SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

Analysis of Reported Adverse Events for First, Second, and Third Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR, TKIs)

By Neil Sundar

AUTHOR BIOGRAPHY

Neil Sundar lives in Charlotte, North Carolina, and is a 9th-grade student at Ardrey Kell High School. He is deeply interested in biology, medicine, and epidemiology, and hopes to pursue a career in these fields. Neil wrote this paper to explore his passion for biomedical research and deepen his understanding of targeted cancer therapies.

ABSTRACT

One of the main causes of death from cancer globally is non-small cell lung cancer (NSCLC). In patients with epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) have grown into an effective targeted therapy that improves quality of life and prolongs survival. However, their usage is frequently linked to several negative outcomes, which may have an impact on patients' quality of life and commitment to therapy. This paper focuses on reported adverse events for EGFR TKIs, comparing the safety profiles of first-, second-, and third-generation inhibitors and evaluating how these profiles influence optimal treatment decisions for EGFR-driven NSCLC. Adverse event data for gefitinib, erlotinib, afatinib, and osimertinib were obtained from the FDA Adverse Event Reporting System (FAERS) and visualized using charts on Google Sheets. Osimertinib, a third-generation TKI, accounted for the majority of reported adverse events among the four EGFR TKIs that were examined. Death, cancer progression, diarrhea, and rash were the most frequently reported side effects of all TKIs, and altogether, females accounted for 59.2% of all reported adverse events for which sex was specified. These results show the importance of considering adverse events for EGFR TKIs in treating patients with NSCLC. Although effective, these drugs are accompanied by a range of notable adverse effects.

Keywords: *adverse events, afatinib, epidermal growth factor receptor (EGFR), erlotinib, FDA Adverse Event Reporting System (FAERS), gefitinib, non-small cell lung cancer (NSCLC), osimertinib, tyrosine kinase inhibitor (TKI)*

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

INTRODUCTION

Worldwide, lung cancer is the leading cause of cancer-related illness and death, accounting for 2.5 million cases and close to 2 million deaths annually (Bray et al., 2024). Non-small cell lung cancer (NSCLC) constitutes 85% of all lung cancer cases globally. (Zappa & Mousa, 2016). NSCLC is further split into three subtypes: squamous cell carcinoma, large cell carcinoma, and adenocarcinoma.

These three subtypes of NSCLC are driven by genetic mutations. One of the most important pathways involved is the epidermal growth factor receptor (EGFR) signaling pathway. EGFR is a protein located in the plasma membrane that serves as a binding site for epidermal growth factor (EGF) and related molecules. EGFR mutations are present in 32.3% of NSCLC cases, accentuating the importance of this pathway in lung cancer development (Zhang et al., 2016). To understand how EGFR pathway mutations cause overstimulation of cell growth, it is important to first understand its normal activation.

Upon the binding of a ligand to an EGFR, the receptor dimerizes via homodimerization or heterodimerization with another receptor tyrosine kinase (RTK). Dimerization triggers the activation of tyrosine kinase (TK), which resides intracellularly. The TK uses ATP to autophosphorylate multiple tyrosines on the dimer's intracellular C-terminal tail. Residues from autophosphorylation are docking sites for signaling molecules with Src homology 2 (SH2) or phosphotyrosine binding (PTB) domains (Wavreille et al., 2007). These proteins induce a cascade of intermediates, including the mitogen-activated protein kinase (MAPK) pathway (RAS–RAF–MEK–ERK), playing a vital role in cell growth, survival, and differentiation. Forkhead box class O (FOXO) is a type of transcription factor that regulates cell division by promoting apoptosis (Dickerson et al., 2024). In NSCLC, increased MAPK levels and decreased FOXO levels lead to cancer cell proliferation. When EGFR is overexpressed or harbors mutations in its gene, the receptor can signal continuously without the presence of a growth factor ligand, causing cells to divide uncontrollably. As a result, new therapies such as Tyrosine Kinase Inhibitors (TKIs) were designed to specifically target anomalous EGFR activity.

TKIs are an important targeted therapy that block the function of receptor tyrosine kinases like EGFR, preventing uncontrollable cell growth. However, cancers like NSCLC can build resistance to the TKIs because of secondary mutations, hence the need for second, third, and possibly fourth generations of the pharmaceuticals.

The first approved TKI was gefitinib (Figure 1), marketed as Iressa®. Gefitinib was approved by the U.S. Food and Drug Administration (FDA) in May 2003 as a drug to treat patients with EGFR-driven NSCLC (Cohen et al., 2003). Specific structures in these TKIs make them optimal for individuals with specific EGFR

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

mutations; thus, TKIs became the first personalized medicine, prescribed only when an individual carries a specific genetic mutation. Gefitinib has a potent 4-anilinoquinazoline that imitates ATP and prevents EGFR from autophosphorylating. Gefitinib blocks a T790 residue on EGFR by binding its nitrogen to M793 through a hydrogen bond (Dickerson et al., 2024). Compared to non-targeted NSCLC therapies, individuals with NSCLC and EGFR mutations on gefitinib therapy experienced significantly better outcomes. Their progression-free survival (PFS) was 10.8 months, nearly double that of a similar group of patients taking non-targeted therapies, who had a PFS of only 5.4 months (Maemondo et al., 2010). Furthermore, the same group of patients on gefitinib therapy had a median overall survival (OS) of 30.5 months, 6.9 months more than those who received non-targeted therapy. (Maemondo et al., 2010). However, gefitinib does not have a proper shape to bind tightly with the TK domain, regulating its ability to block the kinase from phosphorylation. This will eventually lead to the development of resistance by secondary mutations such as T790M (Yu & Riely, 2013). In addition to gefitinib, other first-generation TKIs include erlotinib (Figure 2). Erlotinib was approved by the FDA in November 2004 for patients who have experienced failure of at least one chemotherapeutic (Johnson, 2005).

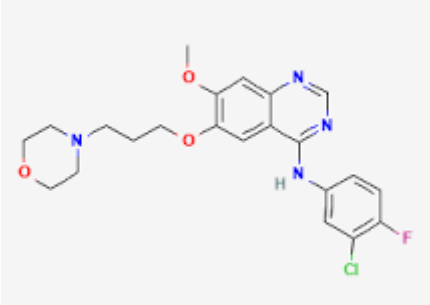

Figure 1. *Chemical structure of gefitinib.*

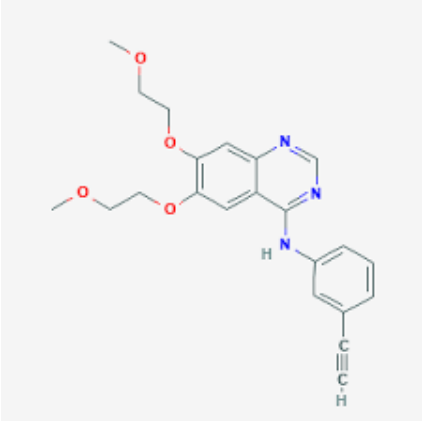

Figure 2. *Chemical structure of erlotinib.*

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

To overcome resistance from mutations like the T790M with first-generation TKIs, a second generation was developed. These TKIs had a "covalent warhead," designed to bind more tightly to the kinase domain, forming covalent bonds with the C797 residue (Yu & Riely, 2013). However, second-generation TKIs such as afatinib (Figure 3) still preserve the anilinoquinazoline core, which was vital to gefitinib and other first-generation TKIs. The FDA approved Afatinib in July 2013 as an EGFR TKI for patients whose tumors carry exon 19 or exon 21 mutations (Yu & Pao, 2013).

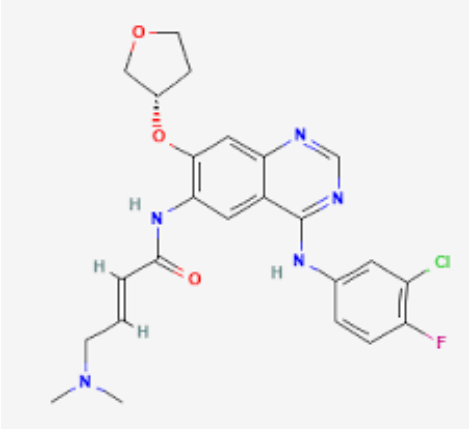

Figure 3. *Chemical structure of afatinib.*

Second-generation TKIs such as afatinib improve the condition and survival of individuals with NSCLC carrying EGFR mutations. In a clinical trial, individuals with NSCLC who carried EGFR mutations had a median time-to-treatment failure (TTF) of 13.7 months on afatinib therapy, 2.2 months greater than that of individuals with NSCLC carrying EGFR mutations on gefitinib therapy (Park et al., 2016). Following the same trend, patients with NSCLC and EGFR mutations on afatinib therapy had a median OS of 27.9 months; in comparison, patients with NSCLC carrying EGFR mutations on gefitinib therapy had a median OS of 24.5 months (Paz-Ares et al., 2017). This highlights the irreversible bond of afatinib's covalent warhead, allowing it to bind to the kinase domain for a longer period without failure. However, second-generation TKIs like afatinib were unable to overcome the T790M mutation even with the covalent warhead's irreversible bonding mechanisms, a challenge that first-generation TKIs also faced (Masuda et al., 2023).

To address this resistance, a third generation of TKIs was developed, notably osimertinib, which carries the same selective binding properties but targets specific mutations like T790M (Figure 4). Osimertinib was approved by the FDA in November 2015 for individuals harbouring a metastatic EGFR T790M mutation present in NSCLC (Greig, 2016).

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

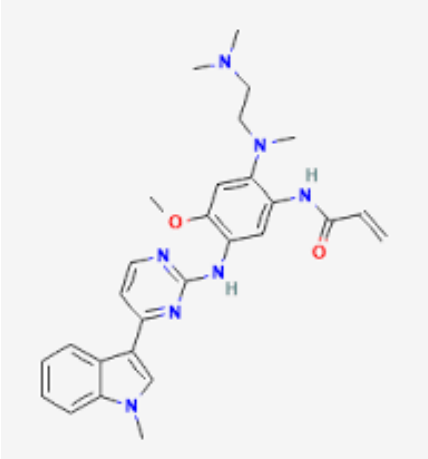

Figure 4. *Chemical structure of osimertinib.*

To achieve this goal, osimertinib and other third-generation TKIs have a pyrimidine ring base, while still retaining the irreversible, tightly-binding covalent warhead. The covalent warhead enables irreversible activity by a covalent bond to the C797 residue, while 2 hydrogen bonds to M793 and S797 amino acid residues further secure the warhead (Butterworth et al., 2017). These covalent bonds lower the half-maximal inhibitory concentration (IC50) of osimertinib when treating individuals with the T790M mutation (Santarpia et al., 2017). IC50 refers to the amount of a drug needed to inhibit activity by 50%. In individuals with NSCLC and EGFR mutations, osimertinib was more effective than gefitinib in treating the T790M mutation, with 74% of individuals with a T790M mutation surviving when given osimertinib for 24 months, compared to 59% of individuals surviving when given gefitinib (Cho et al., 2019). Osimertinib therapy resulted in a considerably greater survival rate, highlighting the drug's efficacy against the T790M mutation.

Despite the effectiveness of TKIs in treating individuals with EGFR mutations in NSCLC, their use is accompanied by a range of side effects that have to be treated carefully. TKIs are associated with many adverse effects that can depend on individual differences and the generation of the drug. The most common adverse effects associated with EGFR-TKI therapy are rash and diarrhea. A meta-analysis found that 78.36% of individuals taking EGFR-TKIs with NSCLC experienced skin toxicity, and 20.75% of individuals developed diarrhea (Obradovic et al., 2022). First-generation TKIs were predominant in the studies used for this meta-analysis. Compared to standard therapy, such as chemotherapy, the adverse effects of gefitinib are mild. Patients' side effects while taking gefitinib were reversible, manageable, and well handled. In a study comparing gefitinib and chemotherapy, the adverse events of rash, diarrhea, and increased aminotransferase levels (ALT) were more common in the gefitinib group, whereas toxic neurologic and hematologic effects were more prevalent in individuals using chemotherapeutic drugs (Ku et al., 2011). Overall, the gefitinib group had less

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

fatigue, nausea, and myelosuppression (lowered ability for bone marrow to make blood cells) than the patients on chemotherapy, making gefitinib an adequate first choice (Ku et al., 2011).

Afatinib, due to its irreversible covalent warhead, leads to broader and stronger adverse events than gefitinib. Treatment-related grade ≥3 adverse events happened in 31.3% of individuals taking afatinib with NSCLC and EGFR mutations, whereas treatment-related grade ≥3 adverse events occurred in 19.5% of the same class of patients on gefitinib therapy (Paz-Ares et al., 2017). A study comparing grade ≥3 adverse events in patients on afatinib therapy vs erlotinib therapy showed higher rates of diarrhea (9.7% vs 2.4%) and stomatitis (3.3% vs 0.0%) for afatinib than erlotinib. However, grade ≥3 rash was more prevalent in the erlotinib group vs the afatinib group (9.0% vs 5.5%) (Joshi et al., 2015). Although afatinib has a larger presence of side effects than first-generation TKIs such as gefitinib and erlotinib, its adverse effect profile is still more manageable than non-targeted, platinum-based therapeutics such as cisplatin. Up to 89.5% of 19 patients on afatinib therapy had skin toxicity, while only 5.6% of individuals on chemotherapy had this adverse event (Chen et al., 2021). However, 5.3% of the afatinib group had a hematologic-related adverse event, while close to 70% of individuals on chemotherapy experienced these toxicities (Chen et al., 2021). In addition, serious adverse events in patients with NSCLC harboring EGFR mutations on afatinib therapy occurred in only 5.9% of these individuals, while serious adverse events occurred in 39.8% of a group of the same type on chemotherapeutics (Biswas et al., 2017). These data show that, although afatinib leads to more frequent skin-related adverse events, this is considerably less dangerous than acute hematologic issues that are commonly associated with chemotherapeutics.

In contrast to first- and second-generation TKIs, third-generation TKIs like osimertinib were created to retain a more acceptable safety profile while overcoming resistance mutations like T790M. This is displayed in a study comparing grade ≥3 adverse events in patients with NSCLC and EGFR mutations on osimertinib therapy versus individuals in the same class on first-generation TKI therapy. In this study, 34% of the osimertinib group experienced a grade 3 or greater adverse event, while this occurred in 45% of the first-generation TKI group (Leighl et al., 2020). Additionally, the discontinuation rate due to an adverse event for individuals with NSCLC and an EGFR mutation taking osimertinib was 13%, while a similar group of patients taking standard TKI therapy had a discontinuation rate due to an adverse event of 18% (Scott, 2018). This improved performance is largely due to selectively inhibiting EGFR that has been mutating, and sparing wild-type EGFR. This eventually leads to fewer gastrointestinal and skin toxicities, which happen prevalently in earlier-generation TKIs. The most frequent adverse events in patients taking osimertinib are paronychia (inflammation around the nail beds, 46%), skin dryness (46%), diarrhea (36%), and rash (36%) (Kiura et al., 2018). Compared to subjects with NSCLC and EGFR mutations on afatinib therapy, a group of the same type taking osimertinib had close to half of the grade ≥3 adverse events that the afatinib group had (22.4% vs 39.4%). By selectively binding mutant EGFR, like exon 19 deletions and T790M resistance mutations, osimertinib limits off-target toxicities (Lamb, 2021).

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

Altogether, the profiles of first, second, and third-generation TKIs highlight the value of targeted therapy in EGFR-related NSCLC. Despite differences in adverse events across gefitinib, afatinib, and osimertinib, TKIs still offer a more manageable adverse effect profile than chemotherapeutics and other non-targeted therapies, supporting their cornerstone role in EGFR-mutated NSCLC. As targeted therapeutics, TKIs are capable of limiting damage to healthy cells, therefore reducing their toxicity. However, TKIs possess their own adverse effects, ranging from diarrhea, rash, and gastrointestinal toxicities to uncommon but dangerous adverse events. These effects vary not only by the structural and functional properties of the drug, but also by the diverse population that suffers from EGFR-driven NSCLC. Understanding these differences is important for enhancing patients' quality of life. As treatment alternatives start to evolve, making the distinction between tolerability and efficacy has become crucial. This paper will focus on these adverse events further, comparing profiles of first-, second-, and third-generation TKIs, and assessing how their safety profiles influence decisions in the optimal treatment of EGFR-driven NSCLC.

METHODS

Adverse event statistics were obtained through the FDA Adverse Event Reporting System (FAERS) database (U.S. Food and Drug Administration, 2025). The data were filtered so that only the generic and brand names of the EGFR TKIs gefitinib, erlotinib, afatinib, and osimertinib were selected for analysis. Gefitinib data were collected from 2001-2024, erlotinib data were obtained from 2005-2024, afatinib data were gathered from 2007-2024, and osimertinib data span the years 2015-2024. Adverse event results were analyzed to determine cases per year, the most frequent adverse event reaction types, and the sex of patients when specified.

RESULTS

The analysis of reported adverse events from the FAERS database reveals a significant increase in total reported adverse events for the four EGFR TKIs, gefitinib, erlotinib, afatinib, and osimertinib, from 2001 to 2024 (Figure 5). Notably, in the decade from 2004 to 2014, the number of total reported adverse events increased from 775 to 2,192; in other words, the number of total reported adverse events in 2014 was 2.8 times that of a decade earlier. In the decade from 2014 to 2024, the number of total reported adverse events increased again from 2,192 to 5,434; the number of total reported adverse events in 2024 was 2.5 times that of a decade earlier.

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

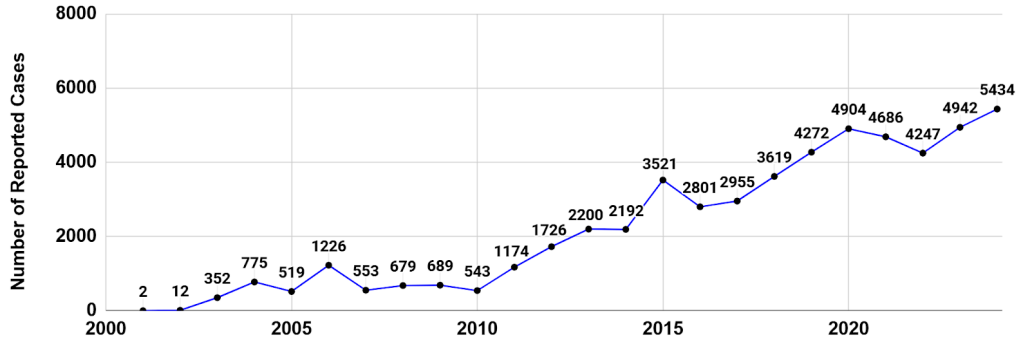

Figure 5. *Total reported adverse events each year for EGFR TKIs gefitinib, erlotinib, afatinib, and osimertinib in FAERS, 2001-2024.*

Examination of the total reported adverse events from the FAERS database indicates notable peaks in total reported adverse events for gefitinib in 2001-2024 (Figure 6). From 2003-2004, the number of reported adverse events more than doubled, increasing from 352 cases in 2003 to 775 reported adverse events in 2004. In addition, from 2005-2006, the total number of reported adverse events more than doubled, increasing from 517 reported adverse events in 2005 to 1,180 reported adverse events in 2006. However, in 2007, the total reported adverse events fell to 226 cases, around 20% of the number of cases in 2006. Another spike in reported adverse events that is worth noting occurred in 2019, jumping from 594 cases in 2018 to 961 cases in 2019; this spike represents a 161.8% increase in reported adverse events. From 2019 onwards, there was a significant decrease in reported adverse events, with the years 2021-2024 having fewer than 400 reported adverse events in each year.

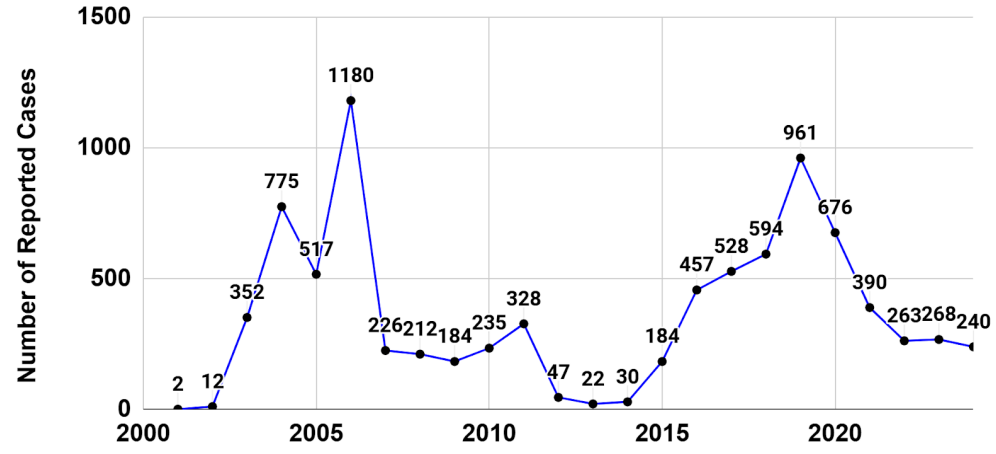

Figure 6. *Total reported adverse events each year for gefitinib in FAERS, 2001-2024.*

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

Reports of erlotinib-related adverse events in the FAERS database from 2005-2024 showed a sudden rise in cases from 2010-2012, followed by a peak in 2015, and a sharp decline from 2016-2024 (Figure 7). There were 1671 reported cases in 2012, which was 5.5 times that of 2010. A steeper decline in reported cases took place between 2015 and 2016, where the total number of reported adverse events fell from 2588 to 949; the number of reported adverse events was 36.7% of that 2 years prior. From 2016 onwards, there was a gradual decline from 949 cases in 2016 to 267 cases in 2024. Despite both erlotinib and gefitinib being first-generation TKIs, erlotinib's trends in total reported adverse events differ significantly from those of gefitinib.

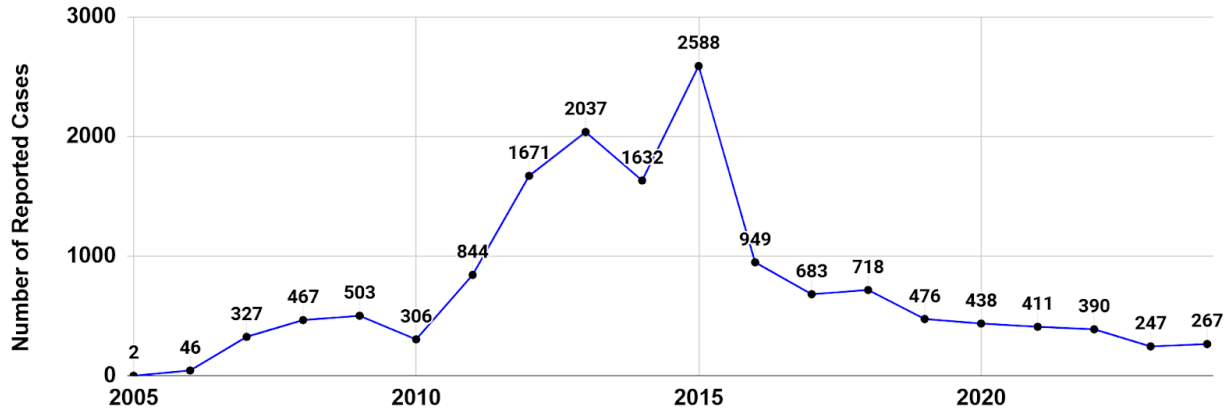

Figure 7. *Total reported adverse events each year for erlotinib in FAERS, 2005-2024.*

Reports of afatinib-related adverse events in the FAERS database from 2007-2024 revealed a sharp increase in reported adverse events from 2013, climbing from 141 reported cases in 2013 to a peak of 921 adverse events in 2016 (Figure 8). This is followed by a drop in 2018, with total reported adverse events falling to 656; this is 71.2% of the previous year. A gradual decrease continued until 2024, with cases decreasing until reported adverse events reached 192 in 2024. This trend for afatinib contrasts with that of gefitinib and erlotinib, showing a later and more subtle peak.

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

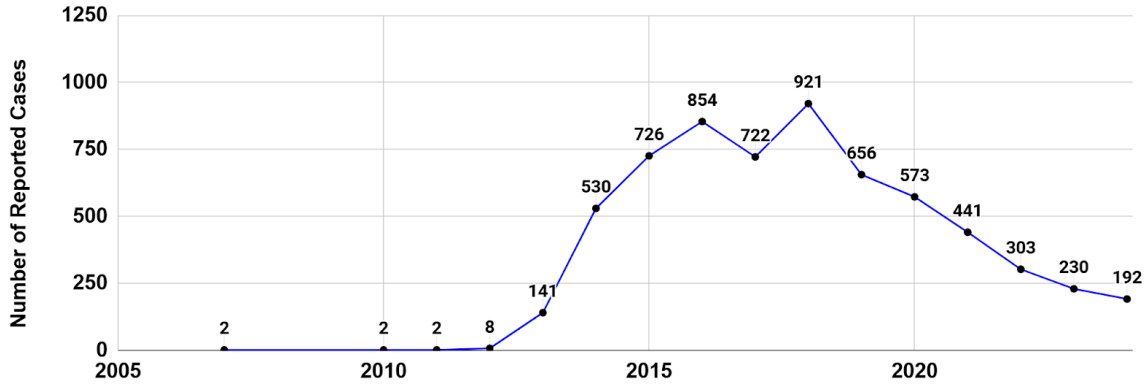

Figure 8. *Total reported adverse events each year for afatinib in FAERS, 2007-2024.*

Total reported adverse events in osimertinib in the FAERS database consistently increased from 2015-2024 (Figure 9). Starting with just 23 cases in 2015, reported adverse events surged to 541 in 2016 and close to doubled in 2017, with 1022 adverse events in 2017. Osimertinib's total adverse events reached 4725 in 2024, over 200 times the amount reported close to a decade earlier. This contrasts with gefitinib, erlotinib, and afatinib but has a similar pattern to the total adverse events for all four EGFR TKIs due to its consistently increasing trend (Figure 5).

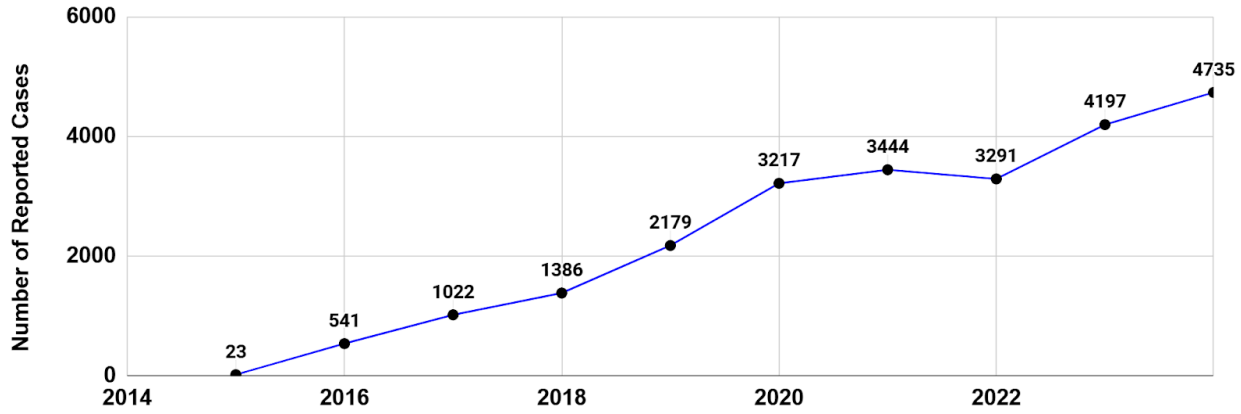

Figure 9. *Total reported adverse events each year for osimertinib in FAERS, 2015-2024.*

When simultaneously analyzing individual trends of the total reported adverse events each year for EGFR TKIs, gefitinib, erlotinib, afatinib, and osimertinib in FAERS from 2001-2004, certain trends become apparent (Figure 10). A peak in adverse events for erlotinib was concurrent with low reported adverse events for

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

TKIs gefitinib and afatinib. In addition, osimertinib surged sharply from 2015, consistently increasing, reaching close to 5,000 reported cases in 2024, while EGFR TKIs gefitinib, erlotinib, and afatinib were all steadily decreasing to less than 300 cases in 2024. The trends also reveal that osimertinib's reported adverse events far exceeded the peaks of other TKIs, being the driver of the total number of adverse events for EGFR TKIs gefitinib, erlotinib, afatinib, and osimertinib (Figure 5).

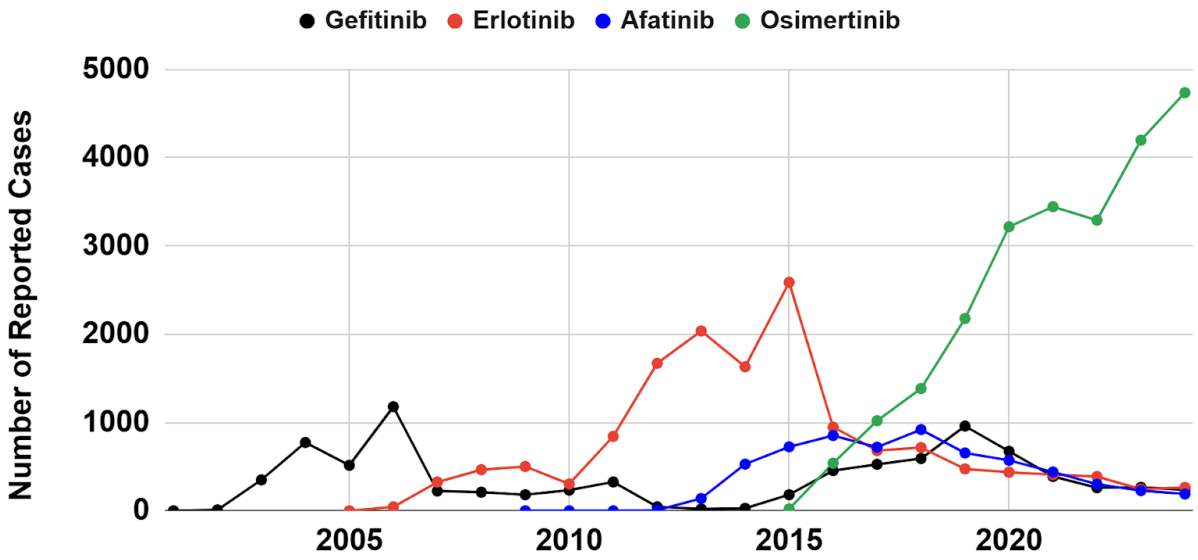

Figure 10. *Total reported adverse events each year for individual EGFR TKIs gefitinib, erlotinib, afatinib, and osimertinib in FAERS, 2001-2024*

The top 7 adverse events by reaction for EGFR TKIs, gefitinib, erlotinib, afatinib, and osimertinib in FAERS varied vastly in seriousness (Figure 11). Death was the most frequently reported adverse event, accounting for 16,074 cases; to put it another way, death accounts for 29.3% of all reported adverse events. The second most common adverse event was cancer progression, which occurred in 8,369 cases, about half as frequently as death. Diarrhea and rash followed with 5,681 and 3,726 reported adverse events, respectively. Drug resistance, nausea, and fatigue were less commonly reported, but they are still major adverse effects and contributed appreciably to the safety profile. These data highlight the prevalence of serious adverse events such as death in EGFR TKI therapy.

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

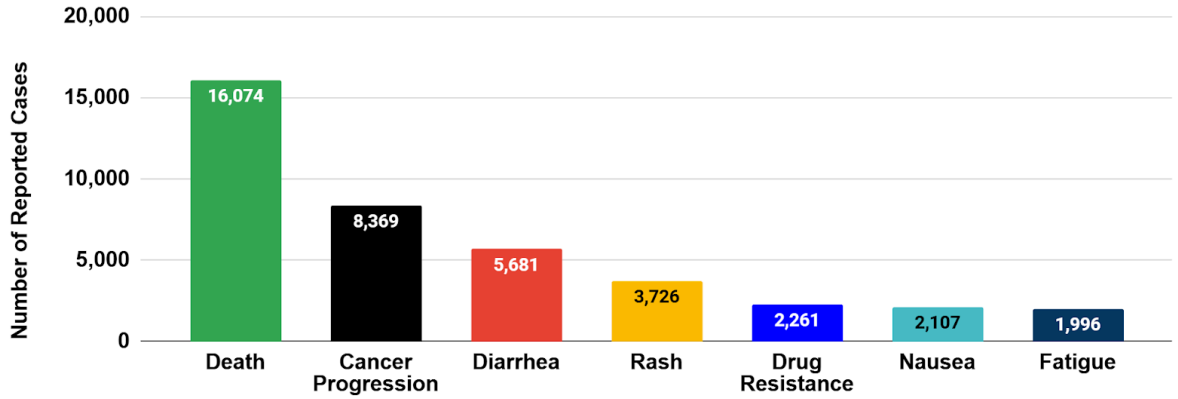

Figure 11. *Top 7 reported adverse events by reaction for EGFR TKIs gefitinib, erlotinib, afatinib, and osimertinib in FAERS.*

The top 7 reported adverse events by reaction associated with gefitinib in the FAERS database was dominated by cancer progression, which had 2,092 reported cases; this is 171.6% of drug resistance, which is the second most common adverse event (Figure 12). Diarrhea followed closely, whereas rash, death, interstitial lung disease, and nausea were less significant but notable as adverse effects. Gefitinib's side effect profile differs from other EGFR TKIs, as it is associated with significantly fewer reported deaths compared to TKIs like erlotinib and osimertinib. Analysis of gefitinib's reported adverse events by reaction indicates that both disease- and treatment-related adverse events occur with gefitinib therapy.

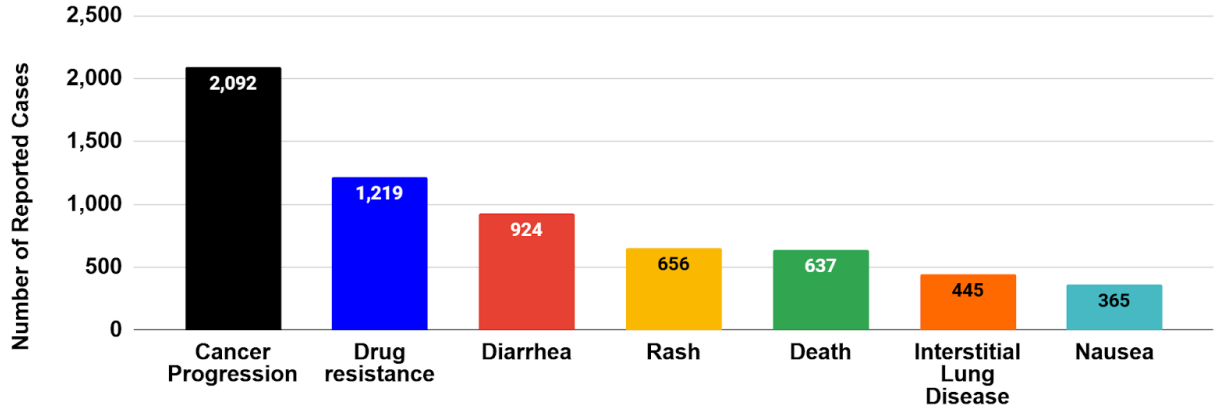

Figure 12. *Top 7 reported adverse events by reaction for gefitinib in FAERS.*

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

In the FAERS database, death was the most common adverse event associated with erlotinib, with 4,862 cases (Figure 13). This is close to 3 times the amount of the second most common adverse event, which was cancer progression; this accounted for 1,706 reported cases and was 35% of reported deaths associated with erlotinib. The two other adverse events with a substantial amount of reported cases were rash and diarrhea, with 1,633 and 1,553 cases, respectively. Off-label use, nausea, and fatigue were the least reported of the 7 side effects, all showing a similar number of reported cases. These data show that erlotinib has a higher association with serious adverse events, such as death, especially when compared with gefitinib and afatinib.

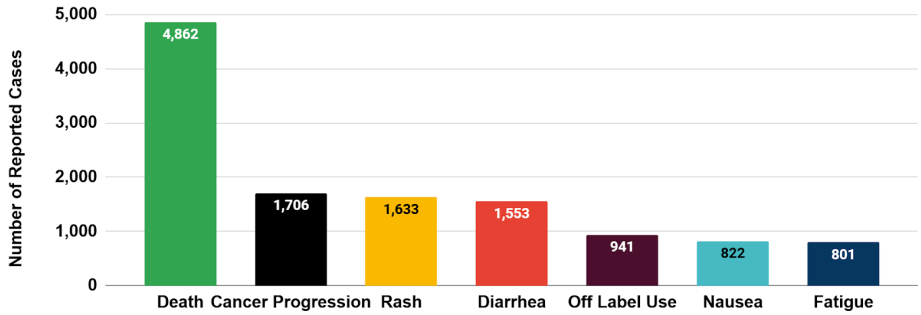

Figure 13. *Top 7 reported adverse events by reaction for erlotinib in FAERS.*

Afatinib's adverse events by reaction in the FAERS database were the highest for diarrhea, which accounted for 2,104 cases; this was 2.45 times more than the next most common event, cancer progression, which had 1,810 reported cases (Figure 14). Rash was the third most common adverse effect, with 859 reported cases associated with afatinib, representing 40.8% of reported diarrhea cases. The four adverse effects that followed (stomatitis, death, nausea, and decreased appetite) each comprised less than 23% of reported diarrhea cases related to afatinib. Afatinib's safety profile is similar to that of gefitinib, erlotinib, and osimertinib in that a large proportion of reported cases come from cancer progression.

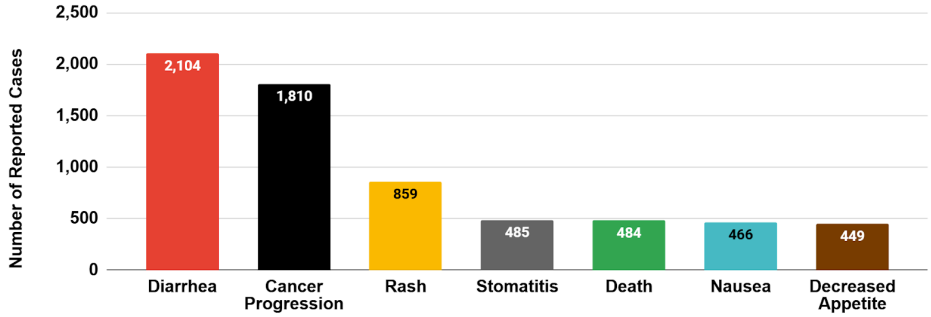

Figure 14. *Top 7 reported adverse events by reaction for afatinib in FAERS.*

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

Analysis of the top 7 osimertinib-related reported adverse events by reaction in FAERS revealed the presence of death as the main side effect, with 10,179 reported cases; put another way, the second most common side effect associated with osimertinib is cancer progression, roughly one-third that of the dominating adverse effect of death (Figure 15). Less frequently reported side effects included diarrhea, drug resistance, fatigue, rash, and decreased appetite. Although osimertinib does not have a largely varied adverse effect profile, these adverse events can be serious and even lethal. These data feature the prevalence and importance of serious adverse events, especially death, in the safety profile of osimertinib.

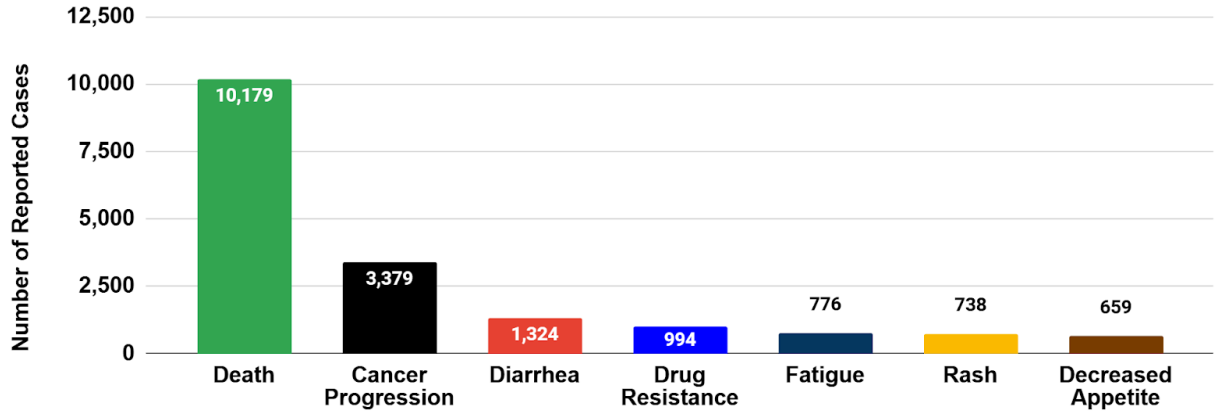

Figure 15. *Top 7 reported adverse events by reaction for osimertinib in FAERS.*

When the adverse event data for EGFR TKIs gefitinib, erlotinib, afatinib, and osimertinib are analyzed together, adverse events were more frequently reported by females than by males (Figure 16). Female-reported adverse events accounted for 27,261 cases; this was 145.0% of adverse events reported by males, who reported 18,802 adverse events. When analyzed individually, the EGFR TKIs gefitinib, afatinib, and osimertinib showed a similar trend, as females reported more adverse events than males for each of these individual EGFR TKIs.

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

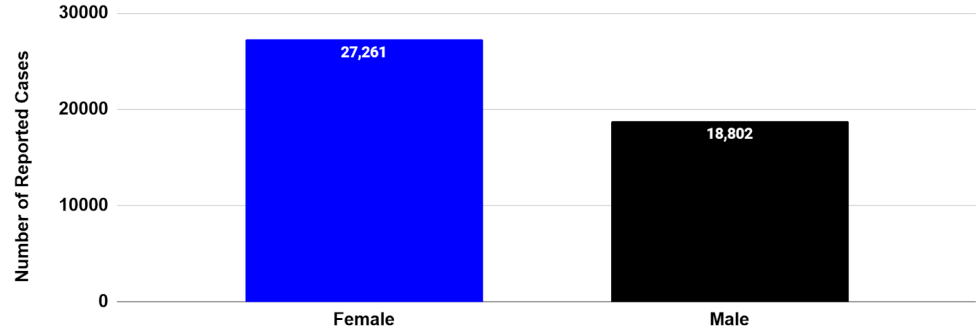

Figure 16. *Total reported adverse events by sex for EGFR TKIs gefitinib, erlotinib, afatinib, and osimertinib in FAERS.*

Analysis of the total reported adverse events by sex for gefitinib in the FAERS database showed more reported cases for females than males, with female cases reaching 4,624 reported adverse events; adverse events reported by males only reached 3,233 cases (Figure 17). Male-reported adverse events represented 69.9% of the total female-reported adverse events and 41.1% of the total adverse events reported by both males and females (not including reported adverse events by non-specified gender individuals). These data follow a similar trend to that of afatinib, osimertinib, and the combined adverse events of EGFR TKIs gefitinib, erlotinib, afatinib, and osimertinib, all having more female-reported cases than male-reported adverse events.

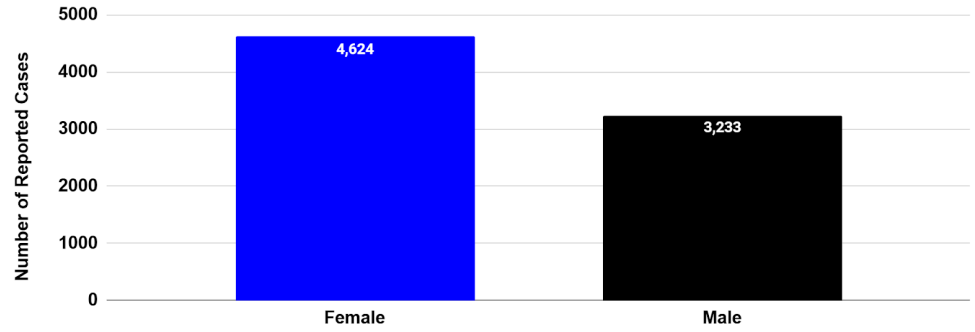

Figure 17. *Total reported adverse events by sex for gefitinib in FAERS.*

For erlotinib, the total number of reported adverse events by sex in FAERS was close to evenly distributed, with 6.427 female-reported cases and 6,705 male-reported cases; male-reported cases account for 51.1% of total male- and female-reported cases, while female-reported cases represent 48.9% (Figure 18). There is no apparent sex-based difference in erlotinib-associated reporting, as indicated by almost equal values, which

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

implies that adverse events happen at similar rates in both categories. Erlotinib is the only EGFR TKI for which there are more male-reported adverse events than those reported by females.

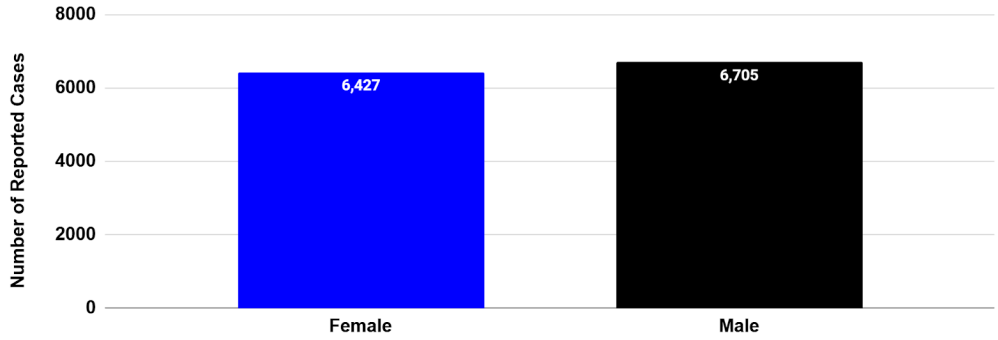

Figure 18. *Total reported adverse events by sex for erlotinib in FAERS.*

The total reported adverse events by sex associated with afatinib in the FAERS database reveal female-reported adverse events reaching 3,368, which is 1.61 times greater than male reports, of 2,095 cases; female-reported adverse events represented 61.6% of the total male- and female-reported adverse events, while males reported 38.4% of the total (Figure 19). Compared to erlotinib, afatinib's reported adverse events are more skewed based on sex, having a 23.2% difference between sexes compared to erlotinib's 2.2% difference in reported adverse events by sex. Although the total number of reported adverse events for afatinib is lower than that of erlotinib, it remains relatively high when compared to other EGFR TKIs such as gefitinib and osimertinib.

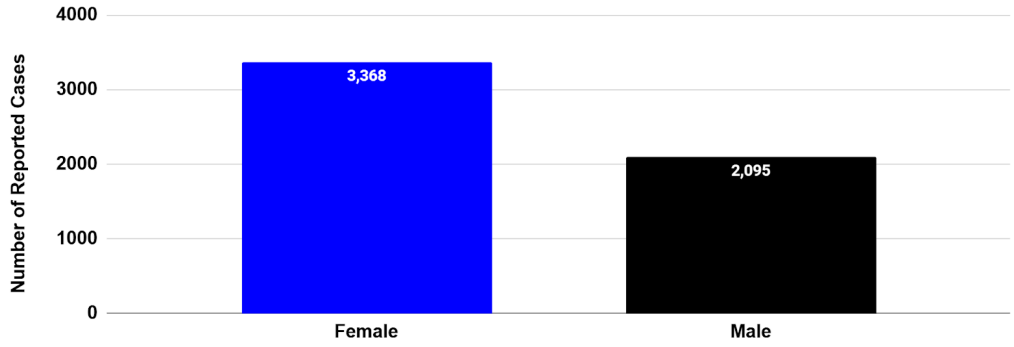

Figure 19. *Total reported adverse events by sex for afatinib in FAERS.*

The total reported adverse events by sex associated with osimertinib in the FAERS database revealed a major skew towards female-reported cases, which accounted for 12,842 reported adverse events; this was nearly

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

double that of male-reported adverse events, which reached 6,769 cases (Figure 20). Female-reported cases represented 65.5% of all reported adverse events, while male-reported cases accounted for 34.5% of the total. Although osimertinib had the highest overall number of reported adverse events among all the EGFR TKIs, its distribution by sex is greatly skewed to females, as they reported 1.90 times the cases that males reported. Compared to gefitinib, erlotinib, afatinib, and combined totals of the EGFR TKIs (gefitinib, erlotinib, afatinib, and osimertinib), osimertinib has the greatest difference between female-reported and male-reported cases, with a 31% gap.

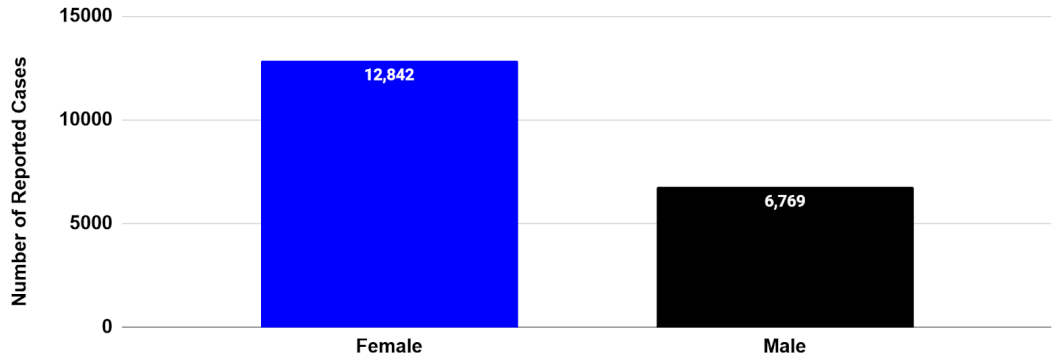

Figure 20. *Total reported adverse events by sex for osimertinib in FAERS.*

DISCUSSION

This study analyzed the reported adverse events in the FAERS database associated with EGFR TKIs gefitinib, erlotinib, afatinib, and osimertinib. Osimertinib carried the majority of reported adverse events, driving the rise in adverse events for EGFR TKIs gefitinib, erlotinib, afatinib, and osimertinib. Not only did osimertinib drive the overall increase of reported adverse events per year, it also accounted for the most frequent and serious adverse events (including death, cancer progression, diarrhea, and rash); osimertinib was also the cause of the heavy skew towards female-reported adverse events when analyzing the EGFR TKIs' reported adverse events by sex. Since 2017, only 2 years after osimertinib's approval by the FDA, the drug had the most reported adverse event cases per year in comparison to gefitinib, erlotinib, and afatinib, all of which had been on the market for years prior. One important trend to observe is that, starting in 2018, adverse event reports for osimertinib started to rise dramatically, whereas the other three TKIs showed consistent decreases. Notably, erlotinib peaked with 2,588 instances in 2015, the year osimertinib received approval, while the other three TKIs had relatively few cases reported. The majority of reported adverse events were associated with erlotinib and osimertinib. Because of the huge number of cases that were reported, osimertinib was the driver for the two most common adverse effects, death and cancer progression, among the four EGFR TKIs combined. However, the top four adverse event types for erlotinib almost exactly matched the top four in the combined dataset. In

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

addition to contributing to the overall increase in adverse events, osimertinib was also the driver for adverse events reported by women. In fact, the majority of adverse events recorded for EGFR TKIs are in women who experience side effects from osimertinib. Even though osimertinib contributed the most to the trends due to its high amount of reported adverse events, gefitinib, erlotinib, and afatinib played considerable roles in the observed trends. These earlier EGFR TKIs still carry their own safety profile with side effects of varying seriousness and frequency.

Although the FAERS database provides insights into adverse events and the safety profile of drugs, its use is accompanied by several limitations. Firstly, the FAERS database includes duplicate and incomplete reports in its data (U.S. Food and Drug Administration, 2023). This can potentially alter the accuracy of the results. Secondly, the existence of a report in the FAERS database for a given drug does not guarantee or prove that the drug was the cause of the adverse event. The adverse event could be due to any medications that are being taken concurrently, or other factors unrelated to the drug. The reports are solely based on the observations of the patient experiencing the adverse event. In addition, a report in the FAERS database is not guaranteed to be verified or medically confirmed. The adverse event could be unrelated to the drug, or it could be inaccurate. Adverse event reports in the FAERS database do not have a clear correlation with the occurrence of adverse events associated with the drug, so these reports cannot estimate how often adverse events occur with a drug. These limitations mean that even though the FAERS database is a useful resource for generating hypotheses and identifying potential risks, its information should be carefully interpreted and supported by controlled clinical trials or other reliable sources of data in order to reach definitive conclusions regarding drug safety.

Looking ahead, there are many possible avenues for further research based on these results. One possible area for future examination would be to analyze the adverse event profiles for individuals with non-small cell lung cancer on anaplastic lymphoma kinase (ALK) inhibitor therapy. ALK inhibition is another form of targeted therapy that is less widely used than TKIs, but still prevalent in the treatment of non-small-cell lung cancer (Zia et al., 2023). ALK inhibitors have the potential to provide notable benefits and are accompanied by adverse events; examining their safety profiles would show similarities and differences among different types of targeted therapies. Examples of first-generation ALK inhibitors include crizotinib, which is followed by second-generation ALK inhibitors such as alectinib and brigatinib. Just like EGFR TKIs, ALK inhibitors have a third generation, which includes drugs like lorlatinib. Another possible pathway is analyzing patient records to reach a more accurate and complete understanding of the safety profile of these drugs. Taking this avenue would overcome the limitations of FAERS, which include the addition of incomplete and duplicate entries, a lack of causation, and unverified reports. This approach would gather patient data in real-time, allowing for more detailed and thorough reports compared to the reports on FAERS. Patient data can be used to correlate concurrent medicines and treatment histories to the severity and frequency of adverse events related to a drug. Using this method, not only can scientists verify the results on the FAERS database, but also produce a clearer picture of the safety profile of these drugs. A final avenue for further research would be to analyze patient

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

survival data. Survival data could tell scientists how therapies affect long-term adverse events and the severity of those events. Scientists could determine whether certain drugs differ from one another not only based on their safety profiles, but also based on the extent to which they lengthen patient life or enhance quality of life. By providing an increased understanding of the risk–benefit balance in EGFR TKI treatment, this kind of analysis could add to safety data. Although EGFR TKIs have changed the way that NSCLC is treated, the side effects that they might cause are still a major problem. To improve outcomes for patients while protecting their quality of life, future studies and initiatives must focus on improving the treatment of these toxicities.

REFERENCES

Biswas, B., Ghadyalpatil, N., Krishna, M. V., & Deshmukh, J. (2017). A review on adverse event profiles of epidermal growth factor receptor-tyrosine kinase inhibitors in nonsmall cell lung cancer patients. *Indian Journal of Cancer*, *54*(5), 55–55. https://doi.org/10.4103/ijc.ijc_589_17

Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA: A Cancer Journal for Clinicians*, *74*(3), 229–263. https://doi.org/10.3322/caac.21834

Butterworth, S., Cross, D. A. E., Finlay, M. R. V., Ward, R. A., & Waring, M. J. (2017). The structure-guided discovery of osimertinib: the first U.S. FDA approved mutant selective inhibitor of EGFR T790M †The authors declare no competing interests. *MedChemComm*, *8*(5), 820–822. https://doi.org/10.1039/c7md90012k

Chen, Y.-Y., Chang, S.-C., Chang, C.-Y., Chang, C.-F., Lai, Y.-C., Wei, Y.-F., & Chen, C.-Y. (2021). Real-world effectiveness of second-line Afatinib versus chemotherapy for the treatment of advanced lung squamous cell carcinoma in immunotherapy-naïve patients. *BMC Cancer*, *21*(1). https://doi.org/10.1186/s12885-021-08920-3

Cho, B. C., Ohe, Y., Zhou, C., Reungwetwattana, T., Cheng, Y., Chewaskulyong, B., Lee, K. H., Planchard, D., Vansteenkiste, J. F., Gray, J. E., Shah, R., Cheema, P. K., Tiseo, M., John, T., Hodge, R., Rukazenkov, Y., Soria, J.-C. ., Lin, M.-C. ., Imamura, F., & Ramalingam, S. S. (2019). Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC (FLAURA): Final overall survival analysis. *Annals of Oncology*, *30*, ix198–ix199. https://doi.org/10.1093/annonc/mdz446.015

Cohen, M. H., Williams, G. A., Sridhara, R., Chen, G., & Pazdur, R. (2003). FDA Drug Approval Summary: Gefitinib (ZD1839) (Iressa ®) Tablets. *The Oncologist*, *8*(4), 303–306. https://doi.org/10.1634/theoncologist.8-4-303

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

Dickerson, H., Diab, A., & Al Musaimi, O. (2024). Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Cancer: Current Use and Future Prospects. *International Journal of Molecular Sciences*, *25*(18), 10008. https://doi.org/10.3390/ijms251810008

Greig, S. L. (2016). Osimertinib: First Global Approval. *Drugs*, *76*(2), 263–273. https://doi.org/10.1007/s40265-015-0533-4

Johnson, J. R. (2005). Approval Summary for Erlotinib for Treatment of Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer after Failure of at Least One Prior Chemotherapy Regimen. *Clinical Cancer Research*, *11*(18), 6414–6421. https://doi.org/10.1158/1078-0432.ccr-05-0790

Joshi, M., Rizvi, S. M., & Belani, C. P. (2015). Afatinib for the treatment of metastatic non-small cell lung cancer. *Cancer Management and Research,* 7, 75–75. https://doi.org/10.2147/cmar.s51808

Kiura, K., Yoh, K., Katakami, N., Nogami, N., Kasahara, K., Takahashi, T., Okamoto, I., Cantarini, M., Hodge, R., & Uchida, H. (2018). Osimertinib in patients with epidermal growth factor receptor T790M advanced non-small cell lung cancer selected using cytology samples. *Cancer Science*, *109*(4), 1177–1184. https://doi.org/10.1111/cas.13511

Ku, G. Y., Haaland, B. A., & de Lima Lopes, G. (2011). Gefitinib vs. chemotherapy as first-line therapy in advanced non-small cell lung cancer: Meta-analysis of phase III trials. *Lung Cancer*, 74(3), 469–473. https://doi.org/10.1016/j.lungcan.2011.04.008

Lamb, Y. N. (2021). Osimertinib: A Review in Previously Untreated, EGFR Mutation-Positive, Advanced NSCLC. *Targeted Oncology*, *16*(5), 687–695. https://doi.org/10.1007/s11523-021-00839-w

Leighl, N. B., Karaseva, N., Nakagawa, K., Cho, B.-C., Gray, J. E., Hovey, T., Walding, A., Rydén, A., & Novello, S. (2020). Patient-reported outcomes from FLAURA: Osimertinib versus erlotinib or gefitinib in patients with EGFR-mutated advanced non-small-cell lung cancer. *European Journal of Cancer, 125*(117), 49–57. https://doi.org/10.1016/j.ejca.2019.11.006

Maemondo, M., Inoue, A., Kobayashi, K., Sugawara, S., Oizumi, S., Isobe, H., Gemma, A., Harada, M., Yoshizawa, H., Kinoshita, I., Fujita, Y., Okinaga, S., Hirano, H., Yoshimori, K., Harada, T., Ogura, T., Ando, M., Miyazawa, H., Tanaka, T., & Saijo, Y. (2010). Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR. *New England Journal of Medicine*, *362*(25), 2380–2388. https://doi.org/10.1056/nejmoa0909530

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

Masuda, T., Miura, S., Sato, Y., Tachihara, M., Bessho, A., Nakamura, A., Miyawaki, T., Yoshimine, K., Mori, M., Shiraishi, H., Hamai, K., Haratani, K., Maeda, S., Tabata, E., Kitagawa, C., Tanizaki, J., Imai, T., Nogami, S., Yamamoto, N., & Nakagawa, K. (2023). Significance of micro-EGFR T790M mutations on EGFR-tyrosine kinase inhibitor efficacy in non-small cell lung cancer. *Scientific Reports*, *13*(1). https://doi.org/10.1038/s41598-023-45337-3

Obradovic, J., Todosijevic, J., & Jurisic, V. (2022). Side effects of tyrosine kinase inhibitors therapy in patients with non-small cell lung cancer and associations with EGFR polymorphisms: A systematic review and meta-analysis. *Oncology Letters*, *25*(2), 62. https://doi.org/10.3892/ol.2022.13649

Park, K., Tan, E.-H., O'Byrne, K., Zhang, L., Boyer, M., Mok, T., Hirsh, V., Yang, J. C.-H., Lee, K. H., Lu, S., Shi, Y., Kim, S.-W., Laskin, J., Kim, D.-W., Arvis, C. D., Kölbeck, K., Laurie, S. A., Tsai, C.-M., Shahidi, M., & Kim, M. (2016). Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *The Lancet Oncology*, *17*(5), 577–589. https://doi.org/10.1016/s1470-2045(16)30033-x

Paz-Ares, L., Tan, E.-H. ., O'Byrne, K., Zhang, L., Hirsh, V., Boyer, M., Yang, J. C.-H. ., Mok, T., Lee, K. H., Lu, S., Shi, Y., Lee, D. H., Laskin, J., Kim, D.-W. ., Laurie, S. A., Kölbeck, K., Fan, J., Dodd, N., Märten, A., & Park, K. (2017). Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. *Annals of Oncology*, *28*(2), 270–277. https://doi.org/10.1093/annonc/mdw611

Santarpia, M., Liguori, A., Karachaliou, N., Gonzalez-Cao, M., Daffinà, M. G., D'Aveni, A., Marabello, G., Altavilla, G., & Rosell, R. (2017). Osimertinib in the treatment of non-small-cell lung cancer: design, development and place in therapy. *Lung Cancer: Targets and Therapy*, Volume 8, 109–125. https://doi.org/10.2147/lctt.s119644

Scott, L. J. (2018). Osimertinib as first-line therapy in advanced NSCLC: a profile of its use. *Drugs & Therapy Perspectives*, *34*(8), 351–357. https://doi.org/10.1007/s40267-018-0536-9

U.S. Food and Drug Administration. (2023). *FDA Adverse Event Reporting System (FAERS) Public Dashboard.* U.S. Department of Health and Human Services, Food and Drug Administration. https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard

U.S. Food and Drug Administration. (2025). *FDA Adverse Event Reporting System (FAERS) Public Dashboard*. U.S. Department of Health and Human Services, Food and Drug Administration.

SCHOLARLY REVIEW

SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380
Published by Leadership & Innovation Lab

WINTER 2025/2026

https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/7a47a261-d58b-4203-a8aa-6d3021737452/state/analysis

Wavreille, A.-S., Garaud, M., Zhang, Y., & Pei, D. (2007). Defining SH2 domain and PTP specificity by screening combinatorial peptide libraries. *Methods, 42*(3), 207–219. https://doi.org/10.1016/j.ymeth.2007.02.010

Yu, H. A., & Pao, W. (2013). Afatinib—new therapy option for EGFR-mutant lung cancer. *Nature Reviews Clinical Oncology*, *10*(10), 551–552. https://doi.org/10.1038/nrclinonc.2013.154

Yu, H. A., & Riely, G. J. (2013). Second-Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Lung Cancers. *Journal of the National Comprehensive Cancer Network*, *11*(2), 161–169. https://doi.org/10.6004/jnccn.2013.0024

Zappa, C., & Mousa, S. A. (2016). Non-small cell lung cancer: current treatment and future advances. *Translational Lung Cancer Research*, *5*(3), 288–300. https://doi.org/10.21037/tlcr.2016.06.07

Zhang, Y.-L., Yuan, J.-Q., Wang, K.-F., Fu, X.-H., Han, X.-R., Threapleton, D., Yang, Z.-Y., Mao, C., & Tang, J.-L. (2016). The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. *Oncotarget*, *7*(48). https://doi.org/10.18632/oncotarget.12587

Zia, V., Lengyel, C. G., Tajima, C. C., & de Mello, R. A. (2023). Advancements of ALK inhibition of non-small cell lung cancer: a literature review. *Translational Lung Cancer Research*, *12*(7), 1563–1574. https://doi.org/10.21037/tlcr-22-619