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ORIGINAL RESEARCH

Exploring Ototoxicity Associated with Capmatinib: Insights from a Real-World Data Analysis of the FDA Adverse Event Reporting System (FAERS) Database

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Background: Capmatinib was approved by the US Food and Drug Administration (FDA) in 2020 for the treatment of non-small cell lung cancer with MET exon 14 mutation (METex14). Real-world studies on the safety of Capmatinib are still lacking. The aim of this study was to explore the significant adverse drug reactions (ADRs) associated with Capmatinib through the FDA Adverse Event Reporting System (FAERS) database.

Methods: We employed the reported odds ratio (ROR), proportional reporting ratio (PRR), Bayesian confidence propagation neural network (BCPNN), and the Empirical Bayes Geometric Mean (EBGM) as primary algorithms for the disproportionality analysis. Adverse events (AEs) were classified as adverse drug reactions (ADRs) solely upon fulfillment of criteria across all four algorithms.

Results: In our study, there were 1767 cases explicitly attributed to Capmatinib. A total of 38 ADRs in preferred terms (PTs) level in 14 system-organ categories (SOCs) were identified after filtering. Notably, unexpected SOC "Ear and labyrinth disorders" and PTs "hypoacusis" and "deafness" were identified, without being specified in the drug label.

Conclusion: Our study identified unexpected ADRs associated with Capmatinib, with a focus on ototoxicity-related events, underscoring the need for enhanced clinical monitoring and further investigation into the underlying mechanisms.

Keywords: Capmatinib, adverse drug reactions, data mining, pharmacovigilance, targeted drug

Introduction

According to the most recent GLOBOCAN 2022 estimates, lung cancer accounted for approximately 2.5 million new cases (12.4% of all cancers) and more than 1.8 million deaths (18.7% of all cancer deaths) worldwide, maintaining its position as the leading cause of cancer incidence and mortality.[1] Non–small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers.[2] Current treatment strategies for NSCLC encompass surgery, radiotherapy, chemotherapy, immunotherapy, and molecularly targeted therapy, administered individually or in combination, depending on disease stage, histological subtype, and the presence of actionable genetic alterations.[3,4] Molecularly targeted therapy now occupies a central role in the management of advanced NSCLC, complementing traditional treatments. Over the past decade, targeted therapies have transformed the treatment landscape of NSCLC, with substantial progress made in identifying actionable genetic alterations. Clinically validated driver mutations now include EGFR, ALK, ROS1, BRAF, KRAS, RET, NTRK, HER2, and MET, among others, each matched to corresponding molecularly targeted agents.[2,5–7] The pipeline continues to grow: next-generation tyrosine-kinase inhibitors (TKIs) can overcome acquired

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resistance, and antibody-drug conjugates (ADCs) now provide targeted cytotoxic delivery for otherwise hard-to-treat molecular subsets. Within this evolving landscape, Capmatinib has emerged as a key option.[8] Capmatinib is approved by the US Food and Drug Administration (FDA) as a MET inhibitor for patients with advanced/metastatic NSCLC harboring MET mutations, achieving satisfactory therapeutic effects.[9]

Drug-related ototoxicity has been under scrutiny due to the importance of hearing as an integral part of daily. Currently, over 150 drugs are known to cause functional damage or cellular degeneration in the inner ear tissues. These drugs include aminoglycosides, platinum-based anticancer drugs, macrolide antibiotics, loop diuretics, quinine, and salicylate painkillers. As an anti-cancer drug, the mechanisms of platinum-related ototoxicity involve damage to cochlear hair cells.[10] A previous study has confirmed the unique role of the hepatocyte growth factor (HGF) and the MET receptor tyrosine kinase signaling pathway in the development of the stria vascularis (a type of non-sensory epithelium) in the mouse cochlea.[11,12] Capmatinib competes with the MET kinase domain for binding, preventing HGF from activating the MET signaling pathway. The function of MET inhibitors on hearing remains to be further explored.[13]

OpenFDA was officially launched on June 2, 2014, as the US Food and Drug Administration's (FDA) public data openness project. As part of the project, the FDA Adverse Event Reporting System (FAERS) is the world's largest pharmacovigilance database, documenting a vast of adverse events and medication errors involving human drugs and therapeutic products, providing valuable information for assessing drug benefits and safety.[14]

In the realm of pharmacovigilance, algorithms play a crucial role in discerning the linkage between medications and adverse reactions. The Reporting Odds Ratio (ROR) directly evaluates the disproportionality of adverse event reporting by comparing the frequency of such events for a specific drug to the background frequency across all other drug.[15] Similarly, the Proportional Reporting Ratio (PRR) employs a frequency-based methodology to assess the ratio of observed to expected reporting rates of adverse events in association with a particular drug.[16] More advanced, the Bayesian Confidence Propagation Neural Network (BCPNN) identifies potential drug safety signals by analyzing complex data patterns in adverse drug reaction databases, utilizing the Information Component (IC) as an indicator of the strength of association between drugs and adverse drug reactions (ADRs).[17,18] Each of these algorithms has its own merits and complements the other.

In this study, we used four algorithms to fully mine the FAERS data for Capmatinib-related ADRs, with the aim of discovering significant ADRs that have not yet been reported and providing a clinical reference to promote the rational use of the drug.

Materials and Methods

Data Source and Collection

The FAERS database is an open-access repository for post-marketing safety surveillance data. It contains reports of adverse events from pharmaceutical companies, healthcare professionals, and individual patients. To evaluate the safety profile during the post-marketing phase, we conducted a retrospective drug safety surveillance study utilizing the FAERS database. We gathered data related to the drug Capmatinib from the first quarter of 2020 to the fourth quarter of 2023. Utilizing SAS and Navicat for MySQL software, we collected and preprocessed Capmatinib-related reports from the FAERS database. To ensure data integrity and eliminate redundant entries, we implemented a structured deduplication process. Specifically, the CASEID field was used to identify unique cases. When multiple records shared the same CASEID, we retained the one with the most recent report date (FDA_DT). If both the CASEID and FDA_DT were identical, the record with the higher PRIMARYID was selected, as it was presumed to be the latest version. Following deduplication, drug names and adverse event terms were standardized using RxNorm and MedDRA, respectively, to facilitate accurate identification and classification of ADRs.[19] All preferred terms (PTs) associated with the system organ class (SOC) categories of MedDRA have been extracted.[20]

Statistical Analysis

Our study employs a case/non-case design, focusing on ADRs caused by the medication while excluding adverse events resulting from underlying disease states. Disproportionality analysis indicates whether the rate of ADRs for the target drug is higher than the expected rate of similar ADRs for all drugs in the database. To enhance the reliability of our analytical

Table 1 Table Matrix

	Target ADR	Non-Target ADR
Capmatinib	a	b
Non-Capmatinib	c	d
N=a+b+c+d		

Abbreviation: ADRs, Adverse Drug Reactions.

outcomes and explore the potential relationship between Capmatinib and ADRs, we utilized four primary algorithms: the ROR, the PRR, the BCPNN, and the Empirical Bayes Geometric Mean (EBGM). Furthermore, to enhance the accuracy of our findings, we meticulously exclude any adverse events that are deemed unrelated to the drug under scrutiny.

When applying the ROR and PRR calculations, the first step is to determine the values of variables a, b, c, and d, which represent the number of individuals with or without exposure to Capmatinib who experience target and non-target AEs. In Table 1, "a" represents the number of cases reporting the target AEs after treatment with Capmatinib; "b" indicates the number of cases experiencing non-target AEs after treatment with Capmatinib; "c" is the number of cases with the target AEs but without treatment with Capmatinib; "d" represents the number of cases without Capmatinib treatment who encounter other adverse reactions. The total count (N) is the sum of a, b, c, and d. The formula used to identify ADRs associated with Capmatinib is as follows.

(i) ROR algorithm

$$ROR = (ad)/(bc)$$

$$95\%\,CI = e^{\ln(ROR)\pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

The criteria of positive safety signal detection: the lower limit of 95% CI>1, N≥3;

(ii) PRR algorithm

$$PRR = [a(c+d)]/[c(a+b)]$$

$$\chi 2 = \frac{(a+b+c+d)(ad-bc)^2}{(a+b)(c+d)(a+c)(b+d)}$$

The criteria of positive safety signal detection: PRR≥2, χ2 ≥4, N≥3;

(iii) BPCNN algorithm

$$IC = \log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$$

$$95\%CI = E(IC) \pm 2 \times \sqrt{V(IC)}$$

The criteria of positive safety signal detection: IC025 >0 (IC025: the lower bound of 95% CI);

(iv) EBGM algorithm

$$EBGM = (aN)/[(a+b)(a+c)]$$

$$95\%CI = e^{\ln(EGBM)\pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

The criteria of positive safety signal detection: EBGM05 >2 (EBGM05: the lower bound of 95% CI).

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Results

General Characteristics

During the the second quarter of 2020 to the fourth quarter of 2023, a total of 1,767 reports were extracted from the FAERS database. Table 2 presents detailed clinical characteristics of patients experiencing AEs after treatment with Capmatinib. Heterogeneity in the gender distribution of AEs was observed more common in females (49.12%) than males (39.39%). Although there was a high proportion of cases with unknown age, those aged over 60 years old accounted for a significantly higher percentage (22.62%) compared to those under 60 years old (2.83%). Additionally, the United States had the highest frequency of Capmatinib use (62.93%), followed by France (4.19%), Japan (1.92%), Italy (0.45%), and Belgium (0.17%) in terms of geographical distribution. The most common severe outcome among AEs was death, occurring in 25.75% of cases. Other outcomes included Disability (1.41%), Hospitalization (12.96%), and Life-threatening (1.58%).

Previously Reported ADRs

In this study, four algorithms were employed to calculate and evaluate ADRs rigorously. After excluding adverse events not related to Capmatinib, 38 adverse drug reactions in the PTs level were associated with 14 System Organ Classes (SOCs). Table 3 exhibits the top 10 PTs ranked by the EBGM algorithm, while the complete table is presented in Supplementary Table 1. The top 10 ADRs were mostly related to swelling. Table 4 exhibits all the SOCs ranked by the

Table 2 Demographic Characteristics of AEs Reported in the FAERS Database (May 2020-December 2023) with Capmatinib as the Primary Suspect Drug

Number of events	Capmatinib	
	Counts 1767	Percentage 100%
Male	696	39.39%
Female	868	49.12%
Unknown	203	11.49%
Age		
<20	2	0.11%
20–29	0	0.00%
30–39	3	0.17%
40–49	9	0.51%
50–59	36	2.04%
60–69	111	6.28%
70–79	178	10.10%
>80	112	6.24%
Unknown	1316	74.48%
Reported Countries (the top ranked)		
US (United States)	1112	62.93%
FR (France)	74	4.19%
JP (Japan)	34	1.92%
IT(Italy)	8	0.45%
BE(Belgium)	3	0.17%
Serious Outcomes		
Death	455	25.75%
Disability	25	1.41%
Hospitalization	229	12.96%
Life-threatening	28	1.58%

Abbreviations: AEs, Adverse Events; FDA, Food and Drug Administration; FAERS, FDA Adverse Event Reporting System.

Table 3 The Top 10 Capmatinib Related ADRs Ranked by IC025 at the Preferred Terms Level in FAERS Source

SOCs	PTs	Case Reports	ROR (95% CI)	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EBGM05)
Reproductive system and breast disorders	Scrotal oedema	4	85.98 (31.65–233.58)	85.79 (31.65–232.55)	323.0227074	6.37 (3.64)	82.71 (30.44)
Cardiac disorders	Oedema peripheral	176	39.36 (33.65–46.04)	35.54 (30.85–40.94)	5833.820499	5.13 (4.61)	35.01 (29.93)
General disorders and administration site conditions	Oedema	101	38.39 (31.36–47)	36.25 (29.95–43.88)	3413.274052	5.16 (4.49)	35.7 (29.16)
General disorders and administration site conditions	Generalised oedema	24	38.97 (25.96–58.49)	38.45 (25.76–57.41)	861.1953459	5.24 (3.95)	37.83 (25.2)
General disorders and administration site conditions	Peripheral swelling	253	22.32 (19.53–25.51)	19.27 (17.18–21.61)	4377.774793	4.26 (3.81)	19.11 (16.72)
Blood and lymphatic system disorders	Lymphoedema	11	21.93 (12.09–39.79)	21.8 (12.06–39.41)	216.3209464	4.43 (2.62)	21.6 (11.91)
Investigations	Blood albumin decreased	6	18.98 (8.49–42.45)	18.92 (8.48–42.19)	101.0079181	4.23 (1.92)	18.77 (8.39)
Musculoskeletal and connective tissue disorders	Joint swelling	85	9.18 (7.38–11.41)	8.78 (7.13–10.81)	587.2234445	3.13 (2.41)	8.75 (7.04)
Renal and urinary disorders	Fluid retention	31	9.79 (6.86–13.97)	9.64 (6.79–13.67)	239.3497518	3.26 (2.12)	9.6 (6.72)
Investigations	Protein total decreased	3	20.33 (6.52–63.42)	20.3 (6.52–63.19)	54.56024289	4.33 (1.4)	20.13 (6.45)

Abbreviations: ADRs, Adverse Drug Reactions; EBGM, Empirical Bayes Geometric Mean; FDA, Food and Drug Administration; FAERS, FDA Adverse Event Reporting System; IC, Information Component; ROR, Reported Odds Ratio; PRR, Proportional Reporting Ratio; PTs, Preferred Terms; SOC, System-Organ Categories.

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Table 4 ADRs at the SOC Level Ranked by Case Reports in the FAERS Database

SOC_name	SOC Code	Case Reports	ROR (95% CI)	PRR (95% CI)	$\chi 2$	IC (IC025)	EBGM (EBGM05)
General disorders and administration site conditions	10018065	725	11.06 (10.06–12.16)	6.93 (6.56–7.33)	3901.183774	2.79 (2.5)	6.91 (6.29)
Gastrointestinal disorders	10017947	207	4.36 (3.77–5.04)	3.97 (3.49–4.51)	472.1665355	1.99 (1.5)	3.96 (3.43)
Respiratory, thoracic and mediastinal disorders	10038738	207	3.65 (3.15–4.21)	3.34 (2.93–3.79)	350.2979841	1.74 (1.26)	3.33 (2.88)
Cardiac disorders	10007541	198	24.34 (20.98–28.23)	21.72 (19.04–24.78)	3897.021838	4.43 (3.94)	21.52 (18.55)
Investigations	10022891	100	7.51 (6.14–9.19)	7.14 (5.9–8.64)	530.7335151	2.83 (2.17)	7.12 (5.82)
Metabolism and nutrition disorders	10027433	100	4.54 (3.71–5.56)	4.34 (3.59–5.25)	260.0859202	2.12 (1.45)	4.34 (3.54)
Musculoskeletal and connective tissue disorders	10029205	85	9.18 (7.38–11.42)	8.78 (7.13–10.81)	587.2234445	3.13 (2.41)	8.75 (7.04)
Renal and urinary disorders	10021881	66	5.91 (4.62–7.56)	5.73 (4.52–7.26)	258.4598834	2.51 (1.71)	5.71 (4.47)
Ear and labyrinth disorders	10013993	38	5.12 (3.71–7.07)	5.03 (3.67–6.9)	123.0771664	2.33 (1.29)	5.02 (3.64)
Hepatobiliary disorders	10019805	27	7.62 (5.21–11.15)	7.52 (5.17–10.94)	152.3774587	2.91 (1.69)	7.5 (5.12)
Blood and lymphatic system disorders	10029104	11	21.93 (12.09–39.79)	21.8 (12.06–39.41)	216.3209464	4.43 (2.62)	21.6 (11.91)
Vascular disorders	10047065	6	6 (2.69–13.4)	5.99 (2.69–13.32)	24.87815329	2.58 (0.28)	5.97 (2.68)
Skin and subcutaneous tissue disorders	10040785	6	5.3 (2.37–11.82)	5.28 (2.37–11.75)	20.79828017	2.4 (0.1)	5.27 (2.36)
Reproductive system and breast disorders	10038604	4	85.98 (31.65–233.58)	85.79 (31.65–232.55)	323.0227074	6.37 (3.64)	82.71 (30.44)

Abbreviations: ADRs, Adverse Drug Reactions; EBGM, Empirical Bayes Geometric Mean; FDA, Food and Drug Administration; FAERS, FDA Adverse Event Reporting System; IC, Information Component; ROR, Reported Odds Ratio; PRR, Proportional Reporting Ratio; SOCs, System-Organ Categories.

case number. We present the top four ranking SOCs. The most common SOC was General disorders and administration site conditions, reported in 725 cases, with an IC of 2.79 (IC025: 2.5) and EBGM of 6.91 (EBGM05: 6.29). Gastrointestinal disorders were reported in 207 cases, with an IC of 1.99 (IC025: 1.5) and EBGM of 3.96 (EBGM05: 3.43). Respiratory, thoracic, and mediastinal disorders were reported in 207 cases, with an IC of 1.74 (IC025: 1.26) and EBGM of 3.33 (EBGM05: 2.88). Cardiac disorders were reported in 198 cases with an IC of 4.43 (IC025: 3.94) and EBGM of 21.52 (EBGM05: 18.55).

Newly Reported Ototoxicity and Other ADRs

By comparing with the drug label, we identified Ear and labyrinth disorders as a new SOC and several PTs affiliated with it, including deafness, and hypoacusis. A total of 38 (2.15%) cases suffered from Ear and labyrinth disorders, with a ROR of 5.12 (95% CI: 3.71–7.07), PRR of 5.03 (95% CI: 3.67–6.9), IC of 2.33 (IC025:1.29), and EBGM of 5.02 (EBGM05: 3.64). Deafness was reported in 16 cases, with a ROR of 7.34 (95% CI: 4.48–12.02), PRR of 7.28 (95% CI: 4.47–11.87), IC of 2.86 (IC025: 1.33), and EBGM of 7.27 (EBGM05: 4.44). And hypoacusis was reported in 22 cases, with a ROR of 4.15 (95% CI: 2.72–6.32), PRR of 4.11 (95% CI: 2.71–6.23), IC of 2.04 (IC025: 0.7), and EBGM of 4.1 (EBGM05: 2.69). We have also uncovered some ADRs that may have clinical significance. Pulmonary oedema reported in 15 cases, with an EBGM of 5.54 (EBGM05: 3.33); pulmonary thrombosis reported in 6 cases, with an EBGM of 5.97 (EBGM05: 2.68); photosensitivity reaction reported in 6 cases, with an EBGM of 5.27 (EBGM05: 2.36).

Discussion

In this study, we collected and evaluated post-marketing pharmacovigilance of Capmatinib based on real-world data. The findings confirmed the already known ADRs and unveiled new potential risks, providing a more comprehensive perspective to drug safety.

Through collecting and analyzing real-world drug safety data, we found that there are some features in the distribution of Capmatinib's ADRs. In terms of gender distribution, women have a higher incidence rate compared to men.[21] This may be related to the increased number of female lung cancer patients, who are more likely to have adenocarcinoma of the lung. While METex14 mutation occurs more frequently in this kind of pathological type. In addition, there is an obviously higher proportion of ADRs in elderly patients, which can be related to the gradual decline of physical functioning in elderly patients. The most frequent serious adverse reaction occurring with Capmatinib was death (25.75%), and the percentage of serious adverse reactions occurring was as high as 41.70%, which may be caused by the association of METex14 mutations with poor prognosis.[22]

In this study, we observed new ADRs at the level of PTs: deafness, and hypoacusis, attributed to SOCs not yet reported in the drug label: Ear and labyrinth disorders. Anti-cancer drugs such as cisplatin, carboplatin, fluorouracil, and methotrexate are known to cause ototoxicity. The stria vascularis within the inner ear is a specialized, highly vascularized epithelium responsible for the production and maintenance of endolymph, a unique extracellular fluid. Additionally, the stria vascularis is equipped with the blood-labyrinthine barrier (BLB), which functions to preclude the entry of most blood-borne toxins into the inner ear.[23,24] Previous studies have highlighted the significant role of melanocytes in the development and protection of the stria vascularis, thereby contributing to the preservation of auditory function.[25,26] Growing experimental evidence underscores the pivotal role of HGF/c-MET signalling in both the development and protection of the inner ear. A genetic-anatomical study by Shibata et al. showed that HGF/c-MET activity is indispensable for melanocyte recruitment into the prospective stria vascularis of the cochlear duct; disruption of this pathway leads to malformation of the stria and profound sensorineural deafness in mice.[12] Functionally, Kikkawa et al. demonstrated that exogenous HGF markedly attenuates neomycin-induced loss of outer hair cells in murine cochlear explants, likely by limiting lipid-peroxidation stress; c-MET is constitutively expressed in hair cells and up-regulated after aminoglycoside injury, highlighting an intrinsic otoprotective role for the HGF–c-MET axis.[11] Complementing these findings, the blood-brain-barrier-permeable HGF mimetic MM-201 affords dose-dependent protection against aminoglycoside ototoxicity in mouse vestibular explants.[27] Capmatinib is a highly selective tyrosine-kinase inhibitor of c-MET. We therefore propose that pharmacological blockade of HGF/c-MET signalling by Capmatinib could compromise both the developmental integrity and the ongoing protective mechanisms of the cochlea, predisposing patients to hearing impairment. Although a definitive causal relationship between Capmatinib and ototoxicity awaits confirmation in prospective clinical or animal studies, these pharmacovigilance data, together with the pre-clinical evidence cited above, warrant focused mechanistic investigations to elucidate this potential association.

Based on the EBGM algorithm, the top 6 ADRs were all associated with edema, while most patients suffered from peripheral swelling. Consistent with previous studies, nearly half of the patients in the METex14 mutation population in the GEOMETRY mono-1 study presented with peripheral edema.[28] Peripheral edema is a common adverse effect of MET-TKIs, and the mechanism by which Capmatinib causes peripheral swelling is currently unclear. Studies by Gallo et al and Hack et al have shown that HGF plays a role in preventing vascular endothelial growth factor (VEGF)-induced endothelial hyperpermeability, thereby inhibiting vascular permeability and inflammation. Conversely, the inhibition of HGF-MET signaling may perturb this protective balance, potentially resulting in endothelial leakage.[29,30] Clinical research by Ulrike Glaenzel et al has revealed that Capmatinib is extensively metabolized and heavily distributed to peripheral tissues. Comorbid conditions in patients, including systemic disorders such as cardiac or renal disease and localized pathologies like primary lymphedema, can lead to the development of edema. Considering that advanced edema may be resistant to MET-TKIs dose reductions and diuretic use, we recommend early vigilant monitoring, such as regular assessment of weight changes to intervene in advance to improve quality of life.

While the data-mining strategy applied in this study confers several advantages, it also has inherent limitations. First, the FAERS database is a voluntary, spontaneous reporting system subject to under-reporting, duplicate reporting, incomplete case documentation, and a lack of standardized toxicity grading. Second, confounding factors such as patients' underlying diseases and concomitant medications, together with missing demographic or dosing information may bias the signal estimates. Third, because FAERS reports originate predominantly from the United States, additional pharmacovigilance data from other regions are required to determine the global generalisability of our findings. To mitigate these issues, we imposed stringent disproportionality thresholds and cross-validated the detected signals against published manufacturer safety data, thereby enhancing their robustness.

Conclusion

In conclusion, this pharmacovigilance analysis identified both known and potentially novel ADRs associated with Capmatinib, including ototoxicity signals, and suggested a possible mechanistic link via HGF–c-MET signaling. These findings may inform safer clinical use and underscore the need for further experimental validation.

Abbreviations

ADC, Antibody-Drug Conjugate; ADRs, Adverse Drug Reactions; AEs, Adverse Events; BCPNN, Bayesian Confidence Propagation Neural Network; BLB, blood-labyrinthine barrier; EBGM, Empirical Bayes Geometric

Mean; FAERS, FDA Adverse Event Reporting System; FDA, US Food and Drug Administration; HGF, Hepatocyte Growth Factor; IC, Information Component; MET, Mesenchymal-Epithelial Transition; METex14, MET exon 14 mutation; NSCLC, Non-Small Cell Lung Cancer; PRR, Proportional Reporting Ratio; PTs, Preferred Terms; ROR, Reporting Odds Ratio; RxNorm, Prescription Normative Terminology; SOCs, System-Organ Categories; TKIs, Tyrosine-Kinase Inhibitors.

Data Sharing Statement

The datasets analyzed during the current study are available in the following resource available in the public domain: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. Further information is available from the corresponding author, Tingting Lin, upon reasonable request.

Ethics Approval and Consent to Participate

This study involved the analysis of anonymized data from the publicly available FDA Adverse Event Reporting System (FAERS) database. In accordance with Article 32 of China's "Notice on the Issuance of Measures for the Ethical Review of Human Life Science and Medical Research" (2023), which permits the waiver of ethical review for studies utilizing public, anonymized data that do not involve harm to individuals, sensitive personal information, or commercial interests, this research was deemed exempt from formal institutional ethical approval. The protocol and data handling procedures were reviewed and approved by the Ethics Committee of Fujian Cancer Hospital, which confirmed that the study complied with the relevant ethical guidelines and was exempt from additional ethical review requirements.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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