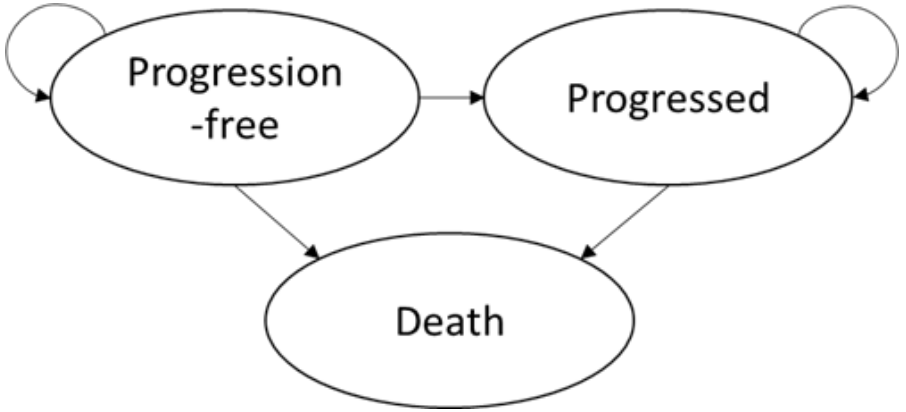
ERG:

- Agree could only feasibly be done for pembrolizumab and carboplatin+pemetrexed
- Agree analysis could only be conducted in a line-agnostic population
- Advantage would be that cost-effectiveness of tepotinib compared to commonly used UK treatments could be evaluated

Q. Is analysis by grouped treatment class appropriate for decision making?

Company's model structure

- Partitioned survival, 3 health states (progression-free, progressed, death)
- 7-day cycle length to capture various dosing regimens included within the model, consistent with other appraisals in NSCLC. No half-cycle correction



Parameter	Source
Tepotinib efficacy and safety	From VISION
Comparator efficacy	• Immunotherapy: from real-world cohort • Chemotherapy: from real-world cohort • Immunotherapy with chemotherapy: not enough patients in real-world cohort (not used in base case model)
Comparator safety	NICE NSCLC appraisals, published literature
Utility values	Derived from the VISION EQ-5D-5L data (mapped to 3L).
Costs	From published literature, from resource utilisation and costs used in previous NSCLC submissions

ERG: Lack of justification for partitioned survival model: state-transition model has potential benefits

Issue 3: Potential bias in selection of survival curves for the comparators

Company:

- To extrapolate PFS and OS beyond data collection period, Kaplan-Meier curves from VISION trial data (for tepotinib) and real-world data (for comparators) were produced
- Different parametric survival models were fitted to the individual patient data
- Goodness of fit statistics, visual assessment, and expert opinion on clinical plausibility of the long-term survival profile were considered
- Clinical experts considered that best fitting models under- or over-estimate PFS or OS at 5 years or between 3 and 5 years
- Do not consider any bias to have been introduced by seeking clinical expert opinion
- In response to technical engagement, used external sources for validation (trials in wildtype NSCLC and published real-world studies in METex14 skipping NSCLC)

ERG:

- Considerable uncertainty in the effectiveness of tepotinib compared with immunotherapy and chemotherapy in extending PFS and OS due to single-arm evidence, limited follow-up, possible imperfect matching of real-world and VISION
- Fitting curves independently to each comparator adds to uncertainty
- Agree clinical plausibility important for selection of curves, but could introduce bias
- Produced alternative (but not preferred) scenarios to explore uncertainty
- Comparative efficacy of tepotinib highly dependent on choice of extrapolations

Issue 3: Chemotherapy OS and PFS extrapolations

Chemotherapy survival extrapolations, overall population

Issue 3: Chemotherapy OS curve, comparisons vs clinical data

- KN189: metastatic NSCLC, non-squamous (1L)
- KN24: advanced NSCLC, PD-L1 at least 50% (1L)
- KN010: advanced NSCLC, PD-L1+ (2L+)
- KN42: metastatic NSCLC, PD-L1+ (1L)
- CM057: advanced NSCLC, non-squamous (2L+)
- CM017: advanced NSCLC, squamous (2L+)

NICE

Abbreviations: 1L, first-line; 2L+, second-line plus; OS, overall survival

Issue 3: Chemotherapy PFS curve, comparisons vs clinical data

- KN189: metastatic NSCLC, non-squamous (1L)
- KN24: advanced NSCLC, PD-L1 at least 50% (1L)
- KN010: advanced NSCLC, PD-L1+ (2L+)
- KN42: metastatic NSCLC, PD-L1+ (1L)
- CM057: advanced NSCLC, non-squamous (2L+)
- CM017: advanced NSCLC, squamous (2L+)

NICE

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

Issue 3: Immunotherapy OS and PFS extrapolations

Immunotherapy survival extrapolations, overall population

Issue 3: Immunotherapy OS curve, comparisons vs clinical data

- KN24: advanced NSCLC, PD-L1 at least 50% (1L)
- KN010: advanced NSCLC, PD-L1+ (2L+)
- KN42: metastatic NSCLC, PD-L1+ (1L)
- CM057: advanced NSCLC, non-squamous (2L+)
- CM017: advanced NSCLC, squamous (2L+)

NICE

Abbreviations: 1L, first-line; 2L+, second-line plus; OS, overall survival

Issue 3: Survival at landmark timepoints

Technology	Curve	1-yr	3-yr	5-yr	10-yr	20-yr
Company: overall survival (overall population)						
Tepotinib	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	Spline 1-knot normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG: overall survival (overall population)						
Tepotinib	Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	Spline 2-knot normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company: progression-free survival (overall population)						
Tepotinib	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	Split 1-knot odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	Piece-wise log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG: progression-free survival (overall population)						
Tepotinib	Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy	Spline 3-knot odds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	Piece-wise log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

- In TA683, 5-year survival of 5-11% felt to be clinically plausible for comparator arm (pemetrexed platinum chemo in 1L wild-type non-squamous NSCLC)

Q. Which extrapolation is most appropriate for decision making?

Issue 4: Time on treatment model for tepotinib (1)

Company:

- Selected generalised gamma for time on treatment (ToT) for tepotinib
- Exponential model is best fitting model according the Bayesian information criterion (BIC) and log-logistic model is the best fitting model according to Akaike information criterion (AIC)
- Extended tail in the Kaplan Meier plot is likely an artifact of patient censoring. Clinical expert opinion suggests a few patients may receive treatment long-term, but most off treatment by 5 years
- Extended tail means that no curve likely to fit well and also be clinically plausible
- Parametric model options considered sufficient for sensitivity analysis.

ERG:

- Cost effectiveness results are sensitive to choice of time-to-event model. ICER for tepotinib significantly higher with log-logistic (one of statistically best-fitting models)
- Log-logistic distribution possibly over-fits tail-end of data, but only parametric models were tried before technical engagement
- None of the additional spline models provided at technical engagement are better fitting than parametric models according to AIC or BIC statistics
- Company's base case model selection may be most appropriate

Q. Which is the most plausible time on treatment model for tepotinib?

Issue 4: Time on treatment model for tepotinib (2)

[redacted]

Issue 5: Uncertainty in the cost estimates for subsequent treatments

Company:

- Subsequent treatment costs applied in model as a one-off average cost per patient after disease progression
- Subsequent treatments are an area of uncertainty and influenced by countries included in clinical trial and real-world cohorts
- For base case, model uses subsequent treatment distributions from VISION for tepotinib and the real-world cohort for the comparators, matching efficacy and costs
- Provided scenario analyses using UK distributions from clinical expert input, but these only impact costs and not efficacy, so is an unfair comparison
- More appropriate to use treatment distribution based on real-world data set for comparators to maintain relationship between effectiveness and cost outcomes

ERG:

- Cost-effectiveness results sensitive to proportion of patients receiving each of the possible subsequent treatments after progression
- Increased use of subsequent treatments after chemotherapy could be due to a number of factors. The relative contribution of each factor is not clear to the ERG
- Provided scenario analysis with equal subsequent treatments between arms

Q. Are the subsequent treatment costs in the model appropriate?

Subsequent treatments and costs

			Based on trial/RW data			Based on clinician estimates		
Category	Treatment	Total cost (incl. admin. costs)	Tepotinib (VISION) N=151	Immuno (RW cohort data) N=150	Chemo (RW cohort data) N=152	Tepotinib	Immuno	Chemo
Immuno-therapy	Pembrolizumab	£43,336	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Atezolizumab	£20,222	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nivolumab	£37,110	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemo-therapy	Pemetrexed	£14,124	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Vinorelbine	£3,453	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Paclitaxel	£2,274	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Docetaxel	£1,888	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gemcitabine	£3,418	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platinum	Cisplatin	£2,216	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Carboplatin	£1,548	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Targeted	Brigatinib*	£188,267	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Nintedanib	£9,211	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MET inhibitor	Crizotinib*	£106,802	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total weighted cost per progressed patient			**£26,638**	**£34,619**	**£51,616**	**£10,040**	**£3,165**	**£7,441**

* Brigatinib and crizotinib not recommended for use in later lines.

Key issues

Model driver

Unknown impact

Small/Moderate impact

Issue	ICER impact	Resolved?	Resolvable?
1. Appropriateness of subgroup analysis (ERG issues 2, 8 & 15)	Model driver	No	No
2. Analysis by treatment class rather than individual comparators (ERG issue 9)	Unknown impact	No	No
3. Selection of survival curves (ERG issue 10)	Model driver	No	Partially (e.g. CDF)
4. Selection of time on treatment model for tepotinib (ERG issue 12)	Model driver	No	Partially (e.g. CDF)
5. Subsequent treatment distribution and costs (ERG issue 14)	Model driver	No	No
6. Cohort A versus Cohort A + C (ERG issue 3)	Small/Moderate impact	No	Yes

Additional areas of uncertainty

ERG Issue	Description	Impact on ICER
1	Lack of clarity in the population: the population in the decision problem appears to be more specific than advanced disease	N/A
4	Some concern from ERG around lack of justification for trials in ITC, but at technical engagement ERG agreed that company had used all available evidence	N/A
5	Source of adverse event (AE) frequencies initially not justified: from targeted literature search	Minimal
6	Method of adjustment for confounding in the ITC: standardised mortality rate (SMR) approach instead of inverse probability of treatment	Unknown
7	Lack of justification for partitioned survival model: state-transition model has potential benefits	Unknown
11	Representativeness of AE utility values for the UK population	Minimal
13	Uncertainty in the cost estimates for immunotherapy and chemotherapy	Minimal

Summary of company and ERG base cases

The ERG presents an alternative base case with different survival models to those of the company (Issue 3 [ERG issue 10])

Technology	Company		ERG	
	OS	PFS	OS	PFS
Overall population				
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
Untreated population				
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
Treated population				
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

Company base case – overall population

Corrected base case fully incremental analysis – overall population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (strict dominance)
Chemotherapies	[redacted]	[redacted]	-	-	-
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£19,781
Immunotherapies	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Base-case pairwise analysis (deterministic) – overall population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	Tepotinib pairwise deterministic ICER	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

Results include PAS price for tepotinib, but not for comparators or subsequent treatments

a Willingness-to-pay threshold is £30,000 vs immunotherapy and £50,000 vs chemotherapy

NICE

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient access scheme; QALYs, quality-adjusted life years

Company base case – untreated population

Base-case fully incremental analysis (deterministic) - untreated population

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	-
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	£23,354
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£418,982
Immunotherapy + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£36,338

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

Base-case pairwise analysis – untreated population

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	Tepotinib deterministic pairwise ICER	Tepotinib probabilistic pairwise ICER
Tepotinib	[redacted]	[redacted]	[redacted]	[redacted]	-	-
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£23,354	£27,934
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£418,982 (SW)	-
Immunotherapy + chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£186,293 (SW)	-

NICE

Results include PAS price for tepotinib, but not for comparators or subsequent treatments

Company base case – treated population

Base-case fully incremental analysis (deterministic) - 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

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

Base-case pairwise analysis – treated population

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	Tepotinib deterministic pairwise ICER	Tepotinib probabilistic pairwise ICER
Tepotinib	[redacted]	[redacted]	-	-	-	-
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£18,176	-
Immunotherapy	[redacted]	[redacted]	[redacted]	[redacted]	£24,823	£29,360

Results include PAS price for tepotinib, but not for comparators or subsequent treatments

ERG alternative base case

- ERG alternative base-case is not preferred to company's base-case model. Differences in results of 2 models should reflect uncertainty in independent selection of survival models for intervention and comparators based on single arm trial data

ERG base-case fully incremental results for overall population (deterministic)							
Technologies	Cost (£)	Incremental Cost (£)	LY	Incremental LY	QALY	Incremental QALY	ERG base-case ICER (£/QALY)
Chemotherapy	[redacted]	-	2.45	-	[redacted]	-	-
Tepotinib	[redacted]	[redacted]	2.85	0.40	[redacted]	[redacted]	33,349*
Immunotherapy	[redacted]	[redacted]	2.02	-0.83	[redacted]	[redacted]	Dominated
ERG base-case fully incremental results for untreated population (deterministic)							
Chemotherapy	[redacted]	-	3.18	-	[redacted]	-	-
Tepotinib	[redacted]	[redacted]	3.06	-0.13	[redacted]	[redacted]	Dominated
Immunotherapy	[redacted]	[redacted]	3.45	0.39	[redacted]	[redacted]	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	1.98	[redacted]	[redacted]	63,768
ERG base-case fully incremental results for treated population (deterministic)							
Immunotherapy	[redacted]	-	1.67	-	[redacted]	-	-
Chemotherapy	[redacted]	[redacted]	2.58	0.92	[redacted]	[redacted]	17,363
Tepotinib	[redacted]	[redacted]	2.61	0.02	[redacted]	[redacted]	55,879

NICE * Probabilistic ICER is £35,922/QALY

Results include PAS price for tepotinib, but not for comparators or subsequent treatments

Impact of comparator survival curve assumptions

Scenario	Comparator OS curve	Comparator PFS curve	ICER
Overall population, versus chemotherapy			
Best case	Weibull (Company)	Spline 1-knot odds (Company)	£19,781
Worst case	Log-normal (ERG)	Spline 3-knot odds (ERG)	£33,349
Overall population, versus immunotherapy			
Best case	Spline 2-knot normal (ERG)	Piecewise log-logistic	Dominant
Worst case	Spline 1-knot normal (Company)	Piecewise log-logistic	Dominant
Untreated population, versus chemotherapy (log-normal [company] tepotinib curves)			
Best case	Weibull (Company)	Spline 3-knot odds (ERG)	£23,012
Worst case	Log-normal (ERG)	Spline 3-knot odds (ERG)	£113,383
Untreated population, versus immunotherapy (log-normal [company] tepotinib curves)			
Best case	Spline 2-knot normal	Piecewise Weibull (Company)	£418,802 (SW)
Worst case	Spline 2-knot normal	Piecewise log-normal (ERG)	£357,311 (SW)
Treated population, versus chemotherapy			
Best case	Weibull (Company)	Log-logistic	£18,176
Worst case	Log-normal (ERG)	Log-logistic	£55,879
Treated population, versus immunotherapy			
Best case	Exponential (ERG)	Spline 1-knot hazard	£22,260
Worst case	Spline 1-knot normal (Company)	Spline 1-knot hazard	£24,824

ERG scenario analyses

Analysis	Technologies	Deterministic ICER* (Tepotinib vs comparator)	
		ERG	Company
Base-case	Immunotherapy	Dominant	Dominant
	Chemotherapy	£32,753	£19,512
Subsequent treatment has a UK-based distribution	Immunotherapy	Dominant	Dominant
	Chemotherapy	£159,726	£85,128
Subsequent treatment has a UK-based distribution matching no. of subsequent lines	Immunotherapy	Dominant	Dominant
	Chemotherapy	£170,989	£90,877
Equal subsequent treatment distribution using the chemotherapy trial data	Immunotherapy	Dominant	Dominant
	Chemotherapy	£146,522	£77,585
Equal subsequent treatment distribution using the chemotherapy UK expert opinion data	Immunotherapy	Dominant	Dominant
	Chemotherapy	£148,173	£79,231
Tepotinib time on treatment (ToT) modelled with a log-logistic model	Immunotherapy	Dominant	Dominant
	Chemotherapy	£65,381	£36,166
Immunotherapy ToT assumption: treatment capped at PFS	Immunotherapy	Dominant	Dominant

* Based on post-clarification model – does not include minor correction to chemotherapy distribution at technical engagement

Results include PAS price for tepotinib, but not for comparators or subsequent treatments

ERG subgroup analysis (1)

Technologies	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY	
ERG base case: untreated, non-squamous PD-L1 ≥50% population							
Tepotinib	[redacted]	[redacted]	3.06				Cost-effective*
Immunotherapy	[redacted]	[redacted]	3.45	[redacted]	[redacted]	0.39	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	1.98	57,774
ERG base case: untreated, non-squamous PD-L1 <50% population							
Chemotherapy	[redacted]	[redacted]	3.18				
Tepotinib	[redacted]	[redacted]	3.06	[redacted]	[redacted]	-0.13	Dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	2.37	63,768
ERG base case: untreated squamous PD-L1 ≥50% population							
Tepotinib	[redacted]	[redacted]	3.06				Cost-effective*
Immunotherapy	[redacted]	[redacted]	3.45	[redacted]	[redacted]	0.39	Extendedly dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	1.98	57,774

* Cost-effective because the comparators are too costly given the additional benefit they provide

ERG subgroup analysis (2)

Technologies	Cost (£)	QALY	LY	Incremental			ICER (£/QALY)
				Cost (£)	QALY	LY	
ERG base case: untreated squamous PD-L1 <50% population							
Chemotherapy	[redacted]	[redacted]	3.18				
Tepotinib	[redacted]	[redacted]	3.06	[redacted]	[redacted]	-0.13	Dominated
Immunotherapy + chemotherapy	[redacted]	[redacted]	5.42	[redacted]	[redacted]	2.37	63,768
ERG base case: untreated, adenocarcinoma/large cell carcinoma PD-L1 <50%							
Chemotherapy	[redacted]	[redacted]	3.18				-
Tepotinib	[redacted]	[redacted]	3.06	[redacted]	[redacted]	-0.13	Dominated
ERG base case: treated squamous PD-L1 <50% population							
Immunotherapy	[redacted]	[redacted]	1.67				
Chemotherapy	[redacted]	[redacted]	2.58	[redacted]	[redacted]	0.92	17,363
Tepotinib	[redacted]	[redacted]	2.61	[redacted]	[redacted]	0.02	55,879
ERG base case: treated squamous PD-L1 ≥50% population							
Chemotherapy	[redacted]	[redacted]	2.58				
Tepotinib	[redacted]	[redacted]	2.61	[redacted]	[redacted]	0.02	55,879

End of life (1)

Company consider tepotinib to meet end of life criteria:

1. In the overall population for patients who would be treated with chemotherapy
2. For all patients in the previously treated population regardless of treatment option

Supported by literature data showing poorer outcomes for patients with advanced NSCLC harbouring METex14 skipping mutations, data from the ITC, model extrapolations

Population and treatment	Life expectancy (months)			Tepotinib benefit (months)	
	Literature	ITC (median)	Model (mean)	ITC (median)	Model (mean)
Overall					
Chemotherapy	8.1	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	13.4 – 18.2	[redacted]	[redacted]	[redacted]	[redacted]
Treated					
Chemotherapy	8.1 – 8.4	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	8.2 – 11.8	[redacted]	[redacted]	[redacted]	[redacted]
Untreated					
Chemotherapy	7.7 – 13.4	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	15.8 – 26.3	[redacted]	[redacted]	[redacted]	[redacted]

NICE Model outputs based on company base case

End of life (2)

Summary of mean life expectancy from the economic model (months)

Technology	Overall population	Untreated	Treated
Company base case			
Tepotinib	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	[redacted]
Immunotherapy + chemotherapy	[redacted]	[redacted]	[redacted]
ERG alternative base case			
Tepotinib	[redacted]	[redacted]	[redacted]
Chemotherapy	[redacted]	[redacted]	[redacted]
Immunotherapy	[redacted]	[redacted]	[redacted]
Immunotherapy + chemotherapy	[redacted]	[redacted]	[redacted]

ERG:

- Data suggests that end-of-life criteria are met:
  - when compared with chemotherapy in the overall population
  - when compared with either chemotherapy or immunotherapy in treated population. Although survival benefit vs chemo not greater than 3 months from ITC results
- Agrees that end-of-life criteria are probably not met in untreated population

End of life (3): comparison of OS KM curves

Vs immunotherapy, untreated

Vs immunotherapy, treated

Vs immunotherapy, overall

Vs chemotherapy, untreated

Vs chemotherapy, treated

Vs chemotherapy, overall

KM: Kaplan-Meier; OS: overall survival

End of life (4)

Recap on 'life-extending treatment at the end of life', from NICE Guide to the Methods of Technology Appraisal 2013

Section 6.2.10:
In the case of a 'life-extending treatment at the end of life', the Appraisal Committee will satisfy itself that all of the following criteria have been met:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months and
- there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.

In addition, the Appraisal Committees will need to be satisfied that:

- the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and
- the assumptions used in the reference case economic modelling are plausible, objective and robust.

Equalities and Innovation

Are there any equalities issues or innovation the committee should consider?

Equalities:

- No equality issues identified

Innovation:

- 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.

Backup slides

PFS and OS from VISION

Cohort A, progression-free survival by treatment line (February 2021 cut off)

Cohort A, overall survival by treatment line (February 2021 cut off)

PFS and OS from VISION

Cohort A, progression-free survival (February 2021 cut off)

Cohort A, overall survival (February 2021 cut off)

Issue 3: Chemotherapy OS curve, overall population

Issue 3: Chemotherapy PFS curve, overall population

[redacted]

Issue 3: Immunotherapy OS curve, overall population

Issue 3: Tepotinib OS curve, untreated population

Issue 3: Tepotinib PFS curve, untreated population

Issue 3: Chemotherapy OS curve, untreated population

Issue 3: Chemotherapy PFS curve, untreated population

Issue 3: Immunotherapy PFS curve, untreated population

Issue 3: Chemotherapy OS curve, treated population

Issue 3: Immunotherapy OS curve, treated population (1)

Issue 3: Immunotherapy OS curve, treated population (2)

Cancer Drugs Fund Recommendation Criteria

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required , and number of patients in NHS in England needed to collect data.

- Final VISION study report due December 2023.
- 2 additional observational studies planned:
  - MS200095-0048: single-arm. Final study report Q4 2025
  - MS200095-0049: comparative vs patients treated with other available therapies. Final study report Q1 2028