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## Comparative-Effectiveness Research/HTA

# Health Utility Analysis of Tepotinib in Patients With Non-Small Cell Lung Cancer Harboring *MET* Exon 14 Skipping

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## ABSTRACT

**Objectives:** The VISION trial showed durable activity of tepotinib in *MET* exon 14 (*MET*ex14) skipping non-small cell lung cancer. We analyzed health state utilities using patient-reported outcomes from VISION.

**Methods:** 5-level version of EQ-5D (EQ-5D-5L) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 responses were collected at baseline, every 6 to 12 weeks during treatment, and at the end of treatment and safety follow-up. EQ-5D-5L and European Organisation for Research and Treatment of Cancer Quality of Life Utility Measure-Core 10 Dimensions (QLU-C10D) utilities were derived using United States, Canada, United Kingdom, and Taiwan value sets, where available. Utilities were analyzed with linear mixed models including covariates for progression or time-to-death (TTD).

**Results:** Utilities were derived for 273/291 patients (EQ-5D-5L, 1545 observations; QLU-C10D, 1546 observations). Mean ( $\pm$  SD) US EQ-5D-5L utilities increased after tepotinib initiation, from  $0.687 \pm 0.287$  at baseline to  $0.754 \pm 0.250$  before independently assessed progression, and decreased post progression ( $0.704 \pm 0.288$ ). US QLU-C10D utilities showed similar trends ( $0.705 \pm 0.215$ ,  $0.753 \pm 0.195$ , and  $0.708 \pm 0.209$ , respectively). Progression-based models demonstrated a statistically significant impact of progression on utilities and predicted higher utilities pre versus post progression. TTD-based models showed statistically significant associations of TTD with utilities and predicted declining utilities as TTD decreased. Prior treatment (yes/no) did not significantly predict utilities in progression- or TTD-based models. Utilities for Canada, United Kingdom, and Taiwan showed comparable trends.

**Conclusions:** In this first analysis of health state utilities in patients with *MET*ex14 skipping non-small cell lung cancer, who received tepotinib, utilities were significantly associated with progression and TTD, but not prior treatment.

**Keywords:** disease progression, health state utilities, *MET* exon 14 skipping, *MET* inhibitor, non-small cell lung cancer, patient-reported outcomes, tepotinib, time-to-death.

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## Introduction

Lung cancer ranks as the second most common malignancy and the leading cause of cancer death worldwide.<sup>1</sup> Approximately 80% to 85% of all lung cancer cases are non-small cell lung cancer (NSCLC), which is usually diagnosed at an advanced stage.<sup>2</sup> For many advanced NSCLCs, the management strategy is determined by testing for certain actionable oncogenic driver alterations that predict response to specific targeted therapies.<sup>3</sup> A recent addition to the list of targetable alterations is *MET* exon 14 (*MET*ex14) skipping, a primary oncogenic driver that causes sustained activation of the *MET* receptor in approximately 3% to 4% of NSCLC tumors.<sup>4-6</sup>

Unlike other oncogenic drivers, *MET*ex14 skipping predominantly affects elderly patients (median age: 72 years) and occurs

relatively evenly between males and females, and between smokers and non-smokers.<sup>6-8</sup> Brain metastases affect up to a third of patients with *MET*ex14 skipping and most have adenocarcinoma tumor histology.<sup>8,9</sup> Overall, the symptom burden of patients with *MET*ex14 skipping — as reflected in European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Lung Cancer 13 scores for chest pain, cough, and dyspnea — is similar to that of the general population of patients with advanced NSCLC.<sup>10,11</sup> Although *MET*ex14 skipping is associated with poor response to standard-of-care therapies and short overall survival,<sup>12,13</sup> management of these tumors has been transformed by the development of *MET* inhibitors that target the underlying oncogenic abnormality to elicit meaningful clinical responses.<sup>4,14</sup>

Tepotinib is a potent, highly selective, oral, once-daily *MET* inhibitor.<sup>15</sup> Following its first approval in Japan in March 2020 for

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treatment of advanced NSCLC harboring *MET*ex14 skipping,<sup>16</sup> tepotinib has been approved by multiple regulatory authorities worldwide and is recommended for eligible patients with *MET* alterations in NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) and European Society for Medical Oncology guidelines.<sup>3,17,18</sup> Pivotal clinical data were provided by the single-arm, multicenter Phase II VISION trial, in which tepotinib demonstrated durable clinical activity in patients with *MET*ex14 skipping identified in tissue and/or liquid biopsy samples.<sup>19,20</sup> Based on independent review committee (IRC) assessment, the objective response rate was 49% and median duration of response was 13.8 months (data cut-off: February 1, 2021), with consistent efficacy observed irrespective of age or treatment history.<sup>20–22</sup> Treatment-related adverse events were manageable and mostly mild-to-moderate.<sup>20</sup> In secondary endpoint analysis, patient-reported outcomes (PROs) indicated stability of overall health-related quality of life (HRQL) during tepotinib treatment.<sup>21</sup>

Following the approval of tepotinib, cost-effectiveness analyses are being undertaken to inform healthcare decision making by payers and policy-makers. The recommended methodology for economic evaluations in many countries is the cost-utility analysis, which employs health utilities as a standardized measure of HRQL.<sup>23</sup> Health utilities are preference-based metrics that are expressed on a scale on which 0 represents HRQL equivalent to being dead and 1 represents full health.<sup>23,24</sup> Utilities can be derived from PROs assessing subjective health status. Based on these analyses, utilities can be assigned to specific health states and factored into economic models.<sup>23</sup> Common approaches for modeling health states in patients with advanced cancer are based on either progression status or time-to-death (TTD).<sup>23</sup>

There are currently no available data on health state utilities in patients with advanced NSCLC harboring *MET*ex14 skipping or other *MET* alterations (eg, *MET* amplification). Furthermore, given increasing use of liquid biopsy in clinical practice and evidence that liquid biopsy may identify patients with a poorer prognosis than conventional tissue biopsy,<sup>25</sup> there is a need to understand how health utilities compare between patients identified by these 2 methods. Data on the impact of histologic subtype on health state utilities in NSCLC are also limited. To address these data gaps and to complement the clinical findings of VISION, we used PRO data collected in the trial to evaluate utilities in patients with *MET*ex14 skipping NSCLC, who were treated with tepotinib.

## Methods

### Data Source

Analyses were based on data collected from Cohorts A and C of the international, multicohort, single-arm, open-label, phase II VISION trial (NCT02864992) (Appendix Fig. 1 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>). As reported elsewhere,<sup>19,20</sup> adults with advanced epidermal growth factor receptor (*EGFR*)/anaplastic lymphoma kinase wild-type NSCLC with *MET*ex14 skipping, who were treatment-naïve or who had received up to 2 prior lines of therapy, were enrolled from September 2016. *MET*ex14 skipping was centrally evaluated in tissue biopsy and/or liquid biopsy (ie, plasma) samples using next-generation sequencing-based assays. Patients received tepotinib until disease progression according to investigator (INV) assessment, intolerable toxicity, or consent withdrawal, and were evaluated for objective response by IRC and INV. Treatment was not continued beyond INV-assessed progression. After tepotinib discontinuation, patients could receive standard-of-care therapy according to local practice.

HRQL was evaluated as a secondary endpoint of VISION using the 5-level version of EQ-5D (EQ-5D-5L) and EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) questionnaires (Appendix Fig. 2 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>). Questionnaires were administered to all the patients on day 1, then every 6 weeks for 9 months, and then every 12 weeks during treatment, as well as at the end of treatment and safety follow-up visits. The EQ-5D-5L is a generic instrument including 5 descriptive dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) rated on a 5-point scale, and a visual analog scale (0–100) assessing overall health status.<sup>26</sup> Better HRQL corresponds to lower scores on the descriptive dimensions and higher scores on the visual analog scale. The EORTC QLQ-C30 is a cancer-specific instrument comprising 30 items relating to functional domains (eg, physical, role, and emotional), common cancer-related symptoms (eg, dyspnea, fatigue, and nausea/vomiting), and global health status.<sup>27</sup> Responses are provided on 4- or 7-point scales, with better HRQL represented by higher scores for functional domains and global health status, and lower scores for symptom scales.

### Derivation of Utility Values

Patient-level data were extracted from the trial database (data cut-off: February 1, 2021). The assembled dataset included information on EQ-5D-5L and EORTC QLQ-C30 responses, time of progression per IRC and INV, time of death, prior treatment status (ie, treatment-naïve or previously treated), method of *MET*ex14 skipping detection (ie, tissue and/or liquid biopsy), and tumor histology.

EQ-5D-5L responses were used to derive EQ-5D-5L utilities based on value sets for the United States,<sup>28</sup> Canada,<sup>29</sup> and Taiwan<sup>30</sup> using the “eq5d” package<sup>31</sup> in the statistical software R (version 4.0.3; R Project for Statistical Computing).<sup>32</sup> UK EQ-5D utilities were derived by first mapping EQ-5D-5L data to 3-level version of EQ-5D responses using a crosswalk algorithm<sup>33</sup> and then applying the value set for 3-level version of EQ-5D-derived weights for the United Kingdom.<sup>34</sup> EORTC QLQ-C30 responses were used to derive EORTC Quality of Life Utility Measure-Core 10 Dimensions (QLU-C10D) utilities based on value sets for the United States, Canada, and United Kingdom using published algorithms.<sup>35–37</sup> Derivation of EQ-5D-5L and EORTC QLU-C10D utilities required complete responses for all dimensions of the corresponding questionnaire.

### Utility Summary Analyses

Each utility observation was classified as occurring pre or post progression based on its timing relative to any recorded progression event for that patient. If no progression event was recorded during follow-up, all observations were classified as occurring pre progression. Separate analyses were conducted for IRC- and INV-assessed progression. Given the treatment administration schedule and timing of HRQL assessments (Appendix Fig. 2 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>), post progression (per INV) utility observations were collected at the end of treatment and safety follow-up visits in patients discontinuing because of INV-assessed progression. Patients discontinuing tepotinib for other reasons, including adverse events, were expected to contribute mostly pre progression utility observations; however, these patients could also contribute post progression (per INV) utility observations if INV-assessed progression occurred subsequent to discontinuation, but before the final HRQL assessment at the safety follow-up. Data on utility after IRC-assessed progression were provided by

patients who had IRC-assessed progression before the safety follow-up visit, irrespective of the reason for treatment discontinuation.

The number of patients, number of observations, and empirical mean ( $\pm$  SD) utility values were summarized overall, at baseline, and according to IRC- or INV-assessed progression status (ie, for the pre and post progression health states). Empirical means for the pre and post progression health states reflect all observations collected before and after the date of progression, respectively. Summaries were prepared for the overall population and for the treatment-naïve and previously treated subgroups.

### Regression Analyses

To account for correlations between repeated measurements within patients over time, utilities were analyzed with linear mixed models, using the “lme4” package in R. Two sets of models were fitted: progression-based models (which include progression status as a covariate) and TTD models (which include different time periods before death as covariates) (Appendix Fig. 3 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>). Model fit was evaluated using the Akaike information criterion and Bayesian information criterion. Separate analyses were conducted for EQ-5D-5L and EORTC QLU-C10D utilities derived using weights for each of the analyzed countries.

The progression-based models included a random intercept and fixed effects for either progression status alone (model 1a) or both progression status and prior treatment status (model 1b). Separate models were fitted based on IRC- or INV-assessed progression. These models were used to estimate mean utilities (with standard errors [SEs]), for the pre and post progression health states, overall (model 1a) and by prior treatment status (model 1b). Versions of these models were also evaluated for the subgroups of patients with METex14 skipping identified in tissue or liquid biopsy samples. In exploratory analyses, progression-based models were used to assess the impact of adenocarcinoma or squamous histology.

The TTD models included a random intercept and fixed effects for TTD, which was analyzed as a categorical variable according to 2 different sets of arbitrary cut-offs taken or adapted from previous analyses.<sup>38,39</sup> Model 2a categorized TTD as  $> 30$ ,  $> 15$  to  $\leq 30$ ,  $> 5$  to  $\leq 15$ , or  $\leq 5$  weeks, whereas model 3a categorized TTD as  $\geq 364$ ,  $\geq 182$  to  $< 364$ ,  $\geq 28$  to  $< 182$ , or  $< 28$  days. Versions of these models including fixed effects for prior treatment status were also constructed (models 2b and 3b, respectively). For patients still alive at the data cut-off, the date of the last survival follow-up was used as the time of death. The models were used to predict mean utilities (with SEs) for each TTD time period, overall (models 2a and 3a), and according to prior treatment status (models 2b and 3b).

## Results

### Patient Population

The study population comprised 291 patients with advanced METex14 skipping NSCLC who were treated with tepotinib for a median duration of 6.3 months (range:  $< 0.1$ -50.6). Of these patients, 273 provided EQ-5D-5L and EORTC QLQ-C30 responses (Appendix Table 1 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>). The median age was 72.0 years (range: 41-94), 138 patients (50.5%) were female, and 130 patients (47.6%) had a history of smoking. Overall, 135 patients (49.5%) were treatment-naïve and 138 (50.5%) had received prior treatment. The majority of patients had adenocarcinoma tumor

histology ( $n = 219$ ; 80.2%), whereas 24 patients (8.8%) had squamous histology. METex14 skipping was detected by tissue biopsy in 177 patients (64.8%) and by liquid biopsy in 158 patients (57.9%), with 62 patients (22.7%) testing positive by both methods.

### US EQ-5D-5L and EORTC QLU-C10D Utility Summary Analysis

Of 1677 responses from 273 patients, 1545 were complete and enabled derivation of utility EQ-5D-5L values. Based on IRC progression status, 1202 utility observations from 268 patients were recorded pre progression and 343 observations from 185 patients were recorded post progression (Appendix Fig. 4A in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>). Mean ( $\pm$  SD) US EQ-5D-5L utilities in the overall population increased after tepotinib initiation, from 0.687 ( $\pm 0.287$ ) at baseline to 0.754 ( $\pm 0.250$ ) before progression and decreased after progression to 0.704 ( $\pm 0.288$ ). Comparable trends were observed in the subgroups of treatment-naïve patients (135 patients; 724 observations) and previously treated patients (138 patients; 821 observations) (Fig. 1A).

Of 1677 available EORTC QLQ-C30 responses from 273 patients, 1546 responses were complete and were used to derive EORTC QLU-C10D utilities (Appendix Fig. 4B in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>). The numbers of observations from the IRC pre and post progression health states, respectively, were 1203 (from 268 patients) and 343 (from 185 patients). Mean ( $\pm$  SD) US EORTC QLU-C10D utilities increased after tepotinib initiation, from 0.705 ( $\pm 0.215$ ) at baseline to 0.753 ( $\pm 0.195$ ) pre progression and decreased after progression to 0.708 ( $\pm 0.209$ ). Trends were similar in patients who were treatment-naïve (135 patients; 724 observations) and patients who were previously treated (138 patients; 822 observations) (Fig. 1B).

US EQ-5D-5L utilities and US EORTC QLU-C10D utilities from data collection time points matched to within 7 days were highly correlated (Pearson's correlation coefficient: 0.728) (Appendix Fig. 5 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>).

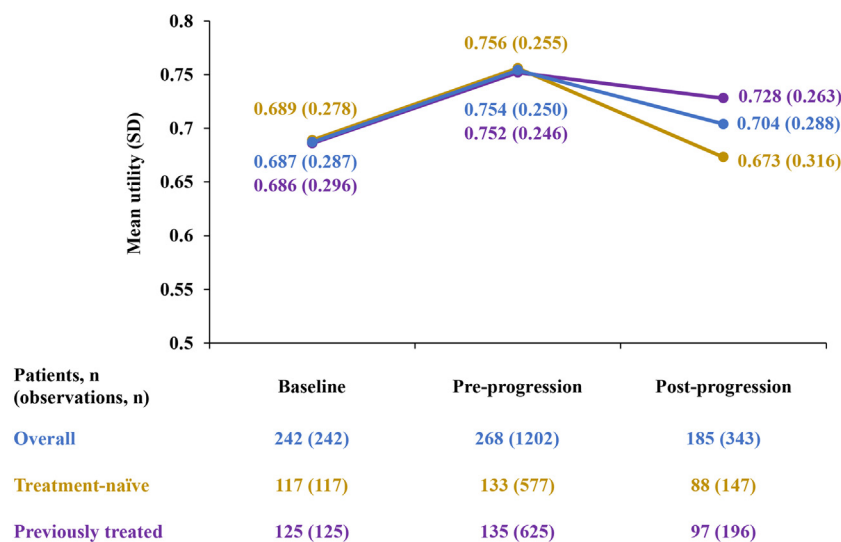
### US EQ-5D-5L Utilities Regression Analyses

Parameters for the IRC progression-based models for US EQ-5D-5L utilities are shown in Table 1. IRC progression status had a significant impact on utility irrespective of whether prior treatment status was included as a covariate ( $P < .001$ ). In contrast, prior treatment status was not significantly associated with utility ( $P = .458$ ), and its inclusion slightly worsened the statistical goodness-of-fit of the model to the data (Appendix Table 2 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>). Mean US EQ-5D-5L utilities estimated using these models showed lower utility values post progression compared with the pre progression health state, both in the overall population and in patients who were treatment-naïve and previously treated (Fig. 2A,B). Analyses based on INV-assessed progression were similar (data not shown).

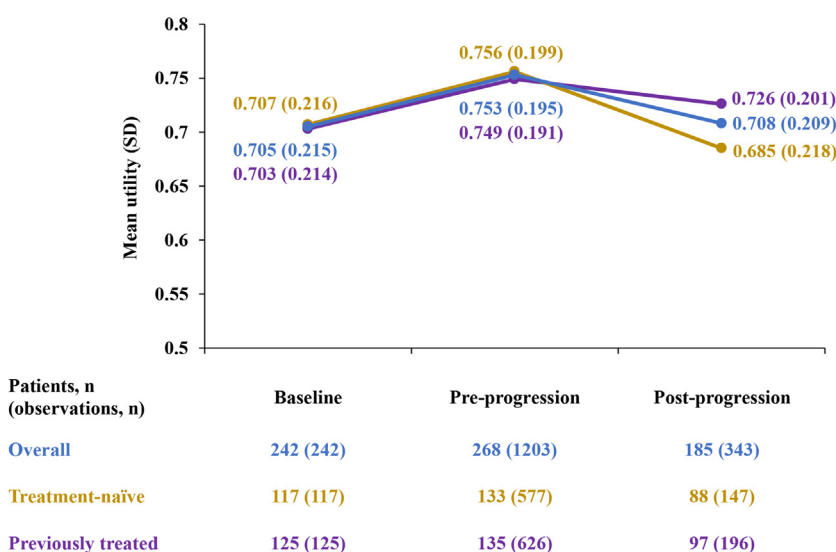
Progression status was also a significant covariate in separate models fitted for the tissue biopsy- and liquid biopsy-positive subgroups ( $P < .001$ ; Appendix Tables 3 and 4 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>). Mean utilities estimated using these models were higher in patients who had tissue biopsy- versus liquid biopsy-positive (Appendix Fig. 6 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>), which is consistent with better prognosis of patients enrolled by tissue compared with liquid biopsy.<sup>25</sup> Although prior treatment status did not significantly

**Figure 1.** Summary statistics for US EQ-5D-5L (A) and US EORTC QLU-C10D (B) utilities, by baseline and IRC progression status, for the overall population and according to prior treatment status.

### A US EQ-5D-5L utilities



### B US EORTC QLU-C10D utilities



EORTC indicates European Organisation for the Research and Treatment of Cancer; EQ-5D-5L, 5-level version of EQ-5D; IRC, independent review committee; QLU-C10D, Quality of Life Utility Measure Core 10 Dimensions.

predict utility, patients who were treatment-naïve and liquid biopsy-positive had the lowest estimated pre progression health state utility. In exploratory analyses using IRC progression-based models, utilities were not significantly predicted by adenocarcinoma ( $P = .400$ ) or squamous histology ( $P = .689$ ).

TTD models for US EQ-5D-5L utilities showed a significant effect ( $P < .05$ ) of all TTD categories included in model 2a ( $> 30$ ,  $> 15$  to  $\leq 30$ , and  $> 5$  to  $\leq 15$  weeks) or model 3a ( $\geq 364$ ,  $\geq 182$  to  $< 364$ , and  $\geq 28$  to  $< 182$  days) (Tables 2 and 3). When incorporated into each regression model, prior treatment status did not significantly predict utility ( $P = .635$  and  $P = .572$ , respectively) and slightly reduced the goodness-of-fit (models 2b and 3b) (Appendix Table 5 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>).

Mean health state utility estimates derived using these models showed that utilities decreased as patients approached death (Fig. 2C,E). Consistent trends were seen in the treatment-naïve and previously treated subgroups (Fig. 2D,F). Although prior treatment status did not significantly predict utility in the TTD models, mean health state utility was numerically slightly higher in patients who were previously treated versus patients who were treatment-naïve.

### US EORTC QLU-C10D Regression Analyses

In the progression-based models, progression status significantly predicted US EORTC QLU-C10D utilities ( $P < .001$ ) in both



**Table 1.** US EQ-5D-5L and EORTC QLU-C10D utility linear mixed model estimated coefficients for progression-based models 1a and 1b, by IRC progression status.

	EQ-5D-5L		EORTC QLU-C10D	
	Model 1a*	Model 1b†	Model 1a*	Model 1b†
Intercept‡ (SE)	<b>0.7271</b> (0.0142)	<b>0.7166</b> (0.0201)	<b>0.7271</b> (0.0107)	<b>0.7211</b> (0.0151)
Post progression (SE)	<b>−0.0682</b> (0.0112)	<b>−0.0683</b> (0.0112)	<b>−0.0441</b> (0.0085)	<b>−0.0442</b> (0.0085)
Previously treated (SE)	–	0.0207 (0.0279)	–	0.0117 (0.0211)

Note. Coefficients for significant covariates are shown in bold.

EORTC indicates European Organisation for Research and Treatment of Cancer; EQ-5D-5L, 5-level version of EQ-5D; IRC, independent review committee; QLU-C10D, Quality of Life Utility Measure Core 10 Dimensions; SE, standard error.

\*Includes a random intercept and fixed effect for progression status.

†Includes a random intercept and fixed effects for progression status and prior treatment status.

‡Corresponds to pre progression utilities overall (model 1a) or pre progression utilities in patients who were treatment-naïve (model 1b).

model 1a (excludes prior treatment) and model 1b (includes prior treatment) (Table 1). Prior treatment status had no significant impact on utility ( $P = .579$ ) and slightly reduced the goodness-of-fit (Appendix Table 6 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>). Mean utilities predicted using these models showed a decrease from the pre to the post progression state in the overall population, and the treatment-naïve and previously treated subgroups (Fig. 2A,B). Although prior treatment did not predict utility, estimated US EORTC QLU-C10D utilities were numerically higher in patients who were previously treated versus patients who were treatment-naïve. Analyses based on INV-assessed progression yielded comparable findings (data not shown).

In the TTD models, all TTD categories had a significant impact on utility except for the  $> 5$  to  $\leq 15$  weeks category ( $P = .094$  in model 2a;  $P = .095$  in model 2b) (Tables 2 and 3). Prior treatment status did not significantly impact on utility (model 2b,  $P = .758$ ; model 3b,  $P = .712$ ) and worsened model fit when included as a covariate (Appendix Table 7 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>). Mean US EORTC QLU-C10D utilities estimated using model 2 decreased progressively with decreasing TTD (Fig. 2C). Estimated using model 3, utility was highest for the TTD category of  $\geq 182$  to  $< 364$  days and decreased thereafter as patients approached death (Fig. 2E). Estimated health state utilities were numerically marginally greater in patients who were previously treated versus patients who were treatment-naïve at each TTD time period in both models (Fig. 2D,F).

### Analyses of Utilities for Canada, the United Kingdom, and Taiwan

Summary analyses of utilities for Canada (EQ-5D-5L and EORTC QLU-C10D), the United Kingdom (EQ-5D crosswalk and EORTC QLU-C10D), and Taiwan (EQ-5D-5L) showed increases in utilities after tepotinib initiation from baseline until progression (Appendix Fig. 7 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>). In linear mixed models, both progression status and TTD were significant predictors of utilities (data not shown). As for US utilities, mean estimated health state utilities for Canada, the United Kingdom, and Taiwan were lower in the post versus pre progression state, and they progressively decreased as patients approached death (Appendix Figs. 8–10 in Supplemental Materials found at <https://doi.org/10.1016/j.jval.2023.02.007>).

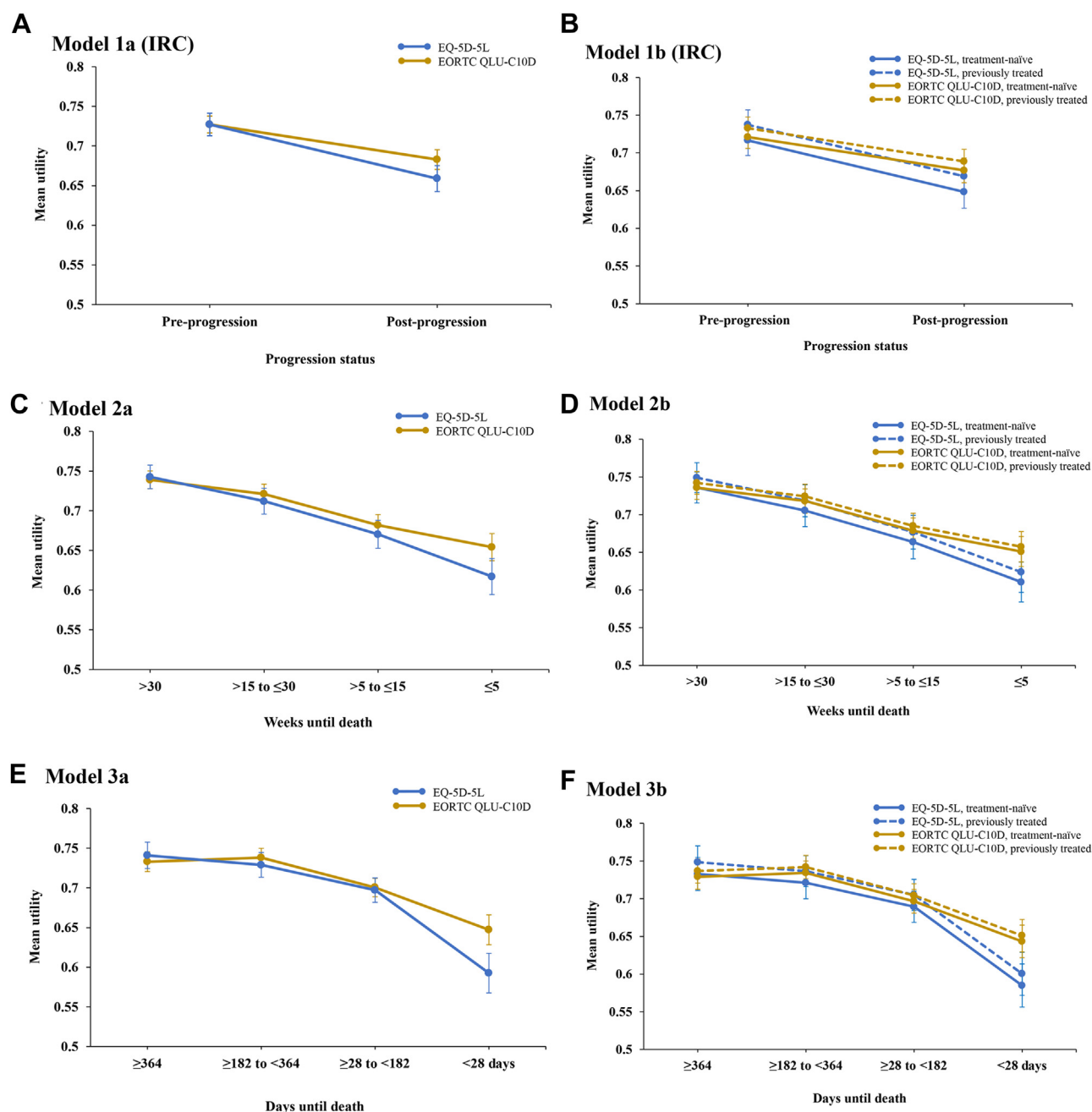
## Discussion

To our knowledge, this analysis of PRO data from VISION provides the first information on health state utilities in patients with METex14 skipping NSCLC. Summary statistics showed that mean utilities increased from baseline during tepotinib therapy until progression in the overall population, and in the treatment-naïve and previously treated subgroups. Mean utilities decreased after progression, but they remained above the baseline level in the overall population (for EQ-5D-5L utilities) and previously treated subgroup (for both EQ-5D-5L and EORTC QLU-C10D utilities), which may favor the use of further lines of therapy. Although the empirical means do not control for repeated measurements and must therefore be interpreted with caution, they are in line with stability in overall HRQL, as well as the durable efficacy and manageable safety of tepotinib, which were observed in the VISION trial.<sup>19,20,40</sup>

US EQ-5D-5L utilities were estimated at 0.727 and 0.659 for the pre and post progression states, respectively. Using TTD models, US EQ-5D-5L utilities were estimated to range between 0.743 (TTD  $> 30$  weeks) and 0.617 (TTD  $\leq 5$  weeks), and between 0.741 (TTD  $\geq 364$  days) and 0.593 (TTD  $< 28$  days). These model-estimated health state utility values for tepotinib-treated METex14 skipping NSCLC fall broadly within the same range as prior estimates for other advanced NSCLC populations,<sup>41–44</sup> including programmed death ligand-1 (PD-L1)-expressing tumors.<sup>45,46</sup> Nevertheless, they appear slightly lower than previously reported for NSCLC with EGFR mutations or anaplastic lymphoma kinase rearrangements treated with targeted therapies,<sup>47–49</sup> which could reflect age-related comorbidities and functional decline in the elderly METex14 skipping population.<sup>50</sup> Of note, targeted therapy has been associated with higher health utilities compared with chemotherapy in patients with other oncogene-driven NSCLC subtypes.<sup>49,51</sup>

Although summary statistics show an increase in health state utilities from baseline after tepotinib initiation until progression, the modeling analyses collectively suggest that health state utilities and HRQL decline as the disease progresses and TTD decreases. The progression- and TTD-based analyses illustrate 2 valid methods to modeling health state utilities that are commonly applied in oncology.<sup>23</sup> Although progression-based models are more closely aligned with standard clinical trial endpoints, TTD models may be valuable in settings where HRQL is not tightly linked to progression status.<sup>52</sup> Because the determinants of HRQL in this setting are not fully understood, the implementation of alternative model structures overcomes the limitations of any single approach and, given the consistency of the results, can

**Figure 2.** Estimated mean (SE) US EQ-5D-5L and EORTC QLU-C10D health state utilities using IRC progression-based Models 1a (A) and 1b (B), and TTD models 2a (C), 2b (D), 3a (E) and 3b (F).



EORTC indicates European Organisation for the Research and Treatment of Cancer; EQ-5D-5L, 5-level version of EQ-5D; IRC, independent review committee; QLU-C10D, Quality of Life Utility Measure Core 10 Dimensions; SD, standard deviation.

increase confidence in the study findings. Furthermore, utilities derived from responses to 2 independent PRO questionnaires (EQ-5D-5L and EORTC QLQ-C30) collected at the same time points ( $\pm 7$  days) were highly correlated (Pearson's correlation coefficient: 0.728) and their respective analyses can be considered mutually supportive.

Whether assessed by IRC or INV, disease progression was a statistically significant predictor of utility in all progression-based models tested, with lower HRQL consistently observed in the post versus pre progression states. One factor that may have contributed to poor post progression HRQL is the use of subsequent

therapies in less than half of patients with *METex14* skipping in VISION.<sup>20,53</sup> Limited use of multiple treatment lines has also been documented in clinical practice<sup>8</sup> and may reflect the older age of the *METex14* skipping population. Our findings are in agreement with a recent large cohort study in which progression was associated with significant and clinically relevant decrements in HRQL across a variety of metastatic tumor types, with the greatest deterioration seen in lung cancer.<sup>54</sup> In patients with advanced NSCLC, decreases in health utilities upon progression have been reported in biomarker-unselected populations,<sup>41,42</sup> as well as in patients with *EGFR*-mutant<sup>47</sup> or PD-L1-expressing tumors.<sup>45</sup>

**Table 2.** US EQ-5D-5L and EORTC QLU-C10D utility linear mixed model estimated coefficients for TTD-based models 2a and 2b.

	EQ-5D-5L		EORTC QLU-C10D	
	Model 2a*	Model 2b <sup>†</sup>	Model 2a*	Model 2b <sup>†</sup>
Intercept <sup>‡</sup> (SE)	<b>0.6171 (0.0227)</b>	<b>0.6107 (0.0264)</b>	<b>0.6541 (0.0171)</b>	<b>0.6510 (0.0199)</b>
> 5 to ≤ 15 weeks to death (SE)	<b>0.0531 (0.0220)</b>	<b>0.0530 (0.0220)</b>	0.0277 (0.0165)	0.0277 (0.0165)
> 15 to ≤ 30 weeks to death (SE)	<b>0.0949 (0.0212)</b>	<b>0.0947 (0.0212)</b>	<b>0.0671 (0.0160)</b>	<b>0.0670 (0.0160)</b>
> 30 weeks to death (SE)	<b>0.1255 (0.0207)</b>	<b>0.1252 (0.0207)</b>	<b>0.0848 (0.0156)</b>	<b>0.0847 (0.0156)</b>
Previously treated (SE)	–	0.0130 (0.0274)		0.0064 (0.0207)

Note. Coefficients for significant covariates are shown in bold.

EORTC indicates European Organisation for Research and Treatment of Cancer; EQ-5D-5L, 5-level version of EQ-5D; QLU-C10D, Quality of Life Utility Measure Core 10 Dimensions; SE, standard error; TTD, time-to-death.

\*Includes a random intercept and fixed effects for TTD categories.

<sup>†</sup>Includes a random intercept and fixed effects for TTD categories and prior treatment status.

<sup>‡</sup>Corresponds to utilities at ≤ 5 weeks to death overall (model 2a) or utilities at ≤ 5 weeks to death in patients who were treatment-naïve (model 2b).

Overall, the present data support the use of separate utility values for the pre and post progression health states.

TTD had a significant impact on health utilities when categorized according to the model 2 and model 3 cut-offs (except for TTD > 5 to ≤ 15 weeks for US EORTC QLU-C10D), which is expected given the strong association between HRQL and survival in lung cancer and other tumor types.<sup>55,56</sup> Similar trends have been reported in TTD analyses of pembrolizumab NSCLC trial participants<sup>43–46</sup> and patients with NSCLC from the general South Korean population.<sup>57</sup> Overall, we observed a progressive decline in utilities with decreasing TTD, with the sharpest fall observed as patients transitioned into the health state closest to death (TTD ≤ 5 weeks in model 2 and < 28 days in model 3). In this final TTD period, estimated utilities were lower in model 3 than model 2, which likely reflects the narrower final TTD period in model 3, in the context of rapidly declining HRQL during the last weeks of life. Conversely, the 2 models produced very similar utility estimates for the time periods furthest from death (> 30 weeks in model 2

and ≥ 364 days in model 3) despite the different time ranges covered, suggesting stability in HRQL at longer TTD. Overall, these models indicate that different utility values should be assigned for each TTD health state.

Although prior treatment status was not significantly associated with utilities in either the progression- or TTD-based models, health state utility estimates were slightly higher in patients who were previously treated versus patients who were treatment-naïve. Interestingly, a real-world cross-sectional survey of patients with advanced NSCLC reported marginally greater pre progression utilities in the second- versus first-line setting.<sup>41</sup> This counterintuitive observation could reflect stronger recollection of premorbid health status in patients who were treatment-naïve and/or psychological adaptation to the disease in previously treated patients. In VISION, there was no indication that differences in baseline characteristics were an explanatory factor, and treatment efficacy was comparable between the 2 subgroups.<sup>20</sup>

**Table 3.** US EQ-5D-5L and EORTC QLU-C10D utility linear mixed model estimated coefficients for TTD-based models 3a and 3b.

	EQ-5D-5L		EORTC QLU-C10D	
	Model 3a*	Model 3b <sup>†</sup>	Model 3a*	Model 3b <sup>†</sup>
Intercept <sup>‡</sup> (SE)	<b>0.5926 (0.0250)</b>	<b>0.5848 (0.0286)</b>	<b>0.6472 (0.0189)</b>	<b>0.6433 (0.0216)</b>
≥ 28 to < 182 days to death (SE)	<b>0.1045 (0.0228)</b>	<b>0.1045 (0.0228)</b>	<b>0.0533 (0.0172)</b>	<b>0.0533 (0.0172)</b>
≥ 182 to < 364 days to death (SE)	<b>0.1364 (0.0235)</b>	<b>0.1362 (0.0235)</b>	<b>0.0910 (0.0177)</b>	<b>0.0909 (0.0177)</b>
≥ 364 days to death (SE)	<b>0.1484 (0.0246)</b>	<b>0.1482 (0.0246)</b>	<b>0.0859 (0.0186)</b>	<b>0.0858 (0.0186)</b>
Previously treated (SE)	–	0.0156 (0.0276)	–	0.0077 (0.0208)

Note. Coefficients for significant covariates are shown in bold.

EORTC indicates European Organisation for Research and Treatment of Cancer; EQ-5D-5L, 5-level version of EQ-5D; QLU-C10D, Quality of Life Utility Measure Core 10 Dimensions; SE, standard error; TTD, time-to-death.

\*Includes a random intercept and fixed effects for TTD categories.

<sup>†</sup>Includes a random intercept and fixed effects for TTD categories and prior treatment status.

<sup>‡</sup>Corresponds to utilities at < 28 days to death overall (model 3a) or utilities at < 28 days to death in patients who were treatment-naïve (model 3b).

A novel aspect of our analysis is the estimation of separate health state utility values for patients in which the same oncogenic driver was detected in either tissue or liquid biopsy samples. Compared with patients with *MET*ex14 skipping positivity by tissue biopsy, those with *MET*ex14 skipping positivity by liquid biopsy had lower utilities, which accords with the worse baseline HRQL and higher prevalence of poor prognostic factors in this subgroup.<sup>25</sup> Because larger or more proliferative tumors are more likely to shed circulating tumor DNA at detectable levels,<sup>58,59</sup> liquid biopsy appears to select a subgroup with greater tumor burden and therefore worse health status.

Study limitations include the single-arm design, which prevented comparison of health state utilities with tepotinib versus other treatments, and the lack of HRQL assessments beyond the 30-day safety visit of the trial, which limited the number of utility observations available post progression. Additionally, the TTD analyses should be interpreted with caution, because of the potential impact of censoring of overall survival for patients alive at the time of the analysis. Exploratory analyses of histology may have been underpowered because of the low number of patients with non-adenocarcinoma subtypes. Although brain metastases have a strong negative impact on HRQL,<sup>60</sup> patients with symptomatic brain lesions were excluded from VISION, as is standard for trials in this setting.<sup>61</sup> Further research is required to understand health state utilities in patients with brain metastases and other clinically important subgroups that may be underrepresented in clinical trials.

## Conclusions

To our knowledge, these analyses provide the first data on health state utilities in patients with NSCLC harboring *MET*ex14 skipping. They highlight the different approaches that can be adopted for the estimation of utilities based on the same data. Compared with any single method, these multiple approaches can increase flexibility for economic modeling and thereby facilitate adaptation according to local health technology assessment body preferences. In the evaluated statistical models, health state utilities increased from baseline during tepotinib treatment until progression, and they were significantly associated with both progression status and TTD.

## Supplemental Material

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.jval.2023.02.007>.

## Article and Author Information

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