NICE National Institute for Health and Care Excellence

PART 1 slides for public: Fully redacted

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

Chair's presentation

Chair: Megan John

ERG: Kleijnen Systematic Reviews

Technical team: Luke Cowie, Chris Griffiths, Linda Landells

Company: Merck Serono

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Tepotinib (Tepmetko, Merck Serono)

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: £xxxxx for 60 x 250 mg tablets (equivalent to a 1-month dose) Annual cost of treatment = £xxxxx A confidential Patient Access Scheme (PAS) has been agreed

ACM1 recap: 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

ACM1 Recap: 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

ACM1 recap: ACD preliminary recommendation

Tepotinib is not recommended, within its marketing authorisation, for treating advanced non-small-cell lung cancer (NSCLC) with MET exon 14 (METex14) skipping alterations in adults.

ACM1 recap: ACD considerations (1)

Issue	Committee's considerations
Population and subgroups (ACD section 3.2)	The company base case population comprised all people with METex14 skipping NSCLC regardless of whether or not they had had prior treatment. Untreated and treated subgroups should be considered separately.
Population and subgroups (ACD section 3.3)	The clinical experts explained that most METex14 skipping NSCLC is of non-squamous histology. The appraisal should focus on untreated non-squamous NSCLC with METex14 skipping alterations.
Comparators (ACD section 3.4)	Company compared tepotinib with 2 grouped treatment classes: chemotherapy and immunotherapy. Chemo-immunotherapy is the most relevant comparator for tepotinib, but insufficient data from real-world cohort.
Clinical effectiveness (ACD section 3.5)	The clinical evidence for tepotinib is uncertain because it is based on 1 single-arm study that may not be generalisable to NHS practice.

ACM1 recap: ACD considerations (2)

Issue	Committee's considerations
Trial cohort used in analysis (ACD section 3.6)	The company used the data from cohort A exclusively for its cost-effectiveness analysis. Using the data from cohort A plus cohort C has little effect on the results, but would be preferable.
Indirect treatment comparison (ACD section 3.7)	The results of the indirect treatment comparisons were inconsistent and counter to expectations, with chemotherapy sometimes appearing to be more effective than immunotherapy. The results of the indirect treatment comparisons were highly uncertain, but are in the correct METex14 population and will still be considered.
Survival extrapolation (ACD section 3.9)	The clinical experts had considerable concerns over the long-term overall survival estimates for the comparators. The comparator overall survival extrapolations are implausible, particularly for chemotherapy and chemo-immunotherapy.
Subsequent treatments (ACD section 3.10)	The company used subsequent treatment distributions from VISION for tepotinib and from the real-world cohort for the comparators. Separate subsequent treatment distributions based on prior treatment status, and for people having chemo-immunotherapy, are needed. These should reflect NHS practice.

ACM1 recap: ACD considerations (3)

Issue	Committee's considerations
Time on treatment (ACD section 3.11)	There is uncertainty about the most appropriate time-on-treatment model for tepotinib, but the company's base case is likely appropriate.
End of life (ACD section 3.12)	Life expectancy for people with METex14 skipping NSCLC is likely to be less than 2 years in the overall population.
End of life (ACD section 3.13)	It is uncertain whether tepotinib extends life by more than 3 months, so it does not meet the end-of-life criteria.

Consultation comments

ACD consultation responses

- **Commentator comments from:**
  - Roy Castle Lung Cancer Foundation
- **Consultee comments from:**
  - Merck (company)
- **Web comments:**
  - None

Consultation comments

Commentator: Roy Castle Lung Cancer Foundation

- We are disappointed that the Appraisal Committee Decision is not to recommend this therapy in this indication.
- As acknowledged in the ACD, this is a small segmented group of lung cancer patients, with poorer prognosis and obvious unmet need.
- Whilst other targeted therapy options are available, this would be the first for patients with MET gene alterations.
- We would urge re-consideration that tepotinib be available through the Cancer Drugs Fund at this time, as data matures. Or that, on discussion with the manufacturer, review is considered earlier than 3 years.

Consultee comments: Merck (company)

General points
Disappointed with decision: high unmet need in this older and frailer population with no access to a targeted treatment
Disagree that VISION is not generalisable to the UK: patient characteristics in VISION align with METex14 population in UK practice
METex14 skipping is a rare mutation: any analysis using data in this small population will have some inherent uncertainty
Original submission used data specific to METex14 skipping NSCLC to inform comparator, to reflect difference to wider NSCLC population: • Accept that real-world cohort chemoTx outcomes higher than expected, but immunoTx (mono) outcomes in line with expectations • New ITC provided using data from wild type NSCLC as requested by committee
Company believe tepotinib now shown to be clinically effective vs main comparator chemo-immunotherapy, despite the uncertainty that using wild-type NSCLC data introduces
Now used all possible data sources (real-world vs trial, METx14 vs wild-type) – tepotinib is effective in range of scenarios and is budget saving

Consultee comments: Merck (company)

The company provided detailed responses and additional analyses on the following:

- Focus on untreated non-squamous NSCLC with METex14 skipping alterations, with chemo-immunotherapy as the most relevant comparator
- Generalisability of VISION to NHS practice
- Use of new ITC/MAICs using wildtype NSCLC trials as way of addressing uncertainty in the original real-world ITC
- Uncertainty in survival extrapolations
- Updated subsequent treatment distributions to better match NHS practice, and
- Whether tepotinib meets NICE end of life criteria

Most relevant subgroup: treatment line and histology

ACD	*"The appraisal should focus on untreated non-squamous NSCLC with METex14 skipping alterations".*
Company response	• Agree. But important to include previously-treated patients, as tepotinib could be used in the previously-treated setting. • Access to tepotinib for squamous patients also preferable: clinical feedback for high unmet need in this very small population. • Squamous patients were included in VISION. Marketing authorisation does not restrict by histology. • Previous NICE appraisals in NSCLC with other oncogenic driver mutations where squamous histology also rare and evidence not provided, final NICE recommendation did not restrict to non-squamous patients only (e.g. TA760).
ERG response	• Company have provided analyses for untreated non-squamous subgroup, and also included analyses of previously treated subgroup. • Unclear how effective tepotinib would be in squamous population given low proportion of people with this histology in VISION trial ([redacted]%) and lack of separate analysis for this subgroup.

Most relevant comparator

ACD	*"Chemo-immunotherapy is the most relevant comparator for tepotinib".*
Company response	• Agree. Specifically pembrolizumab with pemetrexed and platinum chemotherapy (for untreated non-squamous). • Supported by latest clinical feedback. • Provided new ITC comparing tepotinib to pembrolizumab with pemetrexed and platinum, using clinical trial data from NSCLC without specific oncogenic biomarkers (wildtype NSCLC). • Additional comparisons also done but chemo-immunotherapy comparison is most relevant and therefore is base-case comparison.
ERG response	• New ITC provided by company is in addition to the naïve comparison included in the original company submission, as described in the ERG report.

Robustness of clinical effectiveness evidence

ACD	*"The clinical evidence for tepotinib is uncertain because it is based on 1 single-arm study that may not be generalisable to NHS practice".*
Company response	• Disagree. VISION was reflective of age, histology and other characteristics typical of the METex14 skipping NSCLC population. • Supported by recent publication from people treated with tepotinib in UK through Early Access to Medicines Scheme (EAMS). • VISION also reflective of subsequent treatments after tepotinib in NHS practice (most people had chemotherapy or immunotherapy). • Only a minority received non-NHS treatments, such as crizotinib.
ERG response	• Agree sample of UK patients in EAMS was of similar age and histology to VISION, and shows similarity in treatment response (n=15). • Company states single arm design was most feasible and appropriate method, but ERG suggests RCT should be done given uncertainty of treatment effect.

Indirect treatment comparison (1)

	Original company submission	Company response to ACD
What company did:	• ITC with real-world METex14 cohorts • Immunotherapy and chemotherapy comparators as treatment classes only	• Real-world data updated for ITC • New ITC/MAICs using comparator data from trials in wildtype NSCLC
Advantages:	• METex14 population, as per decision problem • Populations more similar, allows more robust statistical analysis	• Specific comparators in line with NHS practice • Addresses uncertainty over 'counterintuitive' survival results from original ITC (particularly for chemotherapy)
Limitations:	• Not enough data for chemo-immunotherapy, which is key comparator • Dissimilar subsequent treatments to UK practice • 'Counterintuitive' survival results for comparators	• Risk of bias in MAICs, matching to the 'wrong' population • Reduced effective sample sizes creates additional uncertainty • Also 'counterintuitive' results from MAICs

Indirect treatment comparison (2)

ACD	*"The indirect treatment comparisons results are highly uncertain".*
Company response	**Original real-world ITC should be considered:** • METex14-specific data (older demographic, poorer prognosis, poorer response to immunotherapy). Large dataset for robust statistical analysis. • Immunotherapy outcomes aligned to outcomes from other published studies in METex14 skipping NSCLC, and clinical expert opinion. • External validation, interviews with clinical experts and targeted mechanism of tepotinib suggest that real-world data underestimates tepotinib survival benefit. **New analysis required after ACM1:** • Limited real-world data for chemo-immunotherapy, which is main comparator. • Counterintuitive survival results, particularly for chemotherapy: likely driven by high proportion of subsequent treatments not aligned with NHS practice. When these removed from the analysis, OS is much lower. • New matching-adjusted indirect comparisons (MAICs) with wildtype NSCLC to address uncertainty of original ITC. • Allows for specific comparators rather than grouped treatment classes.

Indirect treatment comparison (3)

Company response (cont.)	**MAIC for base case best for decision making:** • MAIC for key comparator (chemo-immunotherapy: pembrolizumab + pemetrexed + platinum) provided. Additional supplementary comparisons support clinical effectiveness and address uncertainty. • For base-case chemo-immunotherapy comparison (and supplementary comparison to docetaxel +/- nintedanib for previously treated), company believe MAIC comparisons to wildtype NSCLC data is best for decision making.
ERG response	• Any MAIC prone to substantial remaining risk of bias, particularly not adjusting sufficiently for all prognostic variables or treatment effect modifiers. • VISION trial population adjusted to match comparator cohort: reduces generalisability to the decision problem population (METex14). • In untreated base case, results of MAIC for pembrolizumab combination seem counterintuitive compared to MAIC for pembrolizumab only: tepotinib [redacted] with the former despite it being most appropriate comparator. • MAICs done correctly. Neither approach seems better than the other. • ERG's preference is for company's real-world data analysis because it is METex14 population, superior method to adjust for confounding.

New treatment comparisons

Populations, comparators and trial data for which progression-free and overall survival analyses were conducted for comparators

Population	Comparator	Trial data/analysis type for comparator
Untreated, wildtype NSCLC	Pembrolizumab + pemetrexed + platinum	KEYNOTE-189/MAIC
Untreated, wildtype NSCLC, PD-L1≥50%	Pembrolizumab	KEYNOTE-024 /MAIC
Previously treated, wildtype NSCLC	Docetaxel	TAX320/MAIC
Previously treated, wildtype NSCLC	Docetaxel + nintedanib	LUME-Lung 1 adenocarcinoma population/MAIC
Untreated, METex14 NSCLC *	Immunotherapy monotherapy	Real-world cohort data, updated to include the French/GFPC data set

* Not a new MAIC: original ITC, updated with additional real-world evidence.

Technical team note:
- No new comparisons were made for squamous histology.

New ITC results: untreated non-squamous, compared with pembrolizumab combination (base case)

MAIC outcomes comparing VISION A+C to KEYNOTE-189 (wildtype NSCLC)

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

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

METex14 skipping was not collected or reported in KEYNOTE-189, and is only present in ~3% of NSCLC cases. By matching trial populations, the sample size of VISION was reduced to an effective sample size of 38.7

New ITC results: untreated non-squamous, compared with pembrolizumab monotherapy

MAIC outcomes comparing VISION A+C to KEYNOTE-024 (*)

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

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Key: CI, confidence interval; ESS, effective sample size; NA, not available
* KEYNOTE-024 trial was in NSCLC with PD-L1 ≥50%

New ITC results: previously treated non-squamous, compared with docetaxel + nintedanib

MAIC outcomes comparing VISION A+C to LUME-1 (wildtype NSCLC)

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

New ITC results: previously treated non-squamous, compared with docetaxel*

MAIC outcomes comparing VISION A+C to LUME-1 (wildtype NSCLC)

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

NICE * Clinical experts interviewed stated that 80-100% of non-squamous NSCLC patients are given docetaxel + nintedanib, so docetaxel alone is not as relevant.

Survival extrapolation (1)

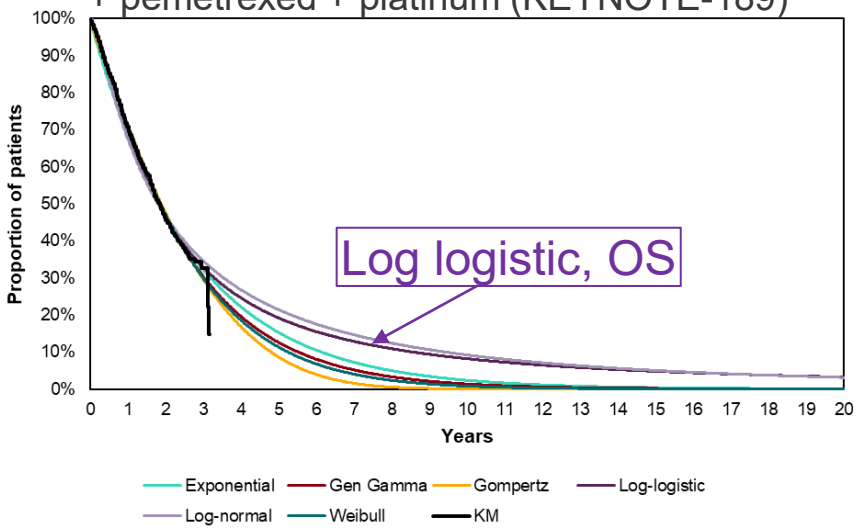
ACD	*"The comparator overall survival extrapolations are implausible, particularly for chemotherapy and chemo-immunotherapy".*
Company response	• New ITCs in wildtype NSCLC alleviate uncertainty with real-world data ITC. • Parametric survival models independently fitted to pseudo-patient level data for each comparison. • Clinical expert opinion: people with wildtype NSCLC treated with chemo-immunotherapy around 15-20% alive at five years and around 5-10% at ten years. • Both log-logistic and log-normal sat within this plausible range, although estimated 10-year OS at the higher end of range. Clinical experts agreed these curves were most plausible. • Based on goodness of fit, visual fit and long-term plausibility, log-logistic was selected to inform the base case OS for chemo-immunotherapy. • Log-logistic also selected for base case PFS (and also for tepotinib OS and PFS).

Survival extrapolation (2)

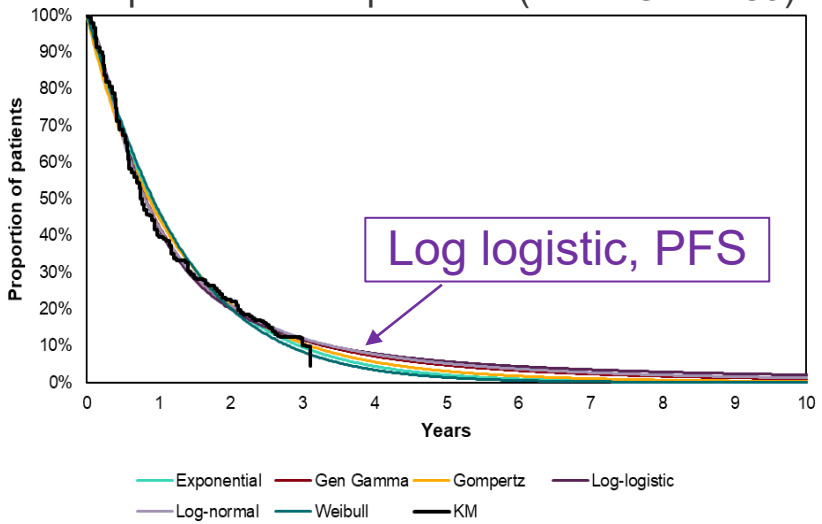
ERG response	• New OS and PFS extrapolations for base-case comparison, and supplementary analyses. • Fitting of the survival curves followed the same procedures as used in original company submission. • ERG would still prefer jointly estimated survival for both tepotinib and the comparator using the pseudo-patient level data generated. • For base case, clinical experts selected model with the greatest survival estimates for comparator OS, so impact is conservative for tepotinib. • Data are very immature, for tepotinib in particular, so almost any survival model could be fitted to the data. Choice is highly uncertain. • ERG would not select alternative survival models based on information given.

Survival extrapolation: OS & PFS

Untreated, wildtype NSCLC: Pembrolizumab + pemetrexed + platinum (KEYNOTE-189)



Untreated, wildtype NSCLC: Pembrolizumab + pemetrexed + platinum (KEYNOTE-189)



Survival extrapolation: base case

Final curves selected to inform tepotinib versus pembrolizumab + pemetrexed + platinum

Company note:

- Important to note that these reflect wildtype NSCLC population. People with METex14 skipping mutations expected to have poorer outcomes with immunotherapy, including chemo-immunotherapy.
- Clinical experts suggest no evidence people with METex14 skipping mutations treated with immunotherapy would respond any better with chemo-immunotherapy.
- Clinical experts expect that METex14 performs worse with chemo-immunotherapy compared to wildtype NSCLC, so estimated differences between tepotinib and pembrolizumab + pemetrexed + platinum are conservative using wildtype data, even after adjusting for patient characteristics.

Subsequent treatment distributions

ACD	*"Separate subsequent treatment distributions based on prior treatment status, and for people having chemo-immunotherapy, are needed".*
Company response	• VISION trial and real-world cohort data largely reflective of subsequent treatment distributions people would receive in NHS practice (main exception crizotinib or other MET inhibitors). • 3 clinical experts advised on subsequent treatments in NHS practice after tepotinib (untreated or previously treated groups). • Economic model updated to reflect NHS practice for subsequent treatment distributions. • Everybody in model assumed to go on to further treatment. Scenarios explore 50% of people not having further treatment, and also different percentage splits to explore variation in NHS practice, as suggested by clinical experts.
ERG response	• New subsequent treatment distributions are different to those in original company submission because comparators in new analyses are specific, but were previously treatment classes only. • Seeking expert opinion is reasonable if there is no published evidence. • ERG did not have time to consult an expert to validate clinical plausibility.

Subsequent treatment distributions - comparators

Population	Intervention/ comparator	Subsequent treatment distribution
Untreated	Pembrolizumab + pemetrexed + platinum	100%: Docetaxel +/- nintedanib (90% with nintedanib)
Untreated, PD-L1≥50%	Pembrolizumab	Second-line treatment: 100%: Platinum-based chemotherapy, specifically carboplatin + pemetrexed, Last-line treatment: 100%: Docetaxel +/- nintedanib (90% with nintedanib)
Previously treated	Docetaxel	No subsequent treatment
Previously treated	Docetaxel + nintedanib	No subsequent treatment
Untreated	Immunotherapy monotherapy (original ITC, updated)	Not stated - same as in the company submission?

Subsequent treatment distributions - tepotinib

Population	Intervention/ comparator	Subsequent treatment distribution
Untreated	Tepotinib	Second-line treatment: 75%: Immunotherapy monotherapy (all pembrolizumab) 25%: Platinum-based chemotherapy (all carboplatin + pemetrexed) Last-line treatment: 100%: docetaxel +/- nintedanib (90% with nintedanib)
Previously treated	Tepotinib	For those with 1L chemo-IO (80% of total): Docetaxel +/- nintedanib (90% with nintedanib) as last line after tepotinib For those with 1L IO (20% of total): Platinum-based chemotherapy, specifically carboplatin + pemetrexed, then docetaxel +/- nintedanib (90% of these patients with nintedanib) as last line after tepotinib

Time on treatment for tepotinib

ACD	*"There is uncertainty about the most appropriate time-on-treatment model for tepotinib, but the company's base case is likely appropriate".*
Company response	• Based on clinical expert feedback, 2 most clinically plausible time-on-treatment (ToT) curves for tepotinib were exponential and generalised gamma. • Company selected ToT curve with higher estimates for tepotinib (generalised gamma) as the more conservative option. • Scenario analyses using the other plausible curve, exponential, results in a decrease to the tepotinib ICER.
ERG response	• Nothing to add.

End of life criteria: life expectancy (1)

ACD	*"Life expectancy for people with METex14 skipping NSCLC is likely to be less than 2 years in the overall population".*
Company response	• Agree that life expectancy of people with advanced NSCLC harbouring METex14 skipping alterations is expected to be below 2 years, regardless of treatment. • Previously provided evidence that tepotinib meets end-of-life criteria in the previously-treated setting specifically. Now also updated for wildtype clinical trial comparison. • Regardless of data source used, tepotinib meets end-of-life criteria in the previously-treated setting.
ERG response	• MAICs cannot be used to provide evidence on life expectancy because the comparator data are in wild-type NSCLC populations.

End of life criteria: life expectancy (2)

Mean and median survival from real-world METex14 cohort comparisons (previously treated)

Evidence, months		Immunotherapy†	Chemotherapy
Observed data (ITC/VISION)	Median	[redacted]	[redacted]
CE model	Mean	[redacted]	[redacted]

Company note:

- 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). Therefore, the modelled mean OS is considered to be the absolute maximum expected, and likely will be lower in practice.

Technical team note:

- Not possible to use mean survival estimates from the model as comparator data from wildtype NSCLC.
- Committee has not seen detailed information on survival for untreated METex14 NSCLC, so cannot consider whether end of life criteria would be met in this population.
- At ACM1, both company and ERG agreed that end of life criteria are probably not met in untreated population.

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† Immunotherapy determined by clinical experts to not be a relevant treatment in the second-line setting, but included for completeness.

End of life criteria: survival gain

ACD	*"It is uncertain whether tepotinib extends life by more than 3 months, so it does not meet the end-of-life criteria".*
Company response	• Previously presented evidence that tepotinib provides 3-month survival gain compared to all comparators in real-world cohort, and key comparators of docetaxel +/- nintedanib in the wildtype clinical trial comparisons for the previously treated population. • In updated comparison to relevant previously treated comparators (docetaxel +/- nintedanib), tepotinib shows a median OS benefit of substantially greater than 3 months ([redacted] and [redacted] months, respectively), and the modelled means also show a benefit for tepotinib substantially greater than 3 months ([redacted] months and [redacted] months, respectively). • Regardless of data source used, tepotinib meets end-of-life criteria in the previously treated setting.
ERG response	• Surprising that estimated survival gain for tepotinib should be greater when compared to docetaxel + nintedanib than to docetaxel only. • Also counterintuitive that tepotinib should do better in median OS versus pembrolizumab + pemetrexed + platinum than pembrolizumab monotherapy.

End of life criteria

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.

Cost-effectiveness results: company base case

Deterministic incremental cost-effectiveness results: Company base case
(analysis does not include confidential prices for comparator treatments)

Technologies	Total			Incremental			ICER (£/QALY)
	Costs (£)	Life years	QALYs	Costs (£)	Life years	QALYs	
Tepotinib	xxxxx	4.26	xxxxx				Dominant
Pembrolizumab + pemetrexed + platinum	xxxxx	3.65	xxxxx	xxxxx	-0.62	xxxxx	Dominated

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

All decision making ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Cost-effectiveness results: supporting analyses

Deterministic incremental cost-effectiveness results: Company supporting analyses

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

Cost-effectiveness results: ERG comments

ERG response	• In original company submission, while combination treatment was associated with an additional XXX QALYs, it was also associated with an additional XXXXXX compared to tepotinib. • In this analysis combination therapy is associated with XXX fewer QALYs compared to tepotinib and an additional XXXXXX. • Difference in cost between this ACD response model and original company model is related to less costly comparator and subsequent treatments included. • Difference in QALY gain estimates is due to different effectiveness evidence used in both models. • ERG considers greatest uncertainty to lie in ITC/MAIC effectiveness evidence.

Key issues after consultation

Issue at ACM2	Questions for committee
Most relevant subgroup: treatment line and histology	• Is the company base case of untreated non-squamous NSCLC with METex14 skipping alterations appropriate for decision making? • What about squamous?
Most relevant comparator	• Is the base case comparison with immuno-chemotherapy appropriate for decision making?
Robustness of clinical effectiveness evidence	• Is the VISION trial generalisable to NHS practice and UK population?
Indirect treatment comparison	• Are the MAICs produced using relevant trials in wildtype NSCLC appropriate for decision making?
Survival extrapolation	• Are the company's selected extrapolations for OS and PFS for tepotinib and comparators the most clinically plausible?
Subsequent treatment distributions	• Are the updated subsequent treatment distributions more aligned with NHS practice?
Time on treatment for tepotinib	• Is the company's choice of ToT model the most clinically plausible?
End of life	• Are NICE's end of life criteria met for any of the populations in this appraisal?

Backup slides

ACM1 Recap: End of life

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