Budget impact of tepotinib in the treatment of adult patients with metastatic non-small cell lung cancer harboring METex14 skipping alterations in the United States

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\textbf{ABSTRACT}

\textbf{Aims:} To estimate the budget impact of adding tepotinib to United States (US) health plans for treating adult patients with metastatic non-small cell lung cancer (mNSCLC) harboring mesenchymal–epithelial transition exon 14 (METex14) skipping alterations.

\textbf{Methods:} The base-case analysis was conducted from the perspective of a hypothetical Medicare plan of 1 million members. Scenarios were analysed for other US health plans. Treatments included tepotinib, capmatinib, crizotinib, and standard of care (SoC). Patients eligible for tepotinib were estimated from published epidemiological data and literature, and real-world evidence. Clinical inputs were derived from the phase II VISION trial, US prescribing information, and published literature. Tepotinib uptake and projected testing rates for METex14 skipping alterations were based on market research. Unit costs (2020 US dollars (USD)) and resource utilization associated with drug acquisition and administration, treatment monitoring, disease and adverse event (AE) management, and subsequent treatment were derived primarily from public sources.

\textbf{Results:} In the base-case, 38–65 patients were eligible for tepotinib each year over the three-year time horizon. The cumulative net budgetary impact of tepotinib was $–592,541 (−2.6%); $26,531,670 in the scenario without tepotinib and $25,839,129 in the scenario with tepotinib. A negligible net budget impact was observed per member per month (PMPM) at $0.2457 and $0.2393, respectively, before and after tepotinib’s introduction. Results were most sensitive to variability in unit costs of capmatinib and tepotinib and their corresponding median treatment durations. Sensitivity and scenario analyses support the conclusion that introducing tepotinib will have minimal budgetary impact for Medicare health plans. Similar results were obtained for other US health plans.

\textbf{Limitations:} Assumptions and expert opinion were applied to address data gaps in key model inputs.

\textbf{Conclusions:} The estimated budgetary impact of tepotinib for the treatment of adult patients with mNSCLC harboring METex14 skipping alterations is minimal from the perspective of US health plans.

\section*{Introduction}

Lung cancer is the most common cancer worldwide and is the leading cause of cancer-related death in the United States (US) \textsuperscript{1–3}. There are an estimated 2.1 million new cases globally each year, with lung and bronchial cancer representing an estimated 12.7% of all new cancer cases in the US in 2020\textsuperscript{4}. Most lung cancers fall into two major classes: small-cell lung cancer and non-small cell lung cancer (NSCLC), with NSCLC accounting for approximately 80–85% of cases\textsuperscript{5,6}.

Mutations that lead to skipping of exon 14 of the mesenchymal–epithelial transition (MET) gene, hereby abbreviated as METex14, have been identified as oncogenic drivers in NSCLC, with an estimated prevalence of about 3–4%\textsuperscript{7–11}. Patients with NSCLC harboring METex14 skipping alterations are typically older than those without the mutation, and have a non-squamous histology\textsuperscript{12,13}; they tend to experience poorer prognoses than those without the mutation due to high rates of brain, bone, and liver metastases\textsuperscript{14}.

Until recently, there were no therapies in the US approved specifically to treat this subset of patients, with standard of care (SoC) typically consisting of some combination of immune checkpoint inhibitors (ICIs), anti-vascular endothelial growth factor antibodies (VEGF), and/or chemotherapy. Crizotinib, a tyrosine kinase inhibitor (TKI) indicated for the treatment of patients with locally advanced or metastatic NSCLC (mNSCLC), is currently prescribed as a first-line treatment in patients who have tested anaplastic lymphoma
kinase (ALK)-positive or ROS-1 positive as detected by a US Food and Drug Administration (FDA)-approved test15. Crizotinib also inhibits some MET TKI mutations including METex14 skipping16, and is recommended by the NCCN as a first-line or subsequent therapy option for patients with mNSCLC harboring the METex14 skipping alteration under certain circumstances (category 2A)16. Still another TKI, cabozantinib, has shown promise in initial case reports and is being evaluated in clinical trials for treatment of mNSCLC patients harboring METex14 skipping alterations17-19, but is not currently recommended by the NCCN in this therapeutic context16. Accordingly, there has historically been a high unmet need for efficacious, targeted, and tolerable treatment options with a convenient dosing schedule, particularly for older patients in whom chemotherapy regimens may be unsuitable. In May 2020, capmatinib became the first TKI approved by the US FDA for adult patients with mNSCLC whose tumors have a mutation that leads to METex14 skipping alterations as detected by an FDA-approved test16.

In February 2021, the US FDA approved a second TKI, tepotinib, for adult patients with mNSCLC harboring the METex14 skipping alterations20. The safety, efficacy, and tolerability of tepotinib was evaluated in the VISION study (NCT02864992), a phase II, single-arm, open-label trial of patients including those with locally advanced stage III/IV NSCLC harboring METex14 skipping alterations. Although the availability of targeted treatments for these patients is anticipated to prolong survival, which will result in additional treatment costs, the management of mNSCLC imposes significant burdens on patients and payers alike21,22, and it is therefore important to quantify the potential budget impact of a new therapy to better inform decision-makers14,23 and provide evidence to support submissions to reimbursement agencies24. To that end, this study aimed to estimate the budget impact of including tepotinib for the treatment of US adult patients with mNSCLC harboring METex14 skipping alterations.

Methods
A Microsoft Excel®-based budget impact model (BIM) was developed in accordance with guidelines from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making on Good Modelling Practices25,26.

Target population
The population included in the BIM was US adult patients with mNSCLC harboring METex14 skipping alterations, as detected through biomarker testing. The number of patients (Table 1) was estimated from published epidemiological data, academic and grey literature, and real-world data, based on a hypothetical plan of 1 million members. Annual incidence of mNSCLC for patients <65 years and 65+, and the age composition of patients in Medicare health plans, were extracted from publicly available national databases and used to derive the number of new patients with mNSCLC for the analysis24,27. The proportion of frontline patients harboring the METex14 skipping alteration, and the staging distribution of NSCLC, were obtained from published literature28,29, while real-world data were used to derive the ratio of newly diagnosed to recurrent frontline patients and the ratio of subsequent-line to frontline patients30. This information was combined to calculate the number of eligible patients entering the model after applying projected METex14 biomarker testing rates. The model assumes only patients who receive testing are eligible for treatment with a MET TKI (i.e. tepotinib, capmatinib, or crizotinib). Testing rates were derived from market research conducted by EMD Serono31, and driven by the anticipation that testing is likely to become increasingly common over time due to advances in testing capabilities, the proliferation of new treatments, and changing general attitudes among healthcare practitioners toward the utility of testing in the context of treatment for NSCLC32. As such, testing rates of 49%, 75%, and 85% were applied in the base-case analysis for years 1, 2 and 3, respectively. Alternative assumptions around testing were explored as scenario analyses. As per the US indication for tepotinib, the base-case analysis includes all patients, irrespective of prior treatment, who are modeled as a line-agnostic aggregation of first-line (1L) and second-line or later (2L+/-) populations. With this approach, a new cohort of patients receiving 1L or 2L+-treatment enters the model each year and is assigned to the various interventions in accordance with their respective market shares.

Treatments
Scenarios included in the model reflect current and emerging treatment alternatives for this patient population. Comparators to tepotinib included capmatinib, crizotinib, and SoC. SoC was modeled as a composite of several comparator classes and constituent treatment regimens30, consisting of ICI monotherapy (atezolizumab, nivolumab, and pembrolizumab), ICI + chemotherapy ± anti-VEGF (pembrolizumab + carboplatin + pemetrexed, and atezolizumab + paclitaxel + carboplatin + bevacizumab), chemotherapy ± anti-VEGF (paclitaxel + carboplatin + bevacizumab, pemetrexed + bevacizumab, docetaxel + bevacizumab, and pemetrexed + carboplatin + bevacizumab), and chemotherapy alone (docetaxel, pemetrexed, carboplatin + pemetrexed, cisplatin + pemetrexed, and carboplatin + paclitaxel). The status quo scenario included targeted treatment with capmatinib, crizotinib and SoC, while the alternative scenario also included tepotinib.

Market shares
Market shares for both the status quo and alternative scenarios are presented in Table 2. Projected shares for capmatinib, crizotinib, and SoC in the status quo were derived from market research31, while the composition of SoC was derived from real-world data30. For the alternate scenario, estimated uptake of tepotinib and shares for capmatinib were again derived from market research31, while shares for crizotinib...
and SoC were informed by the assumption that these would lose market share to tepotinib and capmatinib in proportion to the share they maintained in the status quo.

**Model perspective and time horizon**

The base-case analysis estimated the budgetary impact of tepotinib over a three-year time horizon from the perspective of a hypothetical Medicare payer in the US consisting of 1 million members.

**Model overview**

The budget impact analysis conceptualizes two distinct scenarios: (1) a status quo scenario in which patients have recourse only to current treatment options (i.e. excluding tepotinib) and (2) an alternative scenario in which tepotinib is reimbursed by the Medicare plan, drawing market share from its comparators (Figure 1).

Patients with mNSCLC enter the model after biomarker testing confirms the presence of the MET ex14 skipping alteration, and are allocated to the available treatment options according to the market shares presented in Table 2. The model tracks patients receiving each treatment option throughout the time horizon, assuming median clinical outcomes for each option apply. Annual costs for the status quo and alternative scenarios are estimated by multiplying the number of patients receiving each option by the average cost of treatment and then aggregating over the entire treatment portfolio. The budget impact is the cost difference between the scenarios and reflects the way in which the introduction of tepotinib influences the distribution of patients across treatments.

Calculation of eligible patients for a hypothetical Medicare plan consisting of 1 million members is presented in Table 1, while analogous calculations for a hypothetical commercial plan of similar size, which is presented as a scenario analysis, is outlined in the supplementary materials (Supplementary Material SM1).

**Model cost inputs**

The model includes expenditures associated with drug acquisition and administration, treatment monitoring, disease and adverse event (AE) management, subsequent treatment, and biomarker testing. All costs are expressed in 2020 USD.

The drug cost for oral tepotinib was $20,898.60 per package for a 30-day supply. All drug acquisition costs were based on wholesale acquisition cost (WAC) recorded in IBM Micromedex RedBook. This was done because final prices for drugs are not commonly reported and can vary across settings (e.g. due to differences in discounts and price concessions offered by manufacturers); in one methodological review of US BIMs, this observation led to the recommendation that discounts and cost-sharing be deducted from drug acquisition costs. Medication costs for tepotinib, capmatinib, crizotinib, and ICIs were calculated based on flat dosing,

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| Table 1. Annual number of patients eligible for treatment with tepotinib in the context of a Medicare plan (line-agnostic patient population). |
| Parameters | Values | Sources and notes |
|------------|--------|-------------------|
| Plan total | 1,000,000 | Assumption |
| Incidence rate of NSCLC by age (per 100,000) |
| Age: <65 | 12.2 | 15.50% |
| Age: 65+ | 263.0 | 84.50% |
| Number of patients with NSCLC | 2,241 | Calculation |
| % of 1L patients with NSCLC with the METex14 skipping alterations | 3% | Drilon et al. |
| Number of 1L patients | 67 | Calculation |
| % of patients diagnosed initially with metastatic (stage IV) disease over 1 year | 48.7% | Chen et al. |
| Number of patients diagnosed initially with metastatic (stage IV) disease over 1 year | 33 | Calculation |
| Proportion of frontline metastatic patients | 23.5% | EMD Serono. Flatiron Health EHR-derived deidentified database, Data on File. 2020. |
| Number of recurrent patients | 10 | Calculation |
| Total number of 1L patients | 43 (33 + 10) | Calculation |
| Ratio of 2L + to 1L patients | 79.4% | EMD Serono. Flatiron Health EHR-derived deidentified database, Data on File. 2020. |
| Number of 2L + patients | 34 | Calculation |
| Total number of 1L and 2L + patients | 77 (43 + 34) | Calculation |
| Adults with mNSCLC with the METex14 skipping alterations (confirmed through biomarker testing) |
| Year 1 (2021) | 49.0% | 38 | Market research (data on file, EMD Serono) |
| Year 2 (2022) | 75.0% | 58 |
| Year 3 (2023) | 85.0% | 65 |
| Patients eligible for treatment with tepotinib, 2021–2023 | 160 |

**Abbreviations.** 1L, First line; 2L+; Second line or later; METex14, Mesenchymal–epithelial transition exon 14; NSCLC, Non-small cell lung cancer; SEER, Surveillance, Epidemiology, and End Results.
as per US prescribing information. For anti-VEGF agents and chemotherapies, dosing was based on mean patient body weight and surface area (65.91 kg, 1.73 m²) or glomerular filtration rate (70.42 ml/min; applied to carboplatin dosing by the Cockcroft-Gault equation), as per the characteristics of VISION trial participants\(^3\); costs were derived by estimating the whole number of medication vials required to meet dosage requirements (Supplementary Material SM2). Unit costs associated with treatment monitoring and disease management were extracted from Centers for Medicare & Medicaid Services for the base-case\(^3\)\(^6\), while their composition was derived from a combination of published literature\(^37,38\) and assumptions validated by a practicing oncologist. Monthly monitoring costs were estimated at $25.11 (Supplementary Material SM4), while monthly pre-and post-progression disease management costs were calculated to be $1,013.49 and $6,747.62, respectively (Supplementary Material SM5). It was assumed that pre-and post-progression disease management costs did not vary with the treatment received.

The model also incorporates expenditures attributable to medical resource use required to manage AEs, which were calculated by multiplying the frequency of grade 3/4 AEs occurring in at least 5% of patients, as reported in the product prescribing information or published studies, and unit costs obtained from the Healthcare Cost and Utilization Project (HCUPnet)\(^39\). AE management expenditures were applied in the model as a one-time cost (Supplementary Material SM6, SM7).

Subsequent costs included all active treatments in the model and accounted for acquisition costs, frequencies, and duration of treatment. Average duration of subsequent treatments was estimated from the mean progression-free survival (PFS) for subsequent treatments observed in the VISION trial (3.0 months)\(^3\). The composition of subsequent

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**Table 2. Market share inputs.**

| Treatment regimen within class | Intervention | Without tepotinib market entry\(^5\) | With tepotinib market entry\(^5\) |
|---|---|---|---|
| | 2021 | 2022 | 2023 | 2021 | 2022 | 2023 |
| Original comparators | Tepotinib | 0.0% | 0.0% | 0.0% | 13.9% | 22.8% | 22.8% |
| Capmatinib | 59.2% | 60.0% | 60.0% | 50.3% | 42.3% | 42.3% |
| Crizotinib | 4.9% | 4.8% | 4.8% | 4.3% | 4.2% | 4.2% |
| Experimental treatment | Not applicable | 4.4% | 4.3% | 4.3% | 3.8% | 3.7% | 3.7% |
| ICI monotherapy | Atezolizumab | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% |
| Nivolumab | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% | 0.3% |
| Pemetrexed | 5.9% | 5.8% | 5.8% | 5.2% | 5.1% | 5.1% |
| ICI + chemotherapy ± anti-VEGF | Pembrolizumab + carboplatin + pemetrexed | 5.3% | 5.2% | 5.2% | 4.7% | 4.6% | 4.6% |
| Chemotherapy + anti-VEGF | Paclitaxel + carboplatin + bevacizumab | 0.6% | 0.6% | 0.6% | 0.5% | 0.5% | 0.5% |
| Chemotherapy alone | Docetaxel | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| Carboplatin + paclitaxel | 7.5% | 7.3% | 7.3% | 6.6% | 6.4% | 6.4% |
| Total | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% | 100.0% |

**Abbreviations.** 1L, First line; 2L+, Second line or later; ICI, Immune checkpoint inhibitor; VEGF, Vascular endothelial growth factor.
treatment could vary according to which treatment the patient received before progression, in that it was assumed patients would not be retreated with the same TKI they had previously received (where applicable) but could be administered another product from the same class of therapies (Supplementary Material SM8). Costs for subsequent treatment for tepotinib were $13,993.45, while those accrued following discontinuation from capmatinib, crizotinib and SoC were $13,900.02, $14,336.01, and $13,993.45, respectively.

The model also assumed all patients would incur one-time biomarker testing costs upon entering the model, irrespective of whether they ultimately received a MET TKI. The cost applied in the model ($2,854.73) is the average across current tests available in the US (Supplementary Material SM9).

**Sensitivity analysis**
A deterministic sensitivity analysis (DSA) was conducted by testing the upper and lower bounds of individual model parameters to assess their impact on the model outcomes. Parameters incorporated into the DSA included the number of patients entering the model in each year; uptake of tepotinib in the alternative scenario; median treatment duration, PFS and overall survival (OS) for each MET TKI and each class of treatments constituting SoC, for both 1L and 2L+; additional parameters included costs associated with drug acquisition and administration, treatment monitoring, disease and AE management, and biomarker testing. All non-clinical parameters included in the DSA were varied by 20% above and below the base-case values, while clinical parameters were varied by the upper and lower bounds of the 95% confidence intervals (CIs).

**Scenario analysis**
The DSA was supplemented by several scenario analyses, which explored the impact of varying assumptions around rates of biomarker testing, treatment duration, and line of therapy (i.e. frontline (1L) or relapsed (2L+) patients only) from the Medicare payer perspective, as well as the budgetary impact of tepotinib from the perspective of Medicare Part D prescription drug plan (PDP) and commercial payers.

**Results**

**Cost per course**
The cost per course of therapy for selected interventions (i.e. targeted treatments, ICI monotherapy, and ICI + chemotherapy± anti-VEGF regimens), as calculated using WAC prices, is provided in Table 3. These values include only drug acquisition costs, and are calculated by multiplying the monthly cost of therapy by the weighted treatment duration; the weights were derived with reference to the median time on treatment, the ratio of 2L+ to 1L.
patients from the Flatiron database analysis, and utilization on both lines.

The cost per course for the TKIs was $155,690, $172,916, and $137,190 for tepotinib, capmatinib, and crizotinib, respectively, while the cost for ICI monotherapy was $47,573 for nivolumab, $72,613 for pembrolizumab, and $46,713 for atezolizumab. Finally, the cost of a regimen consisting of pembrolizumab, carboplatin and pemetrexed was $172,127, while expenditures associated with atezolizumab, paclitaxel, carboplatin, and bevacizumab were $179,138.

**Base-case analysis**

In a hypothetical Medicare health plan consisting of 1 million members, the introduction of tepotinib as a treatment for adult patients with mNSCLC harboring METex14 skipping alterations generated a cumulative net budgetary impact of –$692,541 (–2.6%) over three years with –$103,337 in year 1 (38 patients), –$313,790 in year 2 (58 patients), and –$275,414 in year 3 (65 patients). The total per member per month (PMPM) costs before and after the introduction of tepotinib were $0.2457 and $0.2393, respectively. The estimated incremental cost impact PMPM of tepotinib was –$0.0064 over the three-year period. Specifically, the budget impact PMPM of tepotinib to a Medicare health plan was estimated at –$0.0029 in year 1, –$0.0087 in year 2, and –$0.0077 in year 3. A summary of the budget impact results PMPM is presented in Figure 2, while a detailed breakdown by cost category is presented in the supplementary materials (Supplementary Material SM10).

**Sensitivity analysis**

Variability in the cost per month of both capmatinib and tepotinib had the most significant impact on the model estimates of incremental cost PMPM, followed by median duration on both treatments for 1L and 2L +. Total budgetary impact ranged from $152,279 to $1,537,360 when the monthly cost of capmatinib was decreased or increased by 20%, respectively, while incremental costs PMPM ranged from $0.0014 to $0.0142. The opposite pattern was observed when the monthly cost of tepotinib was adjusted similarly (i.e. –$1,469,850 and $84,769 (PMPM: –$0.0136 to $0.0088)). The variability in the number of patients entering the model and survival metrics (OS/PFS) had a smaller impact on estimates of total cost. A tornado diagram illustrating these results on PMPM is presented in Figure 3, while a tabular ranking of scenarios revolving around total costs, PMPM and per treated member per month (PTMPM) is included in the supplementary materials (Supplementary Material SM11). These results reflect the expectation that tepotinib’s market share in the alternative scenario will derive primarily from capmatinib.
Figure 2. Budget impact on cost per member per month over three years in a hypothetical Medicare plan of 1 million members. Abbreviation: PMPM, Per member per month.

Figure 3. Tornado diagram: incremental cost per member per month (PMPM) over a three-year time horizon (Medicare perspective). Abbreviations. 1L, First line; 2L+, Second line or later; PMPM, Per member per month.
Scenario analyses

Conservative testing rates

Conservative testing rates based upon a linear extrapolation from a published source (i.e. 38%, 44%, and 51% over the three-year time horizon, vs. 49%, 75%, and 85% in the base-case) was explored. In a hypothetical Medicare health plan consisting of 1 million members, the introduction of tepotinib using these conservative testing rates resulted in a cumulative budgetary impact of −$416,953 (−2.5%) over a three-year time horizon. Results by year were −$79,084 (year 1, 29 patients), −$173,124 (year 2, 34 patients), and −$164,744 (year 3, 39 patients). The total PMPM costs prior to and after the introduction of tepotinib were $0.1553 and $0.1514, respectively; specifically, the budget impact PMPM was −$0.0022 in year 1, −$0.0048 in year 2, and −$0.0046 in year 3.

A second testing scenario assumed testing rates that were 20% lower than the base-case (i.e. 39% vs. 49% (base-case) in year 1, 60% vs. 75% (base-case) in year 2, and 68% vs. 85% (base-case) in year 3). In this scenario, the introduction of tepotinib resulted in a cumulative budgetary impact of −$554,032 (−2.6%) over the three-year time horizon. Results by year were −$82,669 (year 1, 30 patients), −$251,032 (year 2, 46 patients), and −$220,331 (year 3, 52 patients). The total PMPM cost prior to and after the introduction of tepotinib was $0.1965 and $0.1914, respectively; specifically, the budget impact PMPM was −$0.0023 in year 1, −$0.0070 in year 2, and −$0.0061 in year 3.

In general, lower assumed rates of testing attenuate the cost impact associated with the introduction of tepotinib.

Higher testing rates

Given technological progress in the diagnostics space, continuous increases in testing capacities, and a general trend toward increasing acceptance of testing as a tool for guiding optimal therapeutic decision-making, a scenario assuming higher testing rates was conducted. This scenario assumed testing rates to be up to 20% higher than the base-case, capped at 100% (i.e. 59% vs. 49% (base-case) in year 1, 90% vs. 75% (base-case) in year 2, and 100% vs. 85% (base-case) in year 3). In this scenario, the introduction of tepotinib resulted in a cumulative budgetary impact of −$821,044 (−2.6%) over the three-year time horizon. Results by year were −$124,004 (year 1, 45 patients), −$376,548 (year 2, 69 patients), and −$320,492 (year 3, 77 patients). The total cost PMPM prior to and after the introduction of tepotinib was $0.2925 and $0.2849, respectively; specifically, the budget impact PMPM was −$0.0034 in year 1, −$0.0105 in year 2, and −$0.0089 in year 3. Higher assumed testing rates were seen to amplify the cost impact associated with the introduction of tepotinib. This occurs because testing increases the number of patients eligible to receive a TKI, including tepotinib. As introducing tepotinib reduces overall expenditures in the Medicare base-case, diverting additional patients to this intervention should further reduce spending.

Assuming treatment duration equal to PFS

In the base-case, treatment duration was equal to median time on treatment, where this information was available, and equal to median PFS otherwise. In this scenario, treatment duration was instead assumed to be uniformly equal to median PFS. The rationale for including this scenario was twofold. First, assuming treatment duration to be equivalent to PFS may be conservative as PFS is typically longer than time on treatment, which may result in overstating costs for each treatment. Second, although time on treatment is accessible for tepotinib and a small number of comparators, it was not consistently reported across comparators; accordingly, it is important to assess the implications of applying a measure of treatment duration (i.e. PFS) for which information for all comparators is available. Within the context of this scenario, the introduction of tepotinib in a hypothetical Medicare health plan consisting of 1 million members did not affect the number of eligible patients entering the model relative to the base-case. In this scenario, the cumulative budgetary impact was −$33,462 (−0.1%) over the three-year time horizon. Results by year were $12,365 in year 1, −$45,262 in year 2, and −$565 in year 3. The total PMPM cost prior to and after the introduction of tepotinib was $0.2608 and $0.2605, respectively; specifically, the budget impact PMPM was $0.0003 in year 1, −$0.0013 in year 2, and $0.0000 in year 3.

Medicare Part D prescription drug plan

Medicare’s Part D PDP is a stand-alone plan which provides coverage of outpatient prescription drugs that are found on the plan’s formulary and does not include drug acquisition or administration costs associated with products administered in an inpatient setting, thereby limiting reimbursement to the three MET TKIs. This scenario assessed the impact of introducing tepotinib within the context of a PDP with all other parameters as per the base-case, where treatment duration was assumed to be equal to median time on treatment. This scenario resulted in a net budgetary impact of −$450,950 (−2.0%) over a three-year time horizon. Results by year were −$44,836 (38 patients), −$223,748 (58 patients), and −$182,367 (65 patients) in year 1, year 2, and year 3, respectively. The total costs PMPM prior to and after the introduction of tepotinib were $0.2083 and $0.2041, respectively; specifically, the budget impact PMPM was −$0.0012 in year 1, −$0.0062 in year 2, and −$0.0051 in year 3. Budgetary impact from the perspective of Medicare PDP payers is less than the base-case for Medicare because the former typically would not provide coverage for costly SoC regimens typically delivered in an inpatient setting. This eliminates any cost reductions that would otherwise accrue due to diversion of patients receiving those regimens to tepotinib.

A second scenario using Medicare’s Part D PDP was conducted which instead assumed time on treatment to be equal to median PFS. In this scenario, in a hypothetical PDP consisting of 1 million members, the introduction of tepotinib resulted in a net budgetary impact of $234,700 (1.0%) over a three-year time horizon. Results by year were $77,096, $54,315, and $103,289 in year 1, year 2, and year 3,
respectively. The total PMPM costs prior to and after the introduction of tepotinib were $0.2214 and $0.2236, respectively; specifically, the budget impact PMPM was $0.0021 in year 1, $0.0015 in year 2, and $0.0029 in year 3. The results of this scenario differ significantly from the previous scenario as the median PFS is longer than the median treatment duration; this difference was observed across the tepotinib and capmatinib regimens and both 1L and 2L + treatment lines, and was most pronounced for tepotinib and in 2L + patients (8.1 months for median treatment duration, and 10.9 months for median PFS). This is particularly important given the significant ratio of 2L + to 1L patients (Table 1). With drug acquisition costs contributing to a significant portion of overall costs, a positive budgetary impact was observed.

**Patient population split by 1L only and 2L + only**

In the base-case, a line-agnostic patient population was modeled; all patients, irrespective of prior treatment, were modeled as a single cohort. On this basis, disease management and subsequent treatment costs for 1L are captured in 2L +.

This scenario assumes tepotinib is approved only for frontline (1L) patients but also accounts for the resultant downstream impacts, and therefore encompasses disease management and subsequent treatment costs. In a hypothetical Medicare plan consisting of 1 million members, the introduction of tepotinib resulted in a net budgetary impact of $−365,592 (−1.8%) over the three-year time horizon for the 1L patient population. Results by year were $−57,346 in year 1, $−164,276 (32 patients), and $−173,519 (36 patients) in year 1, year 2, and year 3, respectively. The cost PMPM prior to and after the introduction of tepotinib was $0.1849 and $0.1815, respectively; specifically, the budget impact PMPM was $−0.0008 in year 1, $−0.0046 in year 2, and $−0.0048 in year 3.

A second scenario included only the 2L + patient population. In a hypothetical Medicare plan consisting of 1 million members, the introduction of tepotinib resulted in a net budgetary impact of $245,979 (2.5%) over the three-year time horizon for the 2L + patient population. Results by year were $−7,841 (17 patients), $81,714 (25 patients), and $172,106 (29 patients) in year 1, year 2, and year 3, respectively. The cost PMPM prior to and after the introduction of tepotinib was $0.0924 and $0.0947, respectively; specifically, the budget impact PMPM was $−0.0002 in year 1, $0.0023 in year 2, and $0.0048 in year 3.

The difference in results across the two populations is largely due to increased median time on treatment associated with tepotinib (8.1 months) relative to capmatinib (5.1 months) in the 2L + patient population, which in turn manifests in large differences in drug acquisition costs between the status quo and alternative scenarios.

**Commercial payer perspective**

This scenario examined the impact of tepotinib within the context of a US commercial health plan. Relative to the base-case, the model assumed a significantly younger population in this plan42, and, since incidence of NSCLC is much higher in older (65+ years) adults43, it was assumed fewer participants would be eligible for treatment with tepotinib relative to a Medicare plan (Supplementary Material SM1). In addition, this scenario often employed a different set of costs than that applied in the base-case, although it was assumed resource utilization would not materially differ (Supplementary Materials SM3–SM7). Within this context, eight patients would be eligible to receive tepotinib in year 1, while 12 and 13 patients would be eligible in years 2 and 3, respectively. The model estimated that introducing tepotinib within a commercial plan would generate a cumulative net budgetary impact of $−157,929 (−2.4%) over three years, including $−27,136 in year 1, $−73,447 in year 2, and $−57,346 in year 3. The total PMPM costs prior to and after the introduction of tepotinib were $0.0604 and $0.0589, respectively, implying a difference of $−0.0015 (−2.4%). Specifically, the budget impact PMPM was estimated at $−0.0008, $−0.0020, and $−0.0016 in year 1, year 2, and year 3, respectively (Supplementary Material SM10).

**Discussion**

Understanding the potential budgetary impact of introducing tepotinib – approved by the FDA in February 2021 as a treatment option in adult patients with mNSCLC harboring METex14 skipping alterations – is essential to inform formulary decisions in the context of a rapidly evolving therapeutic landscape. Accordingly, a BIM was developed in accordance with the ISPOR Good Modelling Practices Guidelines25,26 to estimate the financial impact of reimbursing tepotinib. Prior to the approval of tepotinib, patients with this alteration typically received capmatinib (first FDA-approved targeted therapy for this indication), crizotinib (off-label use), or SoC, consisting of combinations of ICI monotherapy, ICI + chemotherapy ± anti-VEGF, chemotherapy ± anti-VEGF, and chemotherapy alone.

In the base-case, the model estimated costs accruing to a hypothetical Medicare plan consisting of 1 million members with or without tepotinib in the market mix. The cumulative net budgetary impact was $−692,541 (−2.6%) over three years, equivalent to a cumulative net budgetary impact of $−0.0064 PMPM. This was primarily driven by the combination of two factors. First, as indicated in Table 2, the model assumes tepotinib will gain the bulk of its market share from capmatinib. Second, although the monthly cost of tepotinib is higher than capmatinib, at the cohort level this is more than offset by differences in median treatment duration in the frontline setting (6.8 vs. 11.1 months for tepotinib and capmatinib, respectively), culminating in a lower overall cost per course of therapy (Table 3).

DSA results suggest variability in the cost of acquiring tepotinib and capmatinib had the largest impact on model outcomes, followed by variability in their respective median treatment durations, whereas the impact of variation in other parameters was comparatively more modest; however, the DSA broadly supports the base-case finding that from a
budgetary standpoint, the financial impact of reimbursing tepotinib for Medicare payers is likely to be limited.

Numerous scenario analyses were also undertaken using the model. Increasing or decreasing testing rates directly impacted the number of patients eligible for treatment, and was therefore observed to amplify or attenuate tepotinib’s budgetary impact, respectively. Uniformly applying median PFS as a proxy for treatment duration inflated treatment costs for tepotinib relative to comparators for which this was already done (i.e. because median treatment duration for those comparators is unavailable), diminishing net budgetary impact relative to the base-case. Other scenarios considered the impact of reimbursing tepotinib in 1L or 2L+ only or estimated the budgetary impact of tepotinib from the perspective of commercial or Medicare Part D PDP payers. Results from all scenarios aligned with expectations and supported the base-case finding that the introduction of tepotinib is unlikely to materially affect the financial position of health plans in the US.

The analyses relied upon numerous assumptions as well as data availability. Key clinical inputs such as time on treatment, PFS, OS, and AE profiles were based on values reported in US prescribing information and published clinical trials, many of which were conducted as multinational studies; however, the model assumed these to be generalizable to the US setting. Clinical inputs specific to the population of patients harboring METex14 skipping alterations do not presently exist for comparators other than tepotinib, capmatinib, and crizotinib; accordingly, data from trials in the general NSCLC population were used instead. In addition, although the model assumes treatment duration equal to median time on treatment where this information was available and PFS otherwise, in real-world treatment settings, oncologists may continue treatment even following progression, particularly where few treatment alternatives are available. However, while data gaps preclude investigating possible implications, this limitation is not expected to bias the results of the analysis, since the same consideration could apply to many of the interventions included in the study. Moreover, the approach chosen for this study was validated by a practicing oncologist. Another limitation is that estimation of subsequent treatment costs accounted only for expenditures associated with drug acquisition and did not consider any possible further impact on clinical and safety outcomes; in addition, the effectiveness of subsequent treatment was implicitly captured by OS data from the VISION trial and publicly available clinical data sources, rather than being modeled explicitly. Further to this, it is important to acknowledge the model’s limitations in capturing downstream impacts attributable to the choice of therapies in earlier treatment lines, and the resultant implications for plan budgets. For example, at present, treatment outcomes in 2L+ do not depend on the class of therapies patients received in frontline. This simplifying assumption is common in budget impact analyses for new oncology agents, although it is also necessitated by a dearth of evidence surrounding clinical outcomes in relation to treatment sequences in the context of adult patients with mNSCLC harboring METex14 skipping alterations. Similarly, data gaps exist in estimates of medical resource utilization associated with disease management and treatment monitoring; therefore, these inputs were supplemented using clinical expert validation and/or assumptions, where necessary. It should also be noted that the model did not account for the availability of patient cost-sharing mechanisms, such as co-payments or coinsurance. Finally, although the results of this study may help to inform decisions regarding the allocation of scarce health care resources in the context of this indication, we acknowledge that cost-effectiveness analyses that consider outcomes alongside costs may also be of significant interest to stakeholders; accordingly, we believe this should be a priority for future research relating to the treatment of adult patients with mNSCLC harboring METex14 skipping alterations.

Conclusions

Results of the base-case analysis suggest the introduction of tepotinib had minimal financial impact associated with the treatment of adult patients with mNSCLC harboring METex14 skipping alterations from the perspective of US Medicare plans. Results of the DSA and the scenario analyses suggest this finding is robust to variation in key model parameters and may extend to US commercial and Medicare Part D PDP payers. These results are driven in part by the low prevalence of the METex14 skipping alterations, assumptions regarding projected rates of biomarker testing and the uptake of tepotinib, and differences in costs and estimated treatment duration between therapies.

Notes

i. Microsoft Excel (Redmond, WA, USA).
ii. IBM Micromedex RedBook (Armonk, NY, USA).
iii. Tepmetko (Merck Healthcare KGaA, Darmstadt, Germany).

Transparency

Declaration of funding

Funding for this study and article was provided by EMD Serono and Merck KGaA, and contracted with Evidera for services on this project and manuscript.

Declaration of financial/other relationships

MS, JT, AA, MM, and RS are employed by Evidera, a consulting company that has received funding from EMD Serono and Merck KGaA, the makers of Tepmetko® (tepotinib). AM was employed by The University of Arizona during the conduct of this study. MY and FL are employed by EMD Serono, and HV is employed by Merck KGaA. JME peer reviewers on this manuscript have received an honorarium from JME for their review work, but have no other relevant financial relationships to disclose.

Author contributions

All authors contributed to the interpretation of data and results and drafting the manuscript. Additionally, AA, MM, MS, and JT contributed to
the model development, conduct of analyses, and implementation of the design. All authors reviewed the final model design, data sources, and results. All authors meet the International Committee of Medical Journal Editors criteria for authorship, take responsibility for the integrity of the entirety of this work, and have given final approval to this version.

Acknowledgements
None reported.

Previous presentations
A related abstract was previously presented at the 2021 American Society of Clinical Oncology Annual Meeting.

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