



e-ISSN: 2319-8753 | p-ISSN: 2347-6710

# IJRSET

International Journal of Innovative Research in  
**SCIENCE | ENGINEERING | TECHNOLOGY**



# INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN SCIENCE | ENGINEERING | TECHNOLOGY

Volume 13, Issue 5, May 2024

**ISSN** INTERNATIONAL  
STANDARD  
SERIAL  
NUMBER  
INDIA

Impact Factor: 8.423

 9940 572 462

 6381 907 438

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# A Review on Tepotinib: Unveiling its Drug Profile and Applications in Managing Metastatic Non-Small Cell Lung Cancer (NSCLC)

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**ABSTRACT:** Tepotinib, a selective small-molecule inhibitor of the MET receptor tyrosine kinase, has emerged as a promising therapeutic option for metastatic non-small cell lung cancer (NSCLC), particularly in patients harboring MET exon 14 skipping mutations. This abstract provides a comprehensive overview of tepotinib, highlighting its drug profile, mechanism of action, pharmacokinetics, and clinical applications in NSCLC therapy. Tepotinib's targeted inhibition of aberrant MET signaling offers a tailored treatment approach for NSCLC patients with MET exon 14 skipping mutations, addressing a previously unmet medical need. Clinical studies, including pivotal trials such as the VISION study, have demonstrated its efficacy as a monotherapy and in combination with other agents, leading to durable responses and improvements in progression-free survival. Biomarker-driven treatment strategies, guided by the identification of MET exon 14 skipping mutations, optimize patient selection and treatment outcomes. Ongoing research aims to further elucidate tepotinib's therapeutic potential, including its efficacy in specific patient subgroups and mechanisms of resistance. Overall, tepotinib represents a paradigm shift in the management of metastatic NSCLC, offering personalized treatment options and redefining the standard of care for this genetically defined subset of patients.

**KEYWORDS:** Tepotinib, MET inhibitor, NSCLC treatment, Pharmacokinetics, Exon 14 mutations

## I. INTRODUCTION

Tepotinib, a novel small-molecule inhibitor targeting the MET receptor tyrosine kinase, has emerged as a promising therapeutic option in the management of various cancers, notably metastatic non-small cell lung cancer (NSCLC). Its development represents a significant advancement in precision medicine, particularly for patients harboring MET exon 14 skipping mutations, whose treatment options have historically been limited. This introduction aims to provide a comprehensive overview of tepotinib, elucidating its drug profile, mechanism of action, pharmacokinetics, and clinical applications in NSCLC therapy. Tepotinib, also known by its trade name Tepmetko, is developed by Merck KGaA, Darmstadt, Germany, and its efficacy in targeting MET-driven malignancies has been extensively studied in preclinical and clinical settings. The MET receptor tyrosine kinase plays a crucial role in cell proliferation, survival, and angiogenesis, and aberrant activation of the MET pathway has been implicated in the pathogenesis and progression of various cancers, including NSCLC. Notably, MET exon 14 skipping mutations, characterized by the loss of regulatory elements, result in MET protein dysregulation and have been identified in approximately 3-4% of NSCLC cases, making them a clinically relevant molecular target. Tepotinib acts as a highly selective and potent inhibitor of the MET receptor tyrosine kinase, exerting its antitumor effects by blocking MET signaling pathways implicated in cancer cell proliferation, migration, and survival. By binding to the MET receptor's catalytic domain, tepotinib competitively inhibits ATP binding, thereby disrupting downstream signaling cascades involved in tumor growth and metastasis. Importantly, its selectivity for MET kinase distinguishes tepotinib from multitargeted tyrosine kinase inhibitors, minimizing off-target effects and potentially enhancing therapeutic efficacy. Pharmacokinetic studies have revealed favorable drug properties for tepotinib, including good oral bioavailability, a manageable half-life conducive to once-daily dosing, and predictable dose-proportional exposure. Furthermore, its favorable safety profile, characterized by manageable adverse events such as peripheral edema, nausea, and diarrhea, underscores its clinical utility and tolerability in NSCLC patients. In clinical trials, tepotinib has demonstrated remarkable efficacy as a monotherapy and in combination with other agents in the treatment of advanced NSCLC harboring MET exon 14 skipping mutations. Clinical data from pivotal trials, such as the VISION study, have showcased its ability to induce durable responses and improve progression-free survival in heavily pretreated NSCLC patients, positioning tepotinib as a promising therapeutic option for this genetically defined subset of patients. In conclusion, tepotinib represents a paradigm shift in

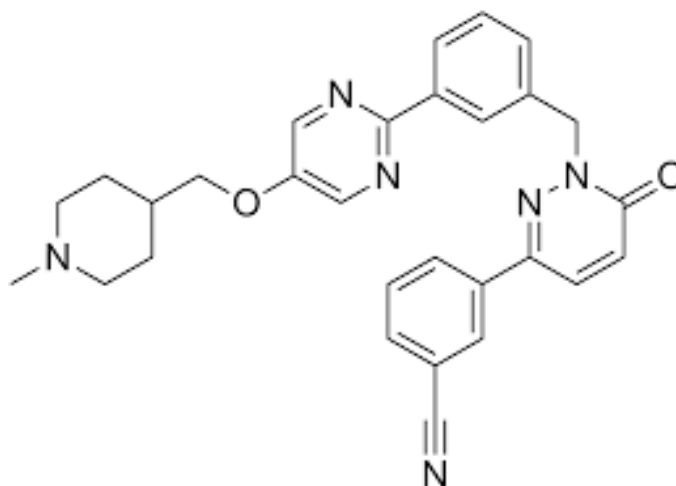
the management of metastatic NSCLC, offering a targeted therapeutic approach for patients with MET exon 14 skipping mutations. Its selective inhibition of the MET receptor tyrosine kinase, favorable pharmacokinetic profile, and demonstrated clinical efficacy underscore its potential as a cornerstone in precision oncology and herald a new era in the personalized treatment of NSCLC.

## II. DRUG PROFILE

### Tepotinib:

**Description:** Tepotinib is a potent small-molecule inhibitor designed to selectively target the MET receptor tyrosine kinase, crucial in regulating cell proliferation and survival. It demonstrates promising efficacy in metastatic non-small cell lung cancer (NSCLC), particularly in patients with MET exon 14 skipping mutations, offering a tailored therapeutic approach to address this genetically defined subset. Tepotinib's favorable safety profile and manageable adverse events contribute to its clinical utility, making it a promising candidate for personalized treatment strategies in NSCLC management.

**Indication:** Tepotinib is indicated for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) who have mesenchymal-epithelial transition (MET) exon 14 skipping alterations.



Structure of Tepotinib

**IUPAC name:** 3-{1-[(3-{5-[(1-methylpiperidin-4-yl)methoxy]pyrimidin-2-yl}phenyl)methyl]-6-oxo-1,6-dihydropyridazin-3-yl}benzonitrile

**CAS number:** 1100598-32-0

**Molecular Weight:** 492.583 g·mol<sup>-1</sup>

**Molecular formula:** C<sub>29</sub>H<sub>28</sub>N<sub>6</sub>O<sub>2</sub>

### Technical Information

|                |   |   |
|----------------|---|---|
| Physical State | : | Solid                                   |
| Solubility     | : | 35 mg/mL (71.05 mM) / 2 mg/mL (4.06 mM) |
| Storage        | : | at -20° C                               |
| pK Values      | : | :9.5                                    |
| Log P          | : | 4                                       |

**Indication:** Investigated for use/treatment in obesity.

### Mechanism of Action:

Tepotinib operates by targeting the Mesenchymal-Epithelial Transition Factor (MET), a receptor tyrosine kinase commonly found in various tumors due to overexpression or mutation. This makes MET an appealing target for therapy due to its critical role in tumor cell proliferation, survival, invasion, and migration. Tepotinib, a highly selective MET kinase inhibitor, specifically focuses on MET variants with exon 14 skipping. By inhibiting MET phosphorylation and

downstream signaling pathways, tepotinib effectively suppresses tumor cell proliferation, anchorage-independent growth, and migration in MET-dependent cancers.

#### Pharmacodynamics:

Tepotinib demonstrates potent inhibition of MET kinase activity, exhibiting an average IC<sub>50</sub> of around 1.7 nmol/L. Its specificity for MET ensures targeted action on the desired target, requiring once-daily administration for optimal therapeutic results due to its moderate duration of action.

#### Safety Considerations:

Despite its therapeutic potential, tepotinib carries the risk of inducing interstitial lung disease (ILD) or pneumonitis, with occasional fatal outcomes. Hence, careful monitoring for respiratory symptoms like dyspnea and cough is essential during treatment. If ILD or pneumonitis is suspected, tepotinib should be immediately halted, pending further evaluation. In the absence of alternative causes, discontinuation of tepotinib is advised indefinitely to mitigate further risk.

**Adsorption:** Tepotinib demonstrates an absolute bioavailability of around 72%, indicating efficient absorption into the bloodstream upon administration.

**Volume of Distribution:** The mean apparent volume of distribution for tepotinib is estimated to be 1,038 liters, suggesting extensive distribution throughout the body tissues beyond the blood.

**Metabolism:** The primary circulating metabolite of tepotinib is M506, constituting approximately 40.4% of total metabolites, indicating significant metabolic processing within the body.

**Route of Elimination:** Approximately 85% of the administered dose of tepotinib is eliminated through fecal excretion, with the remaining 15% excreted in the urine, outlining the predominant route of elimination for this medication.

**Half life:** 32 hours

**Dosage Form:** Tablet

**Brand name:** Tepmetko



### III. APPLICATIONS OF TEPOTINIB IN MANAGING METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

1. **Targeting MET Exon 14 Skipping Mutations:** Tepotinib has shown significant efficacy in the treatment of NSCLC patients with MET exon 14 skipping mutations, a molecular alteration present in approximately 3-4% of NSCLC cases. These mutations lead to dysregulated MET signaling, promoting tumor growth, invasion, and metastasis. Tepotinib's selective inhibition of the MET receptor tyrosine kinase offers a tailored therapeutic approach for this genetically defined subset of patients, addressing a previously unmet medical need.

2. **Monotherapy:** Tepotinib has demonstrated substantial antitumor activity as a monotherapy in advanced NSCLC patients harboring MET exon 14 skipping mutations. Clinical trials, including the VISION study, have reported durable responses and clinically meaningful improvements in progression-free survival (PFS) among heavily pretreated

NSCLC patients receiving tepotinib. This highlights its potential as a standalone treatment option for patients ineligible for or intolerant to standard chemotherapy or targeted therapies.

**3. Combination Therapy:** Tepotinib has also been investigated in combination with other agents for the treatment of metastatic NSCLC, aiming to enhance therapeutic efficacy and overcome resistance mechanisms. Combinatorial strategies involving tepotinib and immune checkpoint inhibitors (ICIs), such as pembrolizumab, have shown promising results in preclinical and early clinical studies. The rationale behind this approach lies in the synergistic effects of MET inhibition and immune modulation, leading to enhanced antitumor immune responses and improved treatment outcomes.

**4. First-Line and Subsequent Lines of Therapy:** Tepotinib holds promise across various lines of therapy in metastatic NSCLC, including as a first-line treatment option for patients with MET exon 14 skipping mutations. Its efficacy in both treatment-naive and previously treated NSCLC patients underscores its versatility and potential to address the evolving treatment landscape of NSCLC. Moreover, tepotinib's favorable safety profile and manageable adverse event profile contribute to its suitability for use in different treatment settings and patient populations.

**5. Biomarker-Driven Treatment Approach:** Tepotinib exemplifies the growing importance of biomarker-driven treatment approaches in oncology, where therapeutic decisions are guided by the molecular characteristics of individual tumors. The identification of MET exon 14 skipping mutations through comprehensive genomic profiling enables clinicians to select appropriate patients who are most likely to benefit from tepotinib therapy, thereby optimizing treatment outcomes and minimizing unnecessary exposure to potentially ineffective treatments.

**6. Investigational Studies and Future Directions:** Ongoing research efforts continue to explore the full potential of tepotinib in managing metastatic NSCLC, including its efficacy in specific patient subgroups, optimal dosing regimens, and mechanisms of resistance. Additionally, translational studies aim to elucidate the underlying biological mechanisms driving sensitivity or resistance to tepotinib, paving the way for the development of rational combination therapies and predictive biomarkers to further personalize treatment strategies.

Thus, tepotinib represents a promising therapeutic option in the management of metastatic NSCLC, particularly for patients harboring MET exon 14 skipping mutations. Its efficacy as a monotherapy and in combination with other agents, coupled with its favorable safety profile and biomarker-driven treatment approach, underscores its potential to improve clinical outcomes and redefine the standard of care for this genetically defined subset of NSCLC patients.

#### IV. CONCLUSION

In conclusion, tepotinib emerges as a transformative therapeutic agent in the landscape of metastatic non-small cell lung cancer (NSCLC), particularly for patients harboring MET exon 14 skipping mutations. Through its selective inhibition of the MET receptor tyrosine kinase, tepotinib offers a tailored treatment approach, addressing the underlying molecular drivers of tumor growth and metastasis in this genetically defined subset of patients. Clinical studies have underscored tepotinib's efficacy as both a monotherapy and in combination with other agents, demonstrating durable responses and improvements in progression-free survival. The favorable safety profile and manageable adverse event profile of tepotinib further enhance its clinical utility, enabling its use across various lines of therapy and in different patient populations. Biomarker-driven treatment strategies, guided by the identification of MET exon 14 skipping mutations, optimize patient selection and treatment outcomes, heralding a new era in precision oncology. Looking ahead, ongoing research efforts aim to elucidate tepotinib's full therapeutic potential, including its efficacy in specific patient subgroups, optimal dosing regimens, and mechanisms of resistance. Translational studies hold promise for the development of rational combination therapies and predictive biomarkers, further personalizing treatment strategies and improving clinical outcomes for NSCLC patients. In summary, tepotinib represents a paradigm shift in the management of metastatic NSCLC, offering personalized treatment options and redefining the standard of care for this genetically defined subset of patients. Its targeted approach, coupled with biomarker-driven treatment strategies, underscores the potential of tepotinib to improve outcomes and quality of life for NSCLC patients, marking a significant advancement in the field of precision oncology.

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