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ORIGINAL RESEARCH ARTICLE

Modelling the Effectiveness of Tepotinib in Comparison to Standard-of-Care Treatments in Patients with Advanced Non-small Cell Lung Cancer (NSCLC) Harbouring *MET*ex14 Skipping in the UK

Rachael Batteson[1] · Emma Hook[1] · Hollie Wheat[1] · Anthony J. Hatswell[1,2] · Helene Vioix[3] · Thomas McLean[4] · Stamatia Theodora Alexopoulos[4] · Shobhit Baijal[5] · Paul K. Paik[6,7]

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Abstract

Background Patients with non-small cell lung cancer harbouring mesenchymal–epithelial transition exon 14 (*MET*ex14) skipping typically demonstrate poorer prognosis than overall non-small cell lung cancer. Until recently, no targeted treatments were available for patients with non-small cell lung cancer harbouring *MET*ex14 skipping in the UK, with limited treatments available.

Objective This study estimates the long-term survival and quality-adjusted life-year benefit of MET inhibitor tepotinib versus current standard of care from a UK perspective.

Methods A partitioned-survival model assessed the survival and quality-adjusted life-year benefits of tepotinib versus immunotherapy ± chemotherapy and chemotherapy for untreated and previously treated patients, respectively, using evidence from the single-arm VISION trial (NCT02864992). Two approaches were used to inform an indirect treatment comparison: (1) published clinical trials in overall non-small cell lung cancer and (2) real-world evidence in the *MET*ex14 skipping population. Results are presented as median and total quality-adjusted life-year gain and survival for progression-free survival and overall survival. Survival curves were validated against the external literature and uncertainty assessed using a probabilistic sensitivity analysis.

Results Using the indirect treatment comparison against the published literature, tepotinib is estimated to have a median progression-free survival gain versus pembrolizumab ± chemotherapy (11.0 and 9.2 months) in untreated patients, and docetaxel ± nintedanib (5.1 and 6.4 months) in previously treated patients. Across the populations, tepotinib is estimated to have a median survival gain of 15.4 and 9.2 months versus pembrolizumab ± chemotherapy in untreated patients and 12.8 and 5.1 months versus docetaxel ± nintedanib in previously treated patients. The total quality-adjusted life-year gain ranges between 0.56 and 1.17 across the untreated and previously treated populations. Results from the real-world evidence of indirect treatment comparisons are consistent with these findings.

Conclusions Despite the limitations of the evidence base, the numerous analyses conducted have consistently indicated positive outcomes for tepotinib versus the current standard of care.

Extended author information available on the last page of the article

Key Points

Tepotinib was shown to have improved overall and progression-free survival compared with immunotherapy in patients previously untreated and chemotherapy for patients who have been previously treated.

There are limitations to the analyses based on the evidence base for patients with non-small cell lung cancer harbouring *MET*ex14 skipping; however, results are consistent across the analysis methods.

1 Introduction

Lung cancer is one of the most common cancers globally, accounting for 11.4% of all new cancer cases in 2020, with 2.2 million new cases every year [1]. The most common type of lung cancer is non-small cell lung cancer (NSCLC), which is further divided into histological subtypes (approximately 40% of those being adenocarcinoma) [2, 3].

Oncogenic mutations in certain driver genes result in tumour growth and invasiveness [4]. Alterations to the mesenchymal–epithelial transition (*MET*) oncogene, such as *MET* exon 14 (*MET*ex14) skipping and *MET* amplification, have been identified as primary oncogenic drivers in NSCLC [5, 6]. Compared with the overall NSCLC population, patients with NSCLC harbouring *MET*ex14 skipping are typically older with adenocarcinoma histology [7, 8]. Furthermore, patients with NSCLC harbouring *MET*ex14 skipping are more likely to be programmed death-ligand 1 (PD-L1) positive [7–9]. As such, patients with *MET*ex14 skipping NSCLC are a distinct population within NSCLC, with different patient characteristics to the overall NSCLC population, or NSCLC with other oncogenic driver mutations. Until recently, there have been no targeted treatments for patients with NSCLC harbouring *MET*ex14 skipping, with limited efficacious non-targeted treatment options available.

The primary objective of treating advanced, recurrent or metastatic NSCLC is to extend survival and improve quality of life. The choice of treatment depends on the disease stage, histology, prior treatment, biomarker testing in metastatic NSCLC (mutation status and PD-L1), molecular testing and the patient's performance status [10, 11]. In the absence of specific MET-targeted therapies, treatments previously used for patients without any identifiable biomarkers (e.g. epidermal growth factor [EGFR] or anaplastic lymphoma kinase [ALK]) in advanced NSCLC included immunotherapies and/or chemotherapy.

Studies have shown that patients with NSCLC harbouring *MET*ex14 skipping tend to have poor response to non-targeted treatments, specifically response rates and progression-free survival (PFS), with immunotherapy treatments noted for particularly poor efficacy in this population [8, 12]. In addition, platinum-based chemotherapy combinations also show limited efficacy in patients with advanced NSCLC harbouring *MET*ex14 skipping [13].

Tepotinib is a once-daily, oral, 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 [14]. Tepotinib is currently being assessed in an ongoing, single-arm, phase II trial VISION (NCT02864992) [14] and has been approved by the Medicines and Healthcare products Regulatory Agency in October 2021, European Medicines Agency [15] and the US Food and Drug Administration [16], in addition to being recommended in over 40 countries including by the National Institute for Health and Care Excellence (NICE) in England and the Scottish Medicines Consortium in Scotland [17, 18].

In the interim analyses of VISION, tepotinib demonstrated durable clinical activity in patients with advanced NSCLC harbouring *MET*ex14 skipping, particularly in the treatment-naïve setting and robust systemic intracranial outcomes in patients with brain metastases, with an overall response rate of 51.4%, and a median duration of response of 18 months. Progression-free survival and overall survival (OS) also showed positive results with a median PFS of 11.2 months and a median OS of 19.6 months ($N = 313$) in patients with a longer follow-up (VISION data cut-off: November 2022) [19].

Modelling long-term survival from single-arm trials in rare disease areas presents many challenges, and can often be associated with high scrutiny and uncertainty. This study aimed to estimate the long-term survival and quality-adjusted life-year (QALY) benefit of tepotinib versus current standard of care in the UK, using the economic model submitted to NICE for the appraisal of tepotinib for treating advanced NSCLC with *MET* gene alterations [17]. The results presented are obtained from the NICE model, updated with the latest available data cut of VISION (November 2022), and applying two different approaches for the indirect treatment comparison (ITC); (1) using published clinical trials in wild-type NSCLC and (2) real-world evidence in the patient population with NSCLC harbouring *MET*ex14 skipping.

2 Methods

2.1 Model Overview

A de novo model was built in Microsoft® Excel to assess the cost effectiveness of tepotinib using a partitioned survival analysis structure with three health states; progression-free, progressed and death (Fig. 1). This structure revolves around the key secondary endpoints from VISION of OS and PFS and is consistent with the majority of previous advanced NSCLC models submitted to, and accepted by, NICE [20–28]. The progression-free state was designed to capture the relatively higher health-related quality of life (HRQoL) while disease is stable prior to progression. The model therefore captures the changes in HRQoL between the progression-free and progressed states.

A lifetime horizon (30 years) was adopted with a 7-day cycle length as this was considered short enough to capture the various dosing regimens included within the model. Given the short cycle length, a half cycle correction was not included in the economic model. Annual discount rates for costs and QALYs were set to 3.5% as per the NICE reference case [29].

2.2 Comparators and Data Sources

Because of the lack of approved treatments for patients with NSCLC harbouring *MET*ex14 skipping at the time of the analysis, current standard of care was based on therapies used to treat overall NSCLC in England and Wales, including immunotherapy with or without chemotherapy in untreated patients, and chemotherapy in previously treated patients [30].

Pembrolizumab (Keytruda®) monotherapy was recommended by NICE in July 2018 for untreated PD-L1-positive metastatic NSCLC [24], and pembrolizumab in combination with pemetrexed plus platinum-based chemotherapy was recommended by NICE in March 2021 for untreated metastatic non-squamous NSCLC [28]. These treatments were considered the most widely used first-line therapies for patients with non-squamous metastatic NSCLC in the UK based on clinical expert opinion, and therefore the most relevant comparators in the untreated setting for tepotinib based on clinical opinion [17]. Because of a lack of head-to-head comparisons versus tepotinib in VISION and the absence of reported efficacy outcomes in the *MET*ex14 skipping population for these treatments, a match-adjusted indirect comparison (MAIC) was performed whereby patients in VISION were matched to the reported aggregate characteristics from the pivotal clinical trials for the key comparators in the overall NSCLC population, using the latest published information at the time of the analysis, KEYNOTE-189 [31] and KEYNOTE-024 [32], respectively. Studies were matched on patient age, sex, Eastern Cooperative Oncology Group performance status, smoking history, adenocarcinoma histology and disease stage following practicing clinician input, though noting that *MET*ex14 skipping status remains a potential difference between the clinical trials as they did not test for *MET*ex14 status, which it was not possible to match on [33].

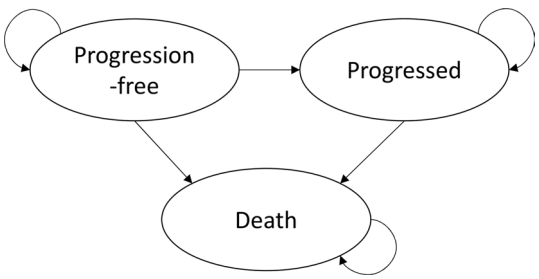

Fig. 1 Model structure

According to clinical experts, previously treated patients mostly receive a chemotherapy-containing regimen in UK practice, given the majority would likely receive immunotherapy at the first line or at an earlier disease stage. Common chemotherapies given to patients with NSCLC include docetaxel monotherapy and docetaxel in combination with nintedanib (Vargatef®), which was recommended by NICE in July 2015 for previously treated locally advanced, metastatic or locally recurrent NSCLC of adenocarcinoma histology [20]. As per the untreated comparisons, MAICs were conducted to compare tepotinib to these comparators in the previously treated setting, using the most relevant pivotal trial in the overall NSCLC population. For docetaxel in combination with nintedanib, the adenocarcinoma cohort from LUME-Lung 1 was selected for the MAIC [34]. For docetaxel, a number of trials were available because of the common use of docetaxel as a control arm. The REVEL trial was considered the most appropriate as it is the most recent trial that would not be impacted by selecting patients via PD-L1 expression, or by immunotherapy as subsequent therapy [35].

There are limitations and uncertainties associated with the MAIC comparisons as the proportion of patients with NSCLC harbouring *MET*ex14 skipping were unable to be matched between populations, which impacted the comparability of outcomes [33]. This limitation is underlined by differences in the unweighted population characteristics (such as mean age and smoking status), which reduced the effective sample size, further increasing the uncertainty around this comparison. Therefore, an analysis using real-world data in a patient population with NSCLC harbouring *MET*ex14 skipping treated with standard-of-care treatments was also conducted [36]. Patient-level data were available from five

real-world data sets, therefore propensity score weighting was implemented to balance the patient characteristics from the real-world data sets to the VISION cohort, after applying the inclusion and exclusion criteria from VISION. A mix of treatments were included within the real-world data; however, patient numbers were too limited to consider individual treatments. Therefore, treatments were categorised into treatment classes; immunotherapies or chemotherapies. The distribution of treatments included in each group is presented in the Table 1 of the Electronic Supplementary Material (ESM). A summary of comparators and data sources is presented in Table 1.

2.3 Overall and Progression-Free Survival

Survival extrapolation was required to inform long-term projections of PFS (used to calculate the proportion of patients in the 'progression-free' health state over time) and OS (used to calculate the proportion of patients who are alive over time and in the 'progressed' health state). For the comparators, published Kaplan–Meier curves were digitised and pseudo patient-level data created using the Guyot algorithm [37]. The available patient-level data from the VISION trial (split between the untreated and previously treated cohorts) were used for tepotinib. For each comparison, the tepotinib data were re-weighted to the published data, using MAIC methodology described previously. Patient-level data from the real-world data set were weighted to the VISION trial using propensity score weighting, and used for the immunotherapy ± chemotherapy comparator cohorts.

Parametric survival models (PSMs) were fitted to PFS and OS data using the exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal and Weibull distributions. The selection of the most appropriate distribution was made in accordance with the NICE Decision Support Unit Technical Support Document 14 [38]. Clinical expert opinion was also sought to inform expected survival in the long term to ensure chosen curves produced clinically plausible projections.

2.4 HRQoL

HRQoL of patients in the VISION trial was assessed using the European Quality of Life five-dimension five-level (EQ-5D-5L) questionnaire every 6 weeks from cycle 1 until 9 months, and every 12 weeks thereafter until disease progression, death or withdrawal of consent. Following progression, questionnaires were continued up to 30 days. These data were used to inform the utility value per health state for tepotinib and comparators in the model. For the economic model, a crosswalk algorithm by van Hout et al. [39] was used to map EQ-5D-5L to European Quality of Life five-dimension three-level (EQ-5D-3L) responses based on a UK value set, in line with NICE preferences at the time of submission [40].

Linear mixed-model regressions were fitted to the utility data to support the interpretation of changes in utility according to progression status [41]. The use of linear mixed models 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. Alternative utility values derived from KEYNOTE-024 are tested in the scenario analysis [26].

Disutilities for adverse events were also included and applied as a one-off disutility in the first cycle of the model. Grade 3+ treatment-related adverse events with greater than 5% occurrence from VISION were used to inform the adverse event rates for tepotinib, with comparator adverse events informed from the literature [20, 22, 24, 42]. Disutility values were taken from published sources with durations of adverse events obtained from the VISION trial. A consequence of obtaining adverse event frequency from the literature for the comparators is the limited reporting for certain adverse events compared to tepotinib, where all adverse events reported in VISION can be included. As

Table 1 Comparators and data sets

Comparator	Method	Efficacy source	
		Tepotinib	Comparator
Pembrolizumab + pemetrexed + platinum	MAIC	VISION[a]	KEYNOTE-189 [50]
Pembrolizumab	MAIC	VISION[a]	KEYNOTE-024 [32]
Docetaxel + nintedanib	MAIC	VISION[a]	LUME-Lung 1 [20]
Docetaxel	MAIC	VISION[a]	REVEL [35]
Immunotherapy	Propensity score weighting	VISION	Real-world data (weighted)
Chemotherapy	Propensity score weighting	VISION	Real-world data (weighted)

MAIC match-adjusted indirect comparison

[a]VISION data have been re-weighted to match the comparator data

such, this approach may produce smaller disutility values for the comparators versus tepotinib given the expectation of an improved safety profile of tepotinib compared with other treatments. Health-related quality-of-life parameters used in the model base case are presented in Table 2 of the ESM.

2.5 Validation

Extensive validation of modelled curves was conducted both internally by comparing against trial data and externally by comparing to alternative datasets and clinical expectation. Modelled curves were compared against the trial data visually and at specific landmarks to ensure they aligned closely. Additionally, the curves were compared against other external data sources for each treatment. This includes: real-world retrospective studies for patients with NSCLC harbouring *MET*ex14 skipping treated with immunotherapy (Sabari et al. [8]; Guisier et al. [43]) or chemotherapy (Awad et al. [7]); trial data in overall NSCLC in first-line treated patients (KEYNOTE-024 [32]; KEYNOTE-042 [44]) or previously treated patients (KEYNOTE-010 [45]; CheckMate 017/057 [46]); and real-world studies of older patients with overall advanced NSCLC treated with immunotherapy (Cramer-van der Welle et al. [47]). Clinical experts ($n = 3$) were consulted on the expected survival projections of standard-of-care therapies, as well as expectations for tepotinib.

2.6 Analysis

In this study, the base-case results presented are median and total QALYs, and survival, which reflect the projected PFS and OS over a patient's lifetime, combined with HRQoL outcomes. A probabilistic sensitivity analysis (PSA) was conducted on efficacy parameters (PSMs, patient characteristics, adverse events and utilities) to demonstrate the impact and spread of the estimated QALY gain over 1000 simulations. Scenario analyses were also undertaken to assess the sensitivity of the base-case curves, choosing alternative plausible distributions.

3 Results

3.1 PFS

A description of the selected base-case PFS curves for each treatment and comparison is provided in the Table 3 of the ESM. All chosen curves visually fit the data well, with main deviations occurring towards the tail of the observed data, likely because of censoring (Table 5 of the ESM).

The PFS outcomes when comparing to clinical trial data in overall NSCLC using the MAIC approach demonstrated that patients receiving tepotinib are expected to have greater PFS than patients receiving standard of care in the untreated and previously treated populations (Figs. 1 and 2 of the ESM).

In the untreated population, the median PFS was estimated to be 20.7 months for tepotinib compared with 9.7 months for pembrolizumab in combination with pemetrexed and platinum. Compared with pembrolizumab monotherapy, tepotinib was estimated to have a median PFS of 17.7 months versus 8.5 months for pembrolizumab. Therefore, tepotinib is projected to have a median PFS gain of 11.0 and 9.2 months versus pembrolizumab in combination with pemetrexed and platinum, and pembrolizumab monotherapy, respectively.

In the previously treated population, tepotinib is shown to have a median PFS gain of 5.1 months versus docetaxel plus nintedanib (median PFS of 8.5 vs 3.5 months, respectively). Compared with docetaxel monotherapy, tepotinib is estimated to have a 6.4-month median PFS gain (median PFS of 9.7 vs 3.2 months, respectively).

Tepotinib is projected to have a total PFS gain of between 18 and 33.6 months in the untreated population and between 9.6 and 13.2 months in the previously treated population. Results of the PFS curves of tepotinib versus real-world data are reported in the Table 5 and Fig. 3 of the ESM.

3.2 OS

A description of the selected base-case OS curves for each treatment and comparison is provided in Table 3 of the ESM. The comparator curves fit the data well; however, some models failed to fit parts of the tepotinib data because of the large steps observed in the Kaplan–Meier estimates. These steps are likely due to the weightings applied where a small number of events can have a larger impact. However, the chosen base-case curves appear plausible when considering the Kaplan–Meier curve and the expected long-term survival based on clinical expert opinion (Table 5 of the ESM).

In the untreated population, tepotinib is projected to have a median survival gain of 15.4 months versus pembrolizumab in combination with pemetrexed and platinum-based chemotherapy (median OS 37.0 vs 21.6 months, respectively), and 9.2 months versus pembrolizumab monotherapy (median OS 34.7 and 25.5 months, respectively). In the previously treated population, median OS was estimated to be 18.2 months for tepotinib versus 13.1 months for docetaxel plus nintedanib showing a 5.1-month median survival gain. Tepotinib is shown to have a median survival gain of 12.8 months versus docetaxel monotherapy (median OS 21.8 vs 9.0 months, respectively). For the untreated and previously treated populations, tepotinib is projected to have a total survival gain between 13.2 and 26.4 months.

The OS outcomes of tepotinib from the MAIC approach suggest tepotinib has consistently greater survival

probabilities when compared with clinical trial data in overall NSCLC (Figs. 1 and 2 of the ESM). Results of the OS curves of tepotinib versus real-world data are reported in Table 5 and Fig. 3 of the ESM.

3.3 QALYs

Combining the time spent in each health state and the health-state utility values, the total QALYs are presented in Table 2. In the untreated population, tepotinib has a total QALY gain of 1.2 versus pembrolizumab plus chemotherapy with 1.4 QALYs gained in the progression-free health state because of less time spent in the progressed state. Compared with pembrolizumab, tepotinib has a QALY gain of 0.8 in the progression-free health state, and a total QALY gain of 0.6. In the previously treated population, tepotinib is estimated to have a QALY gain in both the progression-free and progressed health states with a total QALY gain of 0.8 and 0.9 versus docetaxel plus nintedanib and docetaxel, respectively; 0.5 and 0.7 of which is gained in the progression-free health state. Results of the QALYs of tepotinib versus real-world data are reported in Table 4 of the ESM.

3.4 Validation

The curves were validated against external sources where available (see Fig. 4 of the ESM). In the untreated population, for the modelled pembrolizumab monotherapy group, the PFS curve appears in line with the older cohort of patients with advanced NSCLC treated with pembrolizumab reported in Cramer-van der Welle et al. [47], but looks higher than the cohorts of patients with NSCLC harbouring *MET*ex14 skipping reported in Guisier et al. and Sabari et al. [8, 43]. This is anticipated as patients with overall NSCLC are expected to have better outcomes versus patients with NSCLC harbouring *MET*ex14 skipping. This is also the case for OS, where the modelled pembrolizumab group predicts higher OS estimates than the external sources for patients with NSCLC harbouring *MET*ex14 skipping treated with pembrolizumab.

In the previously treated population, for docetaxel, the PFS and OS curves appeared in line with the external sources. Although there is an expectation that the overall NSCLC docetaxel would perform better than in NSCLC harbouring *MET*ex14 skipping, patients receiving chemotherapy tend to do poorly regardless of the mutation; therefore, these results are considered clinically plausible. There were limited data to compare the pembrolizumab plus chemotherapy and docetaxel plus nintedanib curves outside of the clinical data that were used to inform the original comparison; therefore, validation using other external sources was not possible.

Table 2 Base-case deterministic pairwise quality-adjusted life-year results

Health state	Tepotinib total	Comparator total	Incremental
Vs pembrolizumab + chemotherapy			
Progression-free	2.51	1.05	1.46
Post-progression	0.71	1.00	− 0.29
Adverse events	− 0.02180	− 0.01530	− 0.00650
Total	3.20	2.04	1.17
Vs pembrolizumab			
Progression free	2.44	1.63	0.81
Post-progression	0.89	1.12	− 0.23
Adverse events	− 0.02180	− 0.00311	− 0.01869
Total	3.30	2.74	0.56
Vs docetaxel + nintedanib			
Progression free	0.86	0.33	0.54
Post-progression	0.84	0.61	0.23
Adverse events	− 0.02279	− 0.00724	− 0.01555
Total	1.68	0.93	0.75
Vs docetaxel			
Progression free	1.08	0.34	0.74
Post-progression	0.58	0.45	0.13
Adverse events	− 0.02279	− 0.00783	− 0.01496
Total	1.63	0.78	0.85

3.5 Sensitivity Analyses

A PSA was performed by running 1000 iterations per comparison [48]. Results are presented in Fig. 2. The PSA results are consistent with the base-case analyses, showing robustness of the deterministic results. The distribution of incremental QALYs show that the majority of PSA runs predict a higher QALY gain for tepotinib. Deterministic scenario analyses of alternative curves demonstrate that for all plausible choices of curve, the majority of the QALY gains for tepotinib versus the comparators are positive (Table 6 of the ESM).

4 Discussion and Conclusions

The analyses demonstrate that tepotinib is expected to have longer PFS and OS compared with standard-of-care immunotherapy ± chemotherapy treatments for patients with NSCLC harbouring *MET*ex14 skipping, in addition to improving quality of life by delaying progression. However, there are several limitations associated with this study. First, the evidence available for an indirect comparison was limited, particularly as VISION is a single-arm trial in a rare disease area. The analysis in this study aims to alleviate this limitation using robust statistical methods, though there is a lack of comparator data in the relevant population. Although

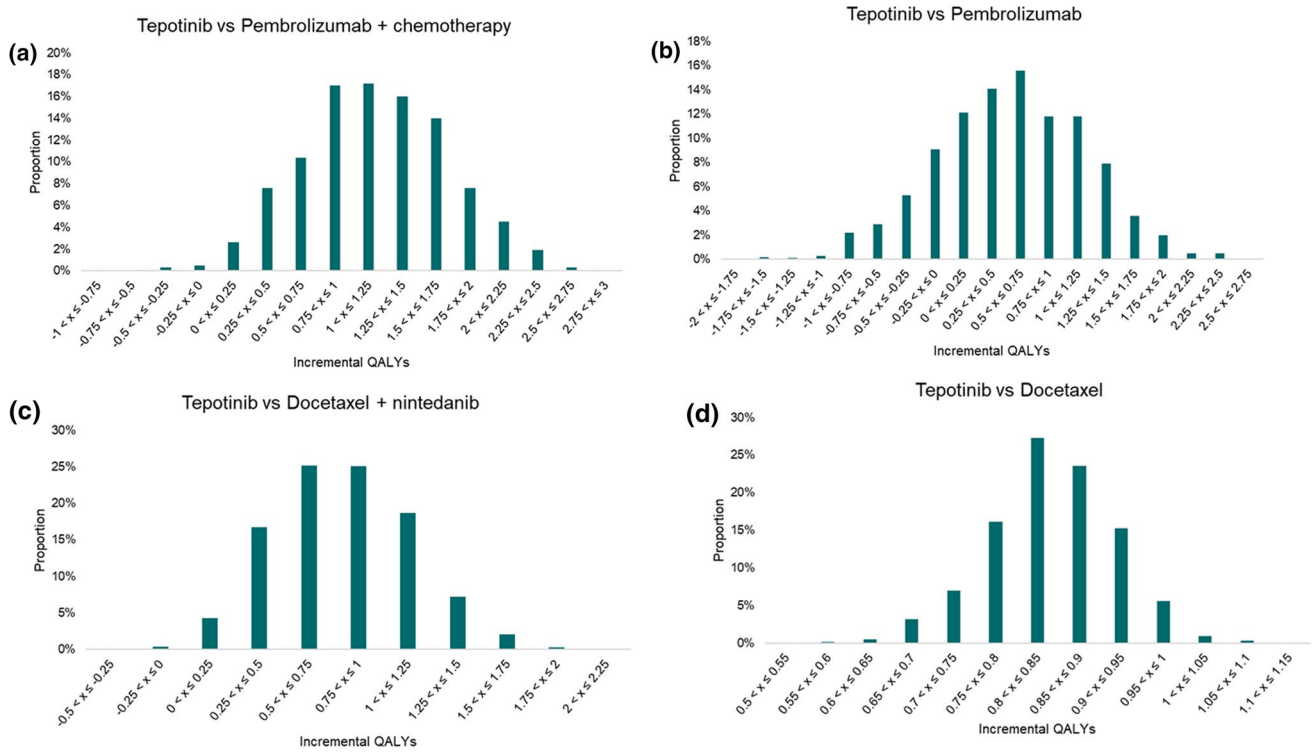

Fig. 2 Distribution of incremental *quality-adjusted life-years (*QALYs*)* from *the probabilistic sensitivity analysis*

real-world data were available of patients with NSCLC harbouring *MET*ex14 skipping, there were notable limitations with the real-world evidence ITC approach because of data collection techniques. Furthermore, not all the real-world data sets collected progression, therefore assumptions were required to generate a comparison on PFS using time on treatment data. In addition, the outcomes for chemotherapy were more favourable than what is expected in clinical practice and observed in the published literature, and therefore may not fully reflect real-world clinical practice [17]. For these reasons, during the NICE appraisal process for tepotinib, the NICE committee concluded that the results of the indirect comparisons using real-world data were highly uncertain. Therefore, the comparisons with published clinical trial data in overall NSCLC populations were considered [17].

A limitation of the MAIC is that comparisons of patients with NSCLC harbouring *MET*ex14 skipping and overall NSCLC populations showed large differences in patient characteristics (i.e. age, sex and smoking history), which led to a large reduction in the effective sample size of VISION patients after matching [49]. Although differences in the observed characteristics could be accounted for, the indirect comparisons were likely impacted by the unobserved confounder of *MET*ex14 skipping status. As patients with NSCLC harbouring *MET*ex14 skipping seem to experience worse outcomes receiving immunotherapy and chemotherapy than patients with overall NSCLC, the results of the MAICs are likely to underestimate the comparative benefit of tepotinib in patients with NSCLC harbouring *MET*ex14 skipping.

The MAIC adjustments to the tepotinib Kaplan–Meier estimates in the comparison to pembrolizumab result in curve projections whereby the PSMs are predicting only slightly higher long-term survival than pembrolizumab. During the tepotinib NICE TA789 submission process, clinical opinion suggested an expectation that tepotinib would produce substantially better outcomes versus immunotherapy [17]. This is due to data that suggest immunotherapy performs poorly in patients with NSCLC harbouring *MET*ex14 skipping and, therefore, a MET-targeted treatment is expected to perform comparatively better than immunotherapy. That this effect was apparently attenuated in our analysis is likely due to several reasons. First, given the low frequency of *MET*ex14 skipping in NSCLC, comparison of the mutation-specific VISION data set to the assumed almost entirely MET-negative KEYNOTE-024 population data set introduces a significant biologic confounder. Added to this, PD-L1 status was not collected in the VISION study, which adds an additional layer of biological uncertainty with regard to comparability as KEYNOTE-024 was conducted in patients with a high PD-L1 tumour proportion score (≥50%). The MAIC is also limited in that the VISION study had to be matched to the KEYNOTE-024 overall population,

whereas the preference would be to generate a comparison in the patient population with NSCLC harbouring *MET*ex14 skipping, which would likely show a difference favouring tepotinib. This is a constraint when access to granular data for comparators is not accessible.

The results of the chemotherapy comparisons in the previously treated setting should be interpreted with caution owing to the available data for docetaxel ± nintedanib. The studies for these two comparators were conducted before first-line immunotherapy was standard practice and therefore do not fully reflect the chemotherapy comparators of today, which predominantly come after first-line immunotherapy. In addition, it is highly unlikely that these second-line and beyond chemotherapy studies will be prospectively re-assessed following first-line immunotherapy-based therapies, providing no meaningful next step to correct for this confounder.

A further limitation is the uncertainty associated with the long-term projections from the PSMs. Subsequent treatments could impact the long-term survival of each treatment and impact the differential treatment effect over time. In addition, the subsequent treatments received in the VISION study or real-world data may differ from standard practice in the UK, resulting in different projections than would occur in clinical practice, while follow-up time is also different between studies that could lead to differences in estimations of subsequent treatment use. It is difficult to account for different treatment patterns over time, and the potential impact of future treatments that may become available.

Despite the limitations of the evidence base, our analyses have consistently indicated positive outcomes for tepotinib versus current standard of care and the results using real-world data are consistent with the findings of the comparisons to published data. Robust validation methods were undertaken to ensure the PSM projections were statistically and visually plausible, and in line with clinical expectations and the external literature. Sensitivity analyses were also conducted to test the impact of alternative selections, while still aligned with clinical expectations. This resulted in similar findings as per the base case. The majority of limitations relating to MAICs could be solved with access to comparator data; therefore, the onus should not be on the specific trial's sponsor to perform these types of analyses, but on active collaboration between trial sponsors.

Tepotinib is the first therapy to be licenced specifically for patients with NSCLC harbouring *MET*ex14 skipping in the UK, filling the previously unmet need for these patients. Although costs have not been presented in this study, because of the oral route of administration and the reduction in regular intravenous administrations, tepotinib is likely to reduce associated healthcare services costs. In addition, tepotinib could reduce the infusion burden for patients, which includes travel time and associated costs.

Modelling the effectiveness of treatments using single-arm trials is notoriously difficult, particularly for health technology agencies who are required to make decisions at a particular point in time based on the evidence available, which is also scarce when considering specific oncogenic driver mutations of NSCLC such as *MET*ex14. This study attempts to overcome these challenges by bringing together all the available evidence, and applying two different approaches (using published clinical trial data and real-world evidence) to compare tepotinib to current standard of care, while noting the limitations of each analysis. Findings from the model suggest that regardless of the data source and methodology, tepotinib is an effective treatment for treating advanced NSCLC with *MET*ex14 skipping in adults.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11523-024-01038-z.

Declarations

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Conflicts of Interest/Competing Interests Helene Vioix and Stamatia Theodora Alexopoulos are employees of Merck. At the time of the analyses, Thomas McLean was an employee of Merck. Rachael Batteson, Emma Hook, Anthony Hatswell and Hollie Wheat are employees of Delta Hat, who were paid consultants for Merck. Shobit Baijal received consulting fees for advisory boards from Merck. Paul Paik holds an advisory role with IDEOlogy, Touch IME, Excerpta Medica, ACE Oncology, Physicians Education Resource, Medscape, Agile, Axis Medical Education, PeerVoice, Aptitude Health, MJH, Annenberg Center and Cardinal Health; receives grants from EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA and Bicara; consulting fees from Novartis, Mirati, Janssen and Bicara; and his research institution receives research expenses from Celgene and EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material The data sets generated during and/or analysed during the current study are not publicly available because of patient confidentiality and data ownership. Any requests for data by qualified scientific and medical researchers for legitimate research purposes will be subject to Merck's (CrossRef Funder ID: 10.13039/100009945) Data Sharing Policy. All requests should be submitted in writing to Merck's data sharing portal (https://www.merckgroup.com/en/research/our-approach-to-research-and-development/healthcare/clinical-trials/commitment-responsible-data-sharing.html).

Code Availability Not applicable.

Authors' Contributions RB drafted the initial manuscript. RB, EH and HW constructed the model. AH performed the statistical analysis to implement in the model. SB and PP provided expert clinical insights. HV, TM and STA reviewed the initial model and provided input into

the overall structure and assumptions, as well as contributing to the original health technology assessment submissions from which the model was based. Data for inclusion within the model were provided by HV, via the pivotal clinical trial and supportive data collection exercises. All authors reviewed each version of the manuscript.

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Authors and Affiliations

Rachael Batteson[1] · Emma Hook[1] · Hollie Wheat[1] · Anthony J. Hatswell[1,2] · Helene Vioix[3] · Thomas McLean[4] · Stamatia Theodora Alexopoulos[4] · Shobhit Baijal[5] · Paul K. Paik[6,7]

✉ Rachael Batteson
rbatteson@deltahat.com

[1] Delta Hat Ltd, Nottingham, UK

[2] Department of Statistical Science, UCL, London, UK

[3] Global Evidence and Value Department, Merck Healthcare KGaA, Darmstadt, Germany

[4] Merck Serono Ltd., an affiliate of Merck KGaA, Feltham, UK

[5] University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

[6] Weill Cornell Medical College, New York, NY, USA

[7] Memorial Sloan Kettering Cancer Center, New York, NY, USA