Osimertinib-Induced Cardiotoxicity
A Retrospective Review of the FDA Adverse Events Reporting System (FAERS)

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ABSTRACT

OBJECTIVES The goal of this study was to compare the risk of cardiotoxicity with osimertinib versus all other drugs and versus epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) (erlotinib, afatinib, and gefitinib) in the U.S. Food and Drug Administration Adverse Events Reporting System (FAERS), a pharmacovigilance database.

BACKGROUND Osimertinib has been shown to improve outcomes in T790M-positive non-small cell lung cancer patients who progress on EGFR-TKI therapy and in the frontline setting in EGFR mutated non-small cell lung cancer. In pivotal trials, osimertinib was associated with higher rates of cardiotoxicity compared with the control arm.

METHODS FAERS was queried for “Cardiac failure,” “Electrocardiogram QT-prolonged,” “Atrial Fibrillation (AF),” “Myocardial Infarction (MI),” and “Pericardial Effusion” secondary to “Osimertinib,” “Erlotinib,” “Afatinib,” “Gefitinib,” and all other drugs from 2016 to 2018. Disproportionality signal analysis was performed by calculating the reporting odds ratio (ROR) with its 95% confidence interval (CI). The ROR was considered significant when the lower limit of the 95% CI was >1.0.

RESULTS The ROR (95% CI) for cardiac failure, atrial fibrillation (AF), QT prolongation, myocardial infarction, and pericardial effusion due to osimertinib versus all other drugs in FAERS was 5.4 (4.2 to 7.1), 4.0 (2.8 to 5.8), 11.2 (7.9 to 15.8), 1.6 (0.9 to 2.6), and 8.2 (4.8 to 14), respectively. The ROR (95% CI) for cardiac failure, AF, QT prolongation, myocardial infarction, and pericardial effusion in comparing osimertinib versus other EGFR-TKIs was 2.2 (1.5 to 3.2), 2.1 (1.3 to 3.5), 6.6 (3.4 to 12.8), 1.2 (0.6 to 2.3), and 1.6 (0.8 to 3.3).

CONCLUSIONS The RORs for cardiac failure, AF, and QT prolongation were higher due to osimertinib compared with other TKIs. Electrocardiographic monitoring for QT prolongation and monitoring for signs and symptoms of heart failure should be considered in patients taking osimertinib. (J Am Coll Cardiol CardioOnc 2019;1:172–8) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
EGFR mutations were believed to be more prevalent among nonsmokers and women, but they are also found in patients with NSCLC who are smokers and men (5). Current guidelines for molecular testing in lung cancer recommend testing for EGFR mutations in all advanced lung adenocarcinoma (NSCLC) patients to guide frontline therapy (6).

Osimertinib first gained U.S. Food and Drug Administration (FDA) approval in the United States in November 2015 for T790M-positive NSCLC patients who had progression with standard EGFR-TKIs (7). More recently, osimertinib showed improved outcomes in the frontline setting in patients with EGFR-mutated NSCLC compared with standard EGFR-TKIs, leading to osimertinib being the preferred TKI for EGFR-mutated NSCLC (8). In this pivotal study, although osimertinib was associated with fewer grade 3 or higher adverse events (AEs) compared with standard EGFR-TKIs (34% vs. 45%), osimertinib was associated with an increased risk of cardiotoxicity compared with the control arm. Specifically, grade 3 or higher QT prolongation was reportedly higher in the osimertinib arm. However, a meta-analysis of pivotal studies showed that osimertinib was associated with not only an increased risk of QT prolongation but also an increased risk of cardiac failure (9).

Herein, we retrospectively reviewed the U.S. Food and Drug Administration Adverse Events Reporting System (FAERS), a pharmacovigilance database, for the incidence of cardiotoxicity due to osimertinib compared with other drugs approved by the FDA and also specifically versus other EGFR-TKIs.

**METHODS**

This study is a retrospective analysis that used data queries from the FAERS pharmacovigilance monitoring database. FAERS is a public database that contains nearly 17 million AE reports, medication error reports, and product quality complaints reported by health care professionals, manufacturers, and consumers from around the world since 1968. These reports are managed by the FDA and evaluated by clinical reviewers in the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research. Data in each event report, where applicable, include individual case identification numbers for reference, the suspected pharmaceutical, reason for use, adverse reactions, nature of the event (i.e., serious), outcomes (e.g., hospitalized, death, other outcomes), sex (male, female, or unknown), age, weight, event date, initial FDA receipt date, latest FDA receipt date, pharmaceutical company, reporter (e.g., health care professional, consumer, pharmaceutical company, unknown), concomitant medications, latest manufacturer received date, country where the event occurred, and manufacturer control number. Individual names and date of birth are excluded from these lists.

The present study involved data queries of the FAERS database between January 1, 2016, and September 30, 2018, for AEs secondary to EGFR-TKIs, namely “Osimertinib,” “Erlotinib,” “Afatinib,” and “Gefitinib.” Only EGFR-TKIs with >100 AEs in the database were chosen for analysis (dacomitinib was excluded). We chose January 1, 2016, as the start date for all TKIs to decrease bias, given that it represents a time period post-osimertinib FDA approval. Of note, other TKIs were FDA-approved before osimertinib. We queried for AEs classified by group queries according to the Medical Dictionary for Regulatory Activities that had ≥30 events. There were 6 cardiac-related AEs due to TKIs that met that criteria, namely: “Cardiac failure,” “Atrial Fibrillation,” “Electrocardiogram QT prolonged,” “Myocardial infarction,” “Pericardial Effusion,” and “Cardiac failure congestive” (Supplemental Table 1). Cardiac failure congestive and cardiac failure AEs were grouped together for analysis. FAERS was accessed on January 28, 2019.

To compare the risk of cardiotoxicity in osimertinib-treated cases versus reported events from other drugs in the database, a disproportionality analysis was conducted by using the reporting odds ratio (ROR) (Supplemental Table 2). ROR is a measure of the magnitude of association between an exposure to a pharmaceutical and the odds of a specific outcome occurring (10). ROR was considered significant when the lower limit of the 95% confidence interval (CI) was >1.0. The risk of cardiotoxicity due to osimertinib was compared with all other drugs and with other EGFR-TKIs (gefitinib, afatinib, and erlotinib) during the same time period; disproportionality signal analysis was used to calculate the ROR. The median time and interquartile range for the AE were calculated based on the start date of the TKI. AEs were classified as serious versus nonserious per definitions according to FAERS (Supplemental Methods).

**RESULTS**

The total number of AEs in FAERS from all drugs was 5,138,230. Of those, 8,450 AEs were due to
osimertinib, erlotinib, afatinib, or gefitinib. Of 8,450 AEs, 2,454 were secondary to osimertinib; 5,836 were due to other EGFR-TKIs (erlotinib, afatinib, or gefitinib); and 160 were due to the combination, in which osimertinib and any of the 3 other EGFR-TKIs were listed as a possible cause. A total of 315 cardiac AEs were noted, 150 (6.1%) due to osimertinib, 8 (5%) due to osimertinib combined with other TKIs, and 157 (2.7%) due to other TKIs (Table 1).

As detailed in Table 2, cardiac failure was the most common AE caused by osimertinib, followed by QT prolongation. More than 90% of the reactions due to cardiac failure and QT prolongation were serious. In 19.3% of the cardiac failure cases, osimertinib and at least 1 other non-TKI drug were considered as leading to the AE. Similarly, in the case of QT prolongation, 33% of the cases had osimertinib and at least 1 other non-TKI drug was considered as leading to the AE. For the subset of patients for whom event timing was available, the median time to event was 29 days for cardiac failure and 23 days for QT prolongation.

### Table 1: Adverse Events Due to EGFR-TKIs in FAERS From 2016 to 2018

| Category                        | Total (N = 8,450) | Osimertinib (n = 2,454) | Osimertinib + Other TKIs (n = 160) | Other TKIs (n = 5,836) |
|---------------------------------|-------------------|------------------------|------------------------------------|------------------------|
| Cardiac failure                 | 120 (1.4)         | 57 (2.3)               | 1 (0.6)                            | 62 (1.1)               |
| Atrial fibrillation             | 64 (0.8)          | 30 (1.2)               | 1 (0.6)                            | 33 (0.6)               |
| QT prolongation                 | 49 (0.6)          | 33 (1.3)               | 4 (2.5)                            | 12 (0.2)               |
| Myocardial infarction           | 46 (0.5)          | 16 (0.7)               | 0 (0.0)                            | 30 (0.5)               |
| Pericardial effusion            | 36 (0.4)          | 14 (0.6)               | 2 (1.3)                            | 20 (0.3)               |
| Total                           | 315 (3.7)         | 150 (6.1)              | 8 (0.5)                            | 157 (2.7)              |

Values are n (% of total in each treatment category).

EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor; FAERS = U.S. Food and Drug Administration Adverse Events Reporting System.

### Table 2: Details of Cardiac Related AEs Due to Osimertinib

| Category                        | Total number of reported AEs | Cardiac Failure | QT Prolongation | Atrial Fibrillation | Myocardial Infarction | Pericardial Effusion |
|---------------------------------|------------------------------|----------------|-----------------|--------------------|-----------------------|----------------------|
| Sex                             | 57                           | 33             | 30              | 16                 | 14                    |
| Female                          | 45/56 (80.3)                 | 19/28 (67.9)   | 9/28 (32.1)     | 16/29 (57.9)       | 10/15 (66.6)          | 6/11 (54.5)          |
| Male                            | 11/56 (19.6)                 | 10/28 (35.7)   | 9/28 (32.1)     | 10/29 (34.5)       | 5/15 (33.3)           | 5/11 (45.5)          |
| Age, yrs (n. of patients for whom data was available) | (n = 46) | (n = 25) | (n = 23) | (n = 2) | (n = 7) |
| Range (minimum–maximum)         | 77.5 (48–92)                 | 66/41–85       | 75/59–91        | 78.5/50–91         | 64/42–69              |
| Type of reaction                |                              |                |                 |                    |                       |                      |
| Serious                         | 55 (96.5)                    | 31 (93.9)      | 30 (100.0)      | 16 (100.0)         | 12 (85.7)             |
| Nonserious                      | 2 (3.5)                      | 2 (6.1)        | 0 (0.0)         | 0 (0.0)            | 2 (14.3)              |
| Outcome                         |                              |                |                 |                    |                       |                      |
| Hospitalization                 | 29 (50.9)                    | 13 (39.3)      | 16 (53.3)       | 5 (31.2)           | 6 (42.9)              |
| Death                           | 17 (29.8)                    | 10 (30.3)      | 9 (30.0)        | 6 (37.5)           | 5 (35.7)              |
| Life-threatening                | 2 (3.5)                      | 2 (6.1)        | 1 (3.3)         | 2 (12.5)           | 1 (7.1)               |
| Other outcomes                  | 6 (10.5)                     | 6 (18.2)       | 4 (13.3)        | 3 (18.7)           | 0 (0.0)               |
| Nonserious                      | 2 (3.5)                      | 2 (6.1)        | 0 (0.0)         | 0 (0.0)            | 2 (14.3)              |
| Disabled                        | 1 (1.7)                      | 0 (0.0)        | 0 (0.0)         | 0 (0.0)            | 0 (0.0)               |
| Suspected drugs                 |                              |                |                 |                    |                       |                      |
| Osimertinib                     | 46 (80.7)                    | 22 (66.6)      | 24 (80.0)       | 14 (87.5)          | 13 (92.9)             |
| Osimertinib + 1*                | 11 (19.3)                    | 11 (33.3)      | 6 (20.0)        | 2 (12.5)           | 1 (7.1)               |
| Outcome counts by year received |                              |                |                 |                    |                       |                      |
| 2016                            | 11 (19.3)                    | 5 (15.1)       | 9 (30.0)        | 6 (37.5)           | 5 (35.7)              |
| 2017                            | 23 (40.3)                    | 12 (36.4)      | 6 (20.0)        | 5 (31.2)           | 6 (42.9)              |
| 2018                            | 23 (40.3)                    | 16 (48.5)      | 15 (50.0)       | 5 (31.2)           | 3 (21.4)              |
| Reporter                        |                              |                |                 |                    |                       |                      |
| Health care professional        | 51 (89.5)                    | 33 (100.0)     | 28 (93.3)       | 13 (81.2)          | 11 (78.6)             |
| Consumer                        | 6 (10.5)                     | 0 (0.0)        | 2 (6.6)         | 3 (18.7)           | 3 (21.4)              |
| Region of AE                    |                              |                |                 |                    |                       |                      |
| Asia                            | 28 (49.1)                    | 18 (54.6)      | 12 (39.3)       | 8 (37.5)           | 4 (28.6)              |
| Americas                        | 16 (28.1)                    | 10 (30.3)      | 9 (30.0)        | 6 (37.5)           | 7 (50.0)              |
| Europe                          | 1 (22.8)                     | 5 (15.1)       | 8 (26.7)        | 3 (18.7)           | 2 (14.3)              |
| Australia                       | 0 (0.0)                      | 0 (0.0)        | 1 (6.2)         | 1 (7.1)            |                       |
| Time to AE, days; number of patients for whom data were available | (n = 33) | (n = 19) | (n = 16) | (n = 4) |
| Median (interquartile range)    | 29 (16.5–95.5)               | 23 (14.0–55.0) | 60 (12.5–362.0) | 26.5 (9.0–63.5)    | 65 (11.0–182.0)       |

Values are n, n/N (%), or n (%). *Drugs other than epidermal growth factor receptor-tyrosine kinase inhibitors.

AE = adverse event.
According to the disproportionality signal analysis, the ROR for osimertinib versus all other drugs in FAERS for cardiac failure was elevated at 5.4 (95% CI: 4.2 to 7.1); for atrial fibrillation, 4.0 (95% CI: 2.8 to 5.8); for QT prolongation, 11.2 (95% CI: 7.9 to 15.8); for pericardial effusion, 8.2 (95% CI: 4.8 to 14.0); and for myocardial infarction, not significantly different at 1.6 (95% CI: 0.9 to 2.6) (Figure 1, Supplemental Table 3). Among reactions with elevated RORs, the reported outcome of death was highest for pericardial effusion at 35.7%.

The ROR comparing osimertinib versus other EGFR-TKIs for cardiac failure was elevated at 2.2 (95% CI: 1.5 to 3.2); for atrial fibrillation, 2.1 (95% CI: 1.3 to 3.5); for QT prolongation, 6.6 (95% CI: 3.4 to 12.8); for myocardial infarction, not significantly different at 1.2 (95% CI: 0.6 to 2.3); and for pericardial effusion, not significantly different at 1.6 (95% CI: 0.8 to 3.3) (Figure 1).

### DISCUSSION

In FAERS, of all the AEs reported with osimertinib, 6.1% were cardiac related. Osimertinib was found to have an increased risk of cardiac failure, atrial fibrillation, QT prolongation, and pericardial effusion compared with all other drugs in the FAERS (Central Illustration). The risk of myocardial infarction was not increased compared with other drugs in FAERS. The ROR was highest for QT prolongation followed by pericardial effusion, cardiac failure, and atrial fibrillation.

In the comparison of osimertinib versus other EGFR-TKIs for risk of cardiotoxicity, there was an increased risk of cardiac failure, atrial fibrillation, and QT prolongation. Again, the ROR for QT prolongation versus other EGFR-TKIs was highest at 6.6. The RORs for myocardial infarction and pericardial effusion were not significantly increased.

Cardiovascular AEs are a well-known toxicity of TKIs used in chronic myeloid leukemia, such as with imatinib (first-generation BCR-ABL1 TKI), dasatinib (second-generation BCR-ABL1 TKI), and ponatinib (third-generation BCR-ABL1 TKI) (11). However, this has not been reported in clinical trials with first-generation anti–EGFR-TKIs (erlotinib or gefitinib) or second-generation anti-EGFR-TKIs (afatinib) (12–15).

The AURA3 trial (Randomized Phase III Study of Osimertinib vs Platinum-Pemetrexed for EGFR T790M-Positive Advanced NSCLC) compared osimertinib versus chemotherapy and determined that cardiotoxicity (defined by a decrease in left ventricular ejection fraction [LVEF] $\leq 10\%$ and to an LVEF $<50\%$) occurred in 5% of the osimertinib arm, with a median time of 5.5 months to onset of LVEF decline (7). The rate of QT prolongation was also high in the osimertinib arm in the AURA3 trial (3% vs. 0%). Similarly, in the FLAURA trial (Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer), which compared osimertinib versus a first-generation EGFR-TKI (gefitinib or erlotinib) in the frontline setting, there was a higher rate of QT prolongation (10% vs. 4%) and LVEF decrease $\geq 10\%$ to $<50\%$ with osimertinib (3% vs. 1%) (8). Osimertinib has also been reported to lead to severe cardiac dysfunction such as myocarditis. Oyakawa et al. (16) described a case of osimertinib-induced myocarditis in which even after 12 weeks of discontinuation of osimertinib, there was no improvement in LVEF.

The underlying mechanism of osimertinib-induced cardiotoxicity remains unclear. Osimertinib and its
active metabolite AZ5104 not only inhibit EGFR but also inhibit HER2 (human epidermal growth factor receptor-2) in vitro (1). Given the known risk of cardiotoxicity with anti-HER2 agents such as trastuzumab (17), HER2 inhibition may be related to cardiotoxicity (18,19). EGFR signaling itself has been shown to be protective in the setting of catecholamine excess in a mouse model in which treatment with erlotinib enhanced myocardial injury induced by isoproterenol infusion (20).

**STUDY LIMITATIONS.** This analysis was a retrospective study of reported events in FAERS, and as such, baseline cardiac characteristics of patients taking TKIs are not known. The time to event for all cases with AEs was not available, nor was the grade of toxicity. Moreover, the actual incidence of cardiotoxicity with osimertinib cannot be determined because it is possible that not all events are reported within FAERS. As such, there are similar limitations in the ROR estimate. AE reporting for a drug may be
influenced by extent of use, publicity, and bias (21). Although the use of disproportionality analysis through pharmacovigilance databases to determine the increased risk of AEs secondary to a particular drug has been shown in various settings (21,22), it is critical that any hypotheses generated by using pharmacovigilance databases are validated through prospective studies.

The significance of the present study is that it informs the potential increased risk of cardiotoxicity with osimertinib, which is now frontline treatment for EGFR-mutated NSCLC. In pivotal studies, the increased risk of cardiac failure and QT prolongation has been reported; analysis of FAERS corroborates this finding and also indicates that osimertinib is associated with an increased risk of atrial fibrillation. NSCLC harboring EGFR mutations accounts for 10% of U.S. patients and 35% in Asia (2–4). As EGFR inhibitors continue to improve survival in NCSLC (23), there remains a need to monitor patients for signs and symptoms of treatment-related toxicity, particularly cardiotoxicity. We recommend that clinicians consider an electrocardiography (ECG) at baseline when initiating osimertinib and at periodic intervals to monitor for QT prolongation. Concomitant drugs that can increase QT prolongation should be avoided while taking osimertinib. As per the osimertinib package insert, if the QT interval is >500 ms the osimertinib should be withheld until the QT interval is <480 ms or recovers to baseline. If the baseline QT is >480 ms, then osimertinib should be resumed at one-half the dose (24). Patients should also be monitored for signs and symptoms of cardiac failure while taking osimertinib, but it is likely that more evidence is needed before recommending standardized echocardiogram monitoring for every patient.

Our study raises many questions that require additional studies; for example, what is the mechanism of osimertinib-induced cardiotoxicity? Is there a patient population that is at increased risk of cardiotoxicity compared with others? Is the cardiotoxicity caused by osimertinib reversible or irreversible?

**CONCLUSIONS**

Rates of QT prolongation, cardiac failure, and atrial fibrillation were found to be higher due to osimertinib compared with other EGFR-TKIs in FAERS, a pharmacovigilance database. ECG monitoring for QT prolongation and monitoring for signs and symptoms of heart failure should be considered while taking osimertinib.

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**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** The risk of cardiotoxicity, as defined by cardiac failure, QT prolongation, and atrial fibrillation, is higher with osimertinib compared with older generation EGFR-TKIs. ECG monitoring for QT prolongation should be considered while taking osimertinib, and any concomitant QT-prolonging medications should be minimized. Patients should be monitored for signs and symptoms for heart failure while taking osimertinib.

**TRANSLATIONAL OUTLOOK:** Further research is needed to determine the underlying mechanism of cardiotoxicity due to osimertinib. Multidisciplinary efforts are needed to identify patients at increased risk for cardiotoxicity due to osimertinib.

**REFERENCES**

1. Cross DA, Ashton SE, Ghioghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4:1046-61.

2. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-39.

3. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.

4. Paos W, Miller V, Zakowski M, et al. EGFR receptor gene mutations are common in lung cancers from “never smokers” and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 2004;101:13306-11.

5. D’Angelo SP, Pietanza MC, Johnson ML, et al. Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas. J Clin Oncol 2011;29:2066-70.

6. Lindeman NI, Cagle PT, Atsner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the
7. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 2017;376:629-40.

8. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113-25.

9. Thein K, Swarup S, Ball S, et al. 1388P Incidence of cardiac toxicities in patients with advanced non-small cell lung cancer treated with osimertinib: a combined analysis of two phase III randomized controlled trials. Ann Oncol 2018;29:mdy292.011.

10. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf 2004;13:519-23.

11. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor-associated cardiovascular toxicity in chronic myeloid leukemia. J Clin Oncol 2015;33:4210-8.

12. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.

13. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.

14. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.

15. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:213-22.

16. Oyakawa T, Nakashima K, Naito T. Cardiac dysfunction caused by osimertinib. J Thoracic Oncol 2017;12:e159-60.

17. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002;20:1215-21.

18. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 2002;346:281-91.

19. Viani GA, Afonso SL, Stefano EJ, De Fendi L, Soares FV. Adjuvant trastuzumab in the treatment of HER-2-positive early breast cancer: a meta-analysis of published randomized trials. BMC Cancer 2007;7:153.

20. Noma T, Lemaire A, Naga Prasad SV, et al. Beta-arrestin-mediated beta-adrenergic receptor transactivation of the EGFR confers cardioprotection. J Clin Invest 2007;117:2445-58.

21. Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with brutinib. J Am Coll Cardiol 2019;74:1667-78.

22. Anand K, Burns EA, Ensr J, Rice L, Pingali SR. Mycobacterial infections with ruxolitinib: a retrospective pharmacovigilance review. Clin Lymphoma Myeloma Leuk 2019 Aug 26 [E-pub ahead of print].

23. Lin JJ, Cardarela S, Lydon CA, et al. Five-year survival in EGFR-mutant metastatic lung adenocarcinoma treated with EGFR-TKIs. J Thoracic Oncol 2016;11:556-65.

24. Astrazeneca Pharmaceuticals. Tagrisso (osimertinib) [package insert]. U.S. Food and Drug Administration website. Revised April 2018. Available at:www.accessdata.fda.gov/drugsatfda_docs/label/2018/208065s008lbl.pdf. Accessed September 15, 2019.

**KEY WORDS** cardiotoxicity, EGFR mutation, non-small cell lung cancer, osimertinib, QT prolongation

**APPENDIX** For supplemental tables and Methods, please see the online version of this paper.