World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Review Article
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2024
Volume: 3; Issue: 5
Page: 353-364

TARGETING MET: BREAKTHROUGH OF TEPOTINIB IN NSCLC THERAPY

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Article Received: 04 August 2024 | | ***Article Revised: 23 September 2024*** | | ***Article Accepted: 15 October 2024***

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DOI: https://doi.org/10.5281/zenodo.14024963

How to cite this Article: Dr. Yuvraj Kaushal and Dr. Pranav Goyal. (2024). TARGETING MET: BREAKTHROUGH OF TEPOTINIB IN NSCLC THERAPY. World Journal of Pharmaceutical Science and Research, 3(5), 353-364. https://doi.org/10.5281/zenodo.14024963

1. ABSTRACT

Objective: The purpose of the presented article is to discuss the clinical implication of tepotinib, for NSCLC patients with MET exon 14 skipping mutations. Furthermore, the article covers topics such as the development of tepotinib, how this drug works, interactions of the drug with others, and the current state of the research on the drug. **Methodology:** We surveyed Science Direct, PubMed, Google Scholar, the USFDA, and the abstracts from the 2023 ASCO conference. Keywords "Tepotinib" and "VISION" and materials till February 2024 were used. We found 146 documents related to our research question and narrowed it to 106, ultimately including 41 articles in our study. **Result:** Lung cancer is the leading cause of cancer-related deaths worldwide, with significant contributions from genetic mutations such as EGFR, RET, KRAS, ALK, ROS1, BRAF, and MET. MET exon 14 (METex14) mutations and gene amplifications are particularly relevant in NSCLC. Tepotinib, a novel selective MET tyrosine kinase inhibitor, has shown clinical success in treating MET-driven tumors. The FDA granted tepotinib breakthrough therapy designation for NSCLC with METex14 skipping alterations. The phase II VISION trial demonstrated an objective response rate (ORR) of 46.5% and significant improvements in progression-free survival (PFS) and overall survival (OS). Its efficacy is enhanced by its ability to cross the blood-brain barrier, making it effective for brain metastases. Compared to other MET inhibitors like capmatinib, savolitinib, and crizotinib, it has shown superior results in certain metrics such as ORR and PFS. Adverse effects are generally mild to moderate, with edema being the most common making its profile safe with minimal withdrawals. **Conclusion:** Tepotinib marks an improvement in MET-directed therapy for the NSCLC patient population with METex14 skipping mutations due to the drugs' impressive therapeutic effectiveness and reasonable safety profiles. The inclusion of this mechanism across several countries supports its possibilities in enhancing the results for this selected patient population.

KEYWORDS: Tepotinib, VISION, MET, exon 14, NSCLC.

1. INTRODUCTION

According to the World Health Organization, lung cancer is the leading cause of cancer-associated deaths worldwide, with the greatest mortality rates observed in both genders. Based on estimates of 9.7 million fatalities in 2022,[1] lung cancer continues to be the leading cause of cancer-related deaths, according to data from the International Agency for Research on Cancer (IARC). The following genetic mutations have been thoroughly investigated and connected to lung cancer: Epidermal growth factor receptor (EGFR), Rearranged during transfection (RET), kristen rat sarcoma viral oncogene homolog (KRAS), anaplastic lymphoma kinase (ALK), ROS proto-oncogene 1, receptor tyrosine kinase (ROS1), and V-Raf murine Sarcoma viral oncogene homolog B (BRAF). Mesenchymal-epithelial transition factor (MET), a proto-oncogene on chromosome 7q21–31 that codes for the MET receptor tyrosine kinase, is one such gene of relevance.[2] Comparing this to other prevalent mutations, it is reasonable to speculate that some non-small cell lung cancers (NSCLCs) may be primarily driven by and dependent on the MET pathway alone.[2] Hepatocyte growth factor (HGF), the ligand that activates MET, causes receptor dimerization and phosphorylation of tyrosine residues in the cytoplasmic tail [Figure 1 subsections B and C], which starts connections with intracellular signaling pathways.[3,4] As of now, MET exon 14 (METex14) mutations and MET gene amplification have emerged as potentially significant MET-related disorders in non-small cell lung cancer (NSCLC).[2,3] Exon 14 can be skipped due to mutations in the MET splicing areas, particularly around exon 14. This shortened gene for MET receptor is then translated in which the juxtamembrane domain of cytoplasmic tail is absent from this truncated receptor.[3,5] The resulting aberrant HGF-MET signaling is linked to angiogenesis, invasive growth, tumor proliferation, and oncogenesis.[5,6] Hepatocellular carcinoma (HCC), gastric cancer, thyroid cancer, and non-small cell lung cancer (NSCLC) are among the malignancies for which MET is a therapeutic target.[2,7] Notably, resistance to traditional anticancer therapies and poor prognoses correlate with MET activation.[2,7] Additionally, a higher proportion of malignancies express elevated levels of programmed death (PD-L1).[8,9]

Treatment options for METex14 skipping non-small cell lung cancer (NSCLC) included immune checkpoint inhibitors (ICI), chemotherapy, either alone or in combination, and the off-label use of multi-kinase inhibitors like crizotinib before the recent approval of MET inhibitors. In contrast to conventional multi-kinase inhibitors, selective type Ib MET inhibitors reduce off-target effects and offer a safer profile, which is required for treating biomarker-selected patients with monotherapy and combination therapies.[10] Tepotinib was therefore created to specifically inhibit MET without resulting in polypharmacology. At therapeutically relevant dosages (450 mg daily) and above, its selectivity has been thoroughly evaluated against more than 400 kinases and kinase variations[11], except MET and mutant MET versions. Following the current guidelines[12], Tepotinib and capmatinib are recommended as first-line therapies, while crizotinib is approved under conditions with specifically the presence of ROS1 or ALK rearrangements in individuals with MET exon 14 skipping mutation.

Tepotinib is a blood-brain barrier-penetrant, highly selective MET tyrosine kinase inhibitor (TKI) that is consumed orally and has demonstrated clinical success in treating MET-driven tumors.[11,13,14] On September 11, 2019, Merck KGaA (Darmstadt, Germany) reported that TEP (Tepmetko®) has been designated by the Food and Drug Administration (FDA) as a breakthrough therapy for the treatment of NSCLCs (non-small cell lung cancers) with MET exon 14 skipping alteration, especially in patients who are progressing after receiving platinum-based therapy.[15] The results of the phase II clinical trial (VISION, NCT02864992) examining tepotinib in patients with non-small cell lung cancer with validated exon 14 skipping mutations support the approval of tepotinib. Tepotinib was the first medication

approved for advanced non-small cell lung cancer (NSCLC) with METex14 skipping, based on the results of the VISION study. The clearance was first given in Japan in March 2020, then in the US, the UK, Singapore, Brazil, Canada, Taiwan, and Switzerland in 2021. Regardless of the lines of previous therapy, current researches now support tepotinib for advanced non-small cell lung cancer (NSCLC) harboring METex14 skipping.[17–22] This review delves into tepotinib's clinical uses, side effects, safety profile, pharmacodynamics, pharmacokinetics, pivotal research trials, and particular practical issues related to drug distribution, adverse reaction management, and prevention. The main properties of tepotinib are listed in Table 1.

Table 1: Key characteristics of tepotinib.

PARAMETERS	KEY FEATURES[23]
Drug class	Kinase inhibitor
Mechanism of action	Inhibits both independent and dependent MET phosphorylation in response to hepatocyte growth factor (HGF) Suppresses downstream pathways of signaling dependent on MET Inhibits the binding sites for Imidazoline 1 Receptor (I1) and Melatonin Receptor Type 2 (MT2).
Indication	Treatment of adult patients with mutations skipping exon 14 of the mesenchymal-epithelial transition (MET) and metastatic non-small cell lung cancer (NSCLC).
Dosage	450 mg taken once a day orally with meals
Administration	Swallow the tablet whole and take the dose approximately at the same time each day. Don't split, chew, or crush tablets. To mitigate adverse effects, 225 mg of TEPMETKO taken once daily is the indicated dose reduction.
Metabolism and clearance	Tmax: 8 h, with a range of 6 – 12 h Geometric mean (%): 71.6 1,038 L constitutes the apparent volume of dispersion (VZ/F) 23.8 L/h constitutes the apparent clearance (CL/F)
Toxicities	General disorders: Edema, fatigue Gastrointestinal disorders: Nausea, vomiting, abdominal pain, constipation, diarrhea Respiratory: Dyspnea, cough, Pleural effusion Infections: Pneumonia Musculoskeletal pain, decreased appetite
Molecular predictors	D1228H/N/Y, Y1230C/H and D1231N
Special considerations	Pregnancy, geriatric use, renal insufficiency, hepatic failure

2. METHODOLOGY

During the preparation of this review, we conducted searches across ScienceDirect, PubMed, and Google Scholar. Due to limited data availability, we extended our search to various websites such as the United States Food and Drug Administration (US FDA), utilizing specific keywords including "Tepotinib," and "VISION," from the beginning of the timeline up to February 2024. Additionally, abstracts and proceedings from prominent international conferences, notably the 2023 American Society of Clinical Oncology (ASCO) annual meeting, were consulted from the website to enhance the depth of this article. We focused on articles published in English and identified 146 documents referencing tepotinib. Among these, 106 were shortlisted as they contained discussions on tepotinib within their abstracts and/or titles. Subsequently, 41 articles were selected for inclusion in this drug review after excluding 36 that either reviewed research data or reiterated information found in drug manuals or official labels. Various ongoing clinical trials were also shortlisted to be mentioned in the manuscript. A visual representation of the search methodology is presented in Figure 1.

Identification of studies via databases and registers

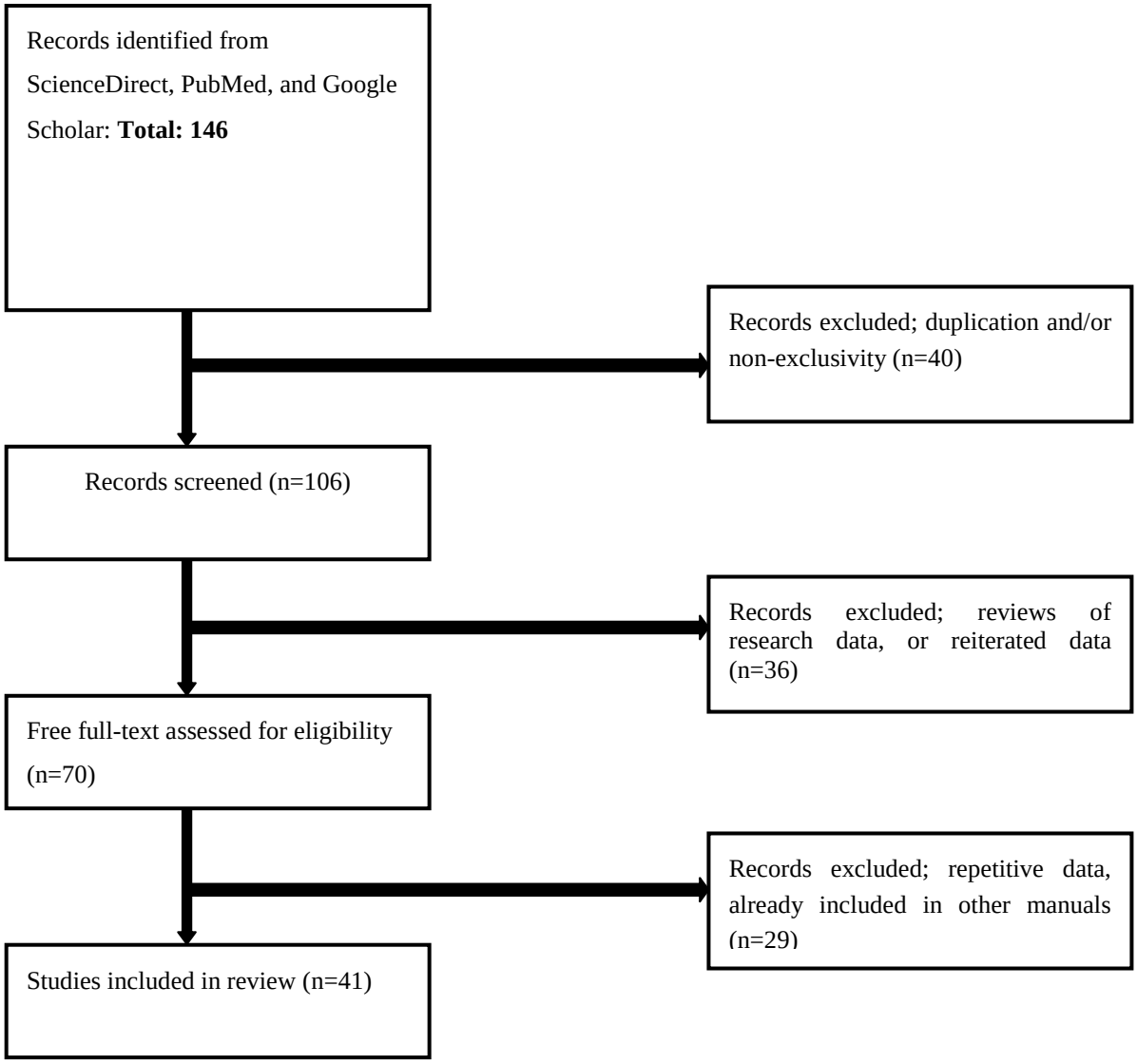

Figure 1: Identification of studies via databases.

3. PHARMACOKINETICS (PK)

The chemical name for tepotinib hydrochloride hydrate is 3-{1-[(3-{5-[(1-methylpiperidin-4-yl)methoxy]pyrimidin-2-yl}phenyl)methyl]-6-oxo-1,6-dihydropyridazin-3- yl}benzonitrile hydrochloride hydrate. The molecular formula is C29H28N6O2·HCl·H2O and the molecular weight is 547.05 g/mol for tepotinib hydrochloride hydrate and 492.58 g/mol for tepotinib (free base).[23] Tepotinib interacts with the kinase domain in tumors that have either METex14 skipping [Figure 2D] or METamp [Figure 2E], which suppresses the intracellular domain of the MET receptor from autophosphorylation. By limiting downstream pathways of signaling such as PI3K/AKT, RAS/ERK, and STAT, this action ultimately prevents tumor cell growth, survival, and metastasis. The ability of tepotinib to bind to the MET receptor is impeded by subsequent mutations in the MET kinase domain, such as those that disrupt Y1230 and D1228 [Figure 2F], which facilitates the continuation of MET signaling. The data collected by Merck, as per VISION Trial, is provided in Table 2.[16,23,27,28]

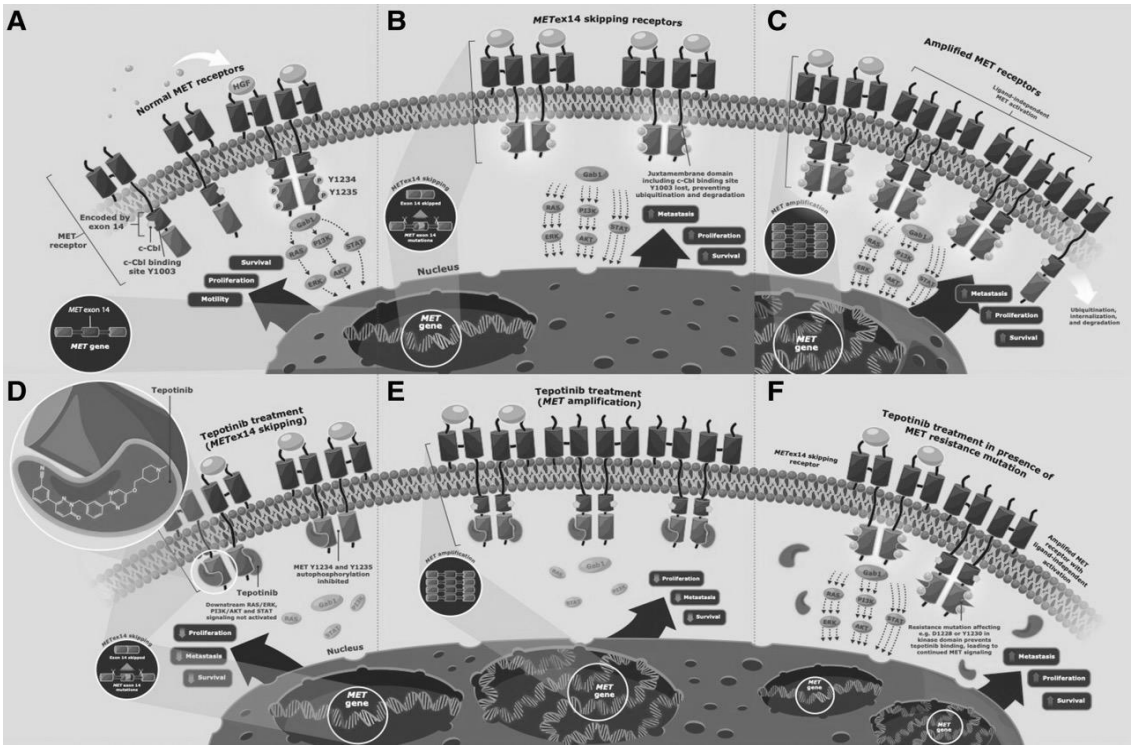

Figure 2: Permitted to be produced from 'Onco Targets Therapeutics' Journal[25] under open access.

Table 2: Data provided by Merck for their study of tepotinib.

Number of patients	313	
Potency (IC50) for MET (nM)	1.7 nM	
Brain penetration	25%	
CNS endpoints	Tumor shrinkage combined with brain metastases, 86.6% intracranial disease control, and 71.4% intracranial control	
Dosing	2 tablets/day (450 mg)	
Testing	Tissue biopsy (NGS) and Liquid (NGS- DNA)	
Parameter	**Overall (T+)**[23]	
Efficacy 1L	**mPFS (months)**	15.9
	mOS (months)	29.7
	ORR (%)	58.6
	mDoR (months)	46.4
Efficacy 2L	**mPFS (months)**	11.5
	mOS (months)	20.4
	ORR (%)	49.5
	mDoR (months)	12.4

(*MET=Mesenchymal Epithelial Transition; mPFS=Median Progression-free survival; mOS= Median overall survival, mORR=Median objective response rate; mDOR=median duration of response.*)

The efficacy of tepotinib in first-line (1L) patients was assessed across various parameters in 313 patients from November 2020 to June 2023.[29] Median Progression-free survival (mPFS) was 22 months, while median overall survival (mOS) was 29.7 months. The objective response rate was 59.3% with a 95% confidence interval ranging from 50.1% to 68.5%, and the median duration of response (mDOR) was 46.4 months. These results highlight tepotinib's potential as a therapeutic option with noteworthy response rates and survival rates.[23,29,30] After a 24-hour intravenous infusion, the brain-to-plasma ratio of 2.87 was determined in Wistar rats, indicating that tepotinib was able to break through the blood-brain barrier (BBB). The partition coefficient of the unbound drug (Kpu,u) was 0.25, exhibiting

limited diffusion but robust brain penetration, surpassing capmatinib and crizotinib in relevant trials. Subcutaneous and intracranial locations showed complete regressions as well as a substantial tumor-shrinking upon further evaluation at clinically relevant doses.[25]

However, tepotinib's efficacy is lower for cancers that have MET amplification. While there may be differences in the level of clinical response, an ORR of 10–20% is often included in identification. The median Progression-Free Survival (PFS) generally falls 3-6 months lower compared to that of MetEx14, while the duration of response (DOR) is significantly shorter.[16] Other selective MET inhibitors include capmatinib for which efficacy data reported an ORR of 41-68% and the median PFS at 5.4-9.7 months with the median DOR of around 9. 7 months. The ORR with savolitinib ranges from 42-49% and the median PFS is about 6.8 months, and a median DOR of approximately 8.3 months. Crizotinib has an ORR of 32-38%, the median PFS is 7. 3 months, and the median DOR is about 9.1 months.[3,15]

When taken orally, tepotinib has a terminal elimination half-life of nearly 32 h and is absorbed with a time to maximum concentration (Tmax) of about 8 h at steady state under fed conditions.[23,31] Tepotinib exhibits a high absolute bioavailability of 72%, even though it is classified as a low-solubility drug.[32] Its volume of distribution (Vd) is approximately 45.1L. It is mostly cleared by the liver through a variety of metabolic pathways and biliary elimination of the drug in its unaltered form.[33] There is no primary metabolic pathway, according to in vitro research and data on human mass balance.[34] The R-enantiomer M506 is the main metabolite in circulation.[35]

4. DRUG INTERACTIONS

The validity of the multi-regional clinical trial was reinforced by the study's finding that ethnicity did not affect tepotinib PK. A flat-dose regimen is supported by the lack of clinically significant impacts from intrinsic characteristics such as age, gender, and body weight. Tepotinib formulations were also tested for bioavailability, and it was discovered that micronizing the drug material improved it. Before micronization, the drug material had a particle size of approximately 250 to 350 micrometers. After micronization, the particle size was reduced to about 10 to 20 micrometers. This size reduction enhances the drug’s surface area, leading to better dissolution and improved bioavailability. Extrinsic factors aside, tepotinib exposure is increased when it is taken with food[36], which is why it is advised to take it with meals, as evidenced by studies like the crucial VISION study.

Tepotinib and opioid analgesics were administered concurrently, and although this affected gastrointestinal motility in 24% of observations, it did not change the AUC in a clinically meaningful way.[23] Tepotinib functions as an inhibitor of P-glycoprotein (P-gp). When TEPMETKO is co-administered, the concentrations of P-gp substrates, such as dabigatran[23], may rise. This could increase the frequency and intensity of side effects associated with these substrates. Furthermore, the co-administration of gefitinib, an EGFR inhibitor, had no significant impact on either drug's exposure, which was expected given their pharmacodynamic characteristics.[37]

5. CLINICAL INDICATIONS

Labeled indications: First-line treatment of adult patients with MET exon 14 skipping mutations in metastatic NSCLC. **Second-line** treatment for patients with metastatic NSCLC harboring MET exon 14 skipping alterations who have previously been treated.[16,23]

Off-label Indications: Medical care for adult patients with NSCLC patients with high-level METamp metastatic disease.

Contraindications: None.

Dosage: Tepotinib (TEPMETKO) tablets are 225 mg concentration, oval and biconvex in shape, film-coated, white-pink in color, and have a plain side and an embossed "M" on the other side.[23] The blister cards consist of a child-resistant blister foil. Keep TEPMETKO between 20°C and 25°C (68°F and 77°F); exceptions are allowed between 15°C and 30°C (59°F and 86°F). Tepotinib should be stored in its original container, protected from light, and kept tightly closed. Tepotinib tablets should be taken whole, with food, at the same time each day. If a dose is missed, it can be taken at a later time as long as it is not the eight-hour window for the next dose. The dosing pattern and storage of tepotinib are discussed in Table 3.

Dose Modification: Oral 225 mg once daily is the recommended dose reduction for TEPMETKO adverse reaction management. Patients who cannot take 225 mg once daily orally should have TEPMETKO permanently stopped.[23,31] The dose modification of tepotinib is shown in Table 4.

Table 3: Dosing pattern and storage of tepotinib.[31]

Half-life	32 h
Daily dose	450 mg
Dose frequency	Once daily
Number of tablets per day	2
Storage	
44087-5000-3	30-tab box: three blister cards with ten pills on each
44087-50000-6	60-tablet box: 6 blister cards with ten tablets on each

Table 4: Dose modification of tepotinib.[23,31]

Adverse reaction	Severity	Dose modification
Interstitial lung disease (ILD) or pneumonitis	Any Grade	Stop using TEPMETKO if you suspect ILD. If ILD is proven, stop TEPMETKO immediately
Elevated ALT/AST levels without increased bilirubin. Reference normal values range of **ALT**: 10-40 U/L **AST**: 7-56 U/L	Grade 3	Retain TEPMETKO until ALT/AST returns to baseline. Restart TEPMETKO at the same dose if you reach your baseline within 7 days; if not, restart TEPMETKO at a lower dose (225 mg)
	Grade 4	Put an end to TEPMETKO permanently
Elevated ALT/AST with elevated bilirubin levels Reference normal values range of **Total bilirubin**: 0.1 to 1.2 mg/dL Direct (conjugated) bilirubin: 0 to 0.3 mg/dL Indirect (unconjugated) bilirubin: 0.2 to 0.8 mg/dL	ALT and/or AST greater than 3 times the upper normal limit and bilirubin greater than 2 times the upper normal limit	Put an end to TEPMETKO permanently
Elevated bilirubin without ALT/AST increase	Grade 3	Retain TEPMETKO until bilirubin returns to normal. Resuming TEPMETKO at a lower dose is recommended if the baseline is reached in 7 days; if not, it should be permanently stopped.
	Grade 4	Put an end to TEPMETKO permanently
Other adverse reactions (edema, fatigue, nausea, diarrhea, musculoskeletal pain, and dyspnea)	Grade 2	Keep the dosage at its current level. If unacceptable, think about stopping TEPMETKO until the issue is resolved, then start TEPMETKO again at a lower dosage
	Grade 3	Stop TEPMETKO until the issue is resolved, then start TEPMETKO again at a lower dosage
	Grade 4	Put an end to TEPMETKO permanently

Monitoring for ILD or pneumonitis is recommended by the FDA[23,31] for patients receiving TEPMETKO. Another adverse effect is hepatotoxicity including a fatal hepatic failure which demands constant liver function checks and possible dose alteration. Based on animal studies, it is teratogenic and linked to fetal damage; it is advisable to use contraceptives while receiving the treatment and up to one week after it. Lack of data in human, pregnant state is contraindicated because it is fatal to the fetus this is supported by a rabbit study. According to the VISION trial, elderly (65+) patients had no changes in efficacy than young patients.[16,23] It has moderate renal clearance, for renal insufficiency, no dosage adjustment is required for patients with mild to moderate renal impairment, however for severe renal impairment the dose adjustment is unknown.[23,34] Consequently, there is no need for dosage change in moderate to severe hepatic impaired patients; however, data for severe hepatic impaired patients is not known.[23,34]

6. ADVERSE DRUG EFFECTS

In the VISION study[17], tepotinib demonstrates good tolerability, exhibiting predominantly mild to moderate adverse events (AEs). The observed manageable safety profile[38,39], with minimal withdrawals attributed to AEs, holds particular significance for the elderly patient population, potentially contributing to optimizing clinical benefits from the treatment while preserving the quality of life (QoL). Edema, a common adverse event in the study, is mostly mild or moderate, with no severe cases (grade ≥4).[23] Management includes dose reduction, treatment interruption, and supportive measures. Conservative management for edema can involve compression garments, lymphatic massage, and kinesiotherapy, with potential consideration of diuretics like furosemide, albeit cautiously to avoid exacerbating creatinine elevation.[16,40] The adverse effects are shown in Table 5.

Table 5: Adverse effects of tepotinib.[23,31]

ADVERSE REACTION	TEPMETKO (n = 225)	
	All Grades (%)	Grades 3 to 4 (%)
General disorders and administration-site conditions		
Edema	70	9
Fatigue	27	1.6
Gastrointestinal disorders		
Nausea	27	0.8
Diarrhea	26	0.4
Abdominal pain	16	0.8
Constipation	16	0
Vomiting	13	1.2
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain	24	2.4
Respiratory, thoracic, and mediastinal disorders		
Dyspnea	20	2
Cough	15	0.4
Pleural effusion	13	5
Nutritional problems and metabolism		
Reduced desire to eat	16	1.2
Others		
Pneumonia	11	3.9

Addressing the role of hypoalbuminemia in edema and emphasizing multimodal management approaches are crucial, drawing on established pathways and multidisciplinary clinics for lymphedema.[40] The percentage of adverse effects of tepotinib, as found by Veillon et al.[38], was in coherence with the study of TEPMETKO.[23,31] Similar results have been reported by other studies[39,41], where edema was found to be the most common adverse drug effect and interstitial lung disease was the most fatal event.

7. FUTURE ASPECTS

The current clinical trials of tepotinib include several phase one trials on the clinical pharmacology and tolerability of tepotinib in various patient groups.[42] Notably, NCT03546608 involves patients with hepatic dysfunction. Many clinical trials like NCT03628339, NCT05213481, NCT05203822, and NCT03531762 investigate the impact of tepotinib and its pharmacodynamic interaction with other drugs including midazolam, carbamazepine, itraconazole, and omeprazole, respectively. Also, NCT03021642 is a phase 1B/II controlled, open-label crossover study in healthy subjects, while NCT01982955 focuses on tepotinib and gefitinib in patients with EGFR mutant, MET-positive NSCLC with resistance to previous EGFR-TKI therapy, locally advanced or metastatic. NCT03492437, NCT03629223, and NCT04204902 all are trials that investigate the drug combination of tepotinib with dabigatran etexilate, as well as the influence of the drug's desired dose in healthy subjects.

Tepotinib was reported to be beneficial in Asian patients with cancer, with a response rate of 56.6%, in a recent study.[43] The patients' median survival was 25.5 months, while their median response duration was 18.5 months. Among 106 Asian patients, 99.1% experienced treatment-related adverse effects (TRAE). These effects resulted in dose reduction in 30.2% of cases, treatment termination in 13.2% of cases, and 10 fatalities, one of which was caused by a TRAE. There is no available research on the effectiveness and safety of tepotinib in patients from India. A 2023 investigation by Mohd. et al. in the Indian context[44] evaluated the relationship between tepotinib and calf thymus DNA (ctDNA) using multispectroscopic and molecular dynamics simulation methods. According to the study, tepotinib exhibited a preference for binding to the minor groove of ctDNA, indicating its ability to bind grooves and providing important information about the molecular interactions of the drug. In India, it generally costs around ₹1,50,000 to ₹2,00,000 per month for a typical dosage.

Collectively, these studies will endeavor to identify the pharmacokinetic variables of tepotinib namely- AUC, Cmax, Tmax, elimination half-life, apparent clearance, and volume of distribution in different circumstances, thus providing valuable insights into this moiety's disposition in different populations. This information can then be used in spreading the study of this drug across different regions and races which can help us assess it better in terms of its actions.

8. CONCLUSION

In a nutshell, the development of tepotinib highlights the efficiency of precision medicine in the medical management of non-small cell lung cancer (NSCLC). The precise determination of biomarkers and comprehension of pharmacokinetics enabled the successful determination of the clinical dose and schedule. As a result of the VISION study's long-lasting effects on patients with non-small cell lung cancer who had mutations in METex14 skipping, tepotinib received regulatory approval in Japan in 2020, making it the first oral MET inhibitor approved worldwide for this use. Tepotinib's targeted strategy shows promise for patients with difficult-to-treat NSCLC tumors, and its subsequent approvals in several locations demonstrate its global significance in advancing customized NSCLC medicines.

9. DECLARATIONS

a) Acknowledgments: Special thanks to Dr. Arshiya Sehgal for her guidance.

b) Funding: No funding received.

c) Conflict of Interest Statement: The authors declare no conflict of interest.

d) Authors' contributions: Credit authorship contribution statement.

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