Heart failure incidence and mortality with EGFR TKIs in patients with NSCLC: targeted literature review

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Question

Does treatment with TKIs impact a patient's risk for HF events?

Investigation

82 publications relevant to HF identified by systematic literature review

- 3 publications reporting HF events in patients with any cancer treated with TKIs
- 79 publications reporting HF events in patients with NSCLC treated with EGFR TKIs

Results

Systematic review → 82 publications

Patients with cancer, treated with TKIs
(3 publications, 28,236 patients)

- **HF Incidence**
  - No cases of HF in 2 studies
  - 1 study reports incidence of HF or cardiomyopathy 13 per 1000 person-years
- **HF Mortality**
  - No deaths reported

Patients with NSCLC, treated with EGFR TKIs
(79 publications, 21,985 patients)

Includes 6 case studies (8 patients)

- **HF Incidence**
  - Observational studies: 0%–5.9%
  - Clinical trials: 0%–8%
- **HF Mortality**
  - 0%–4%

Key Takeaway

Few studies reported incidence of HF events or mortality after treatment with TKIs

Background

- Cardiovascular disease is a known adverse event for certain cancer therapies[1]
- Patients diagnosed with heart failure (HF) and cancer experience decreased survival and limited therapeutic options due to concerns about cardiotoxicity from cancer and treatments[2,3]
  - In particular, HF has been reported in patients with non–small cell lung cancer (NSCLC) who received epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs)[4]
- The aim of this targeted literature review was to provide a foundational understanding of the risk of HF associated with EGFR TKIs in patients with NSCLC

1. ASCO. Cancer.net. 2021. Available at: https://www.cancer.net/coping-with-cancer/physical-emotional-and-social-effects-cancer/managing-physical-side-effects/heart-problems-caused-cancer-treatment. Accessed August 10, 2023. 2. Batra A, et al. BMC Cancer. 2020;20(1):1004. 3. Ambrogi V, et al. Eur J Cardiothorac Surg. 2003;23(5):811-817. 4. AlShatnawi MN, et al. Egypt J Int Med. (2022) 34:85.

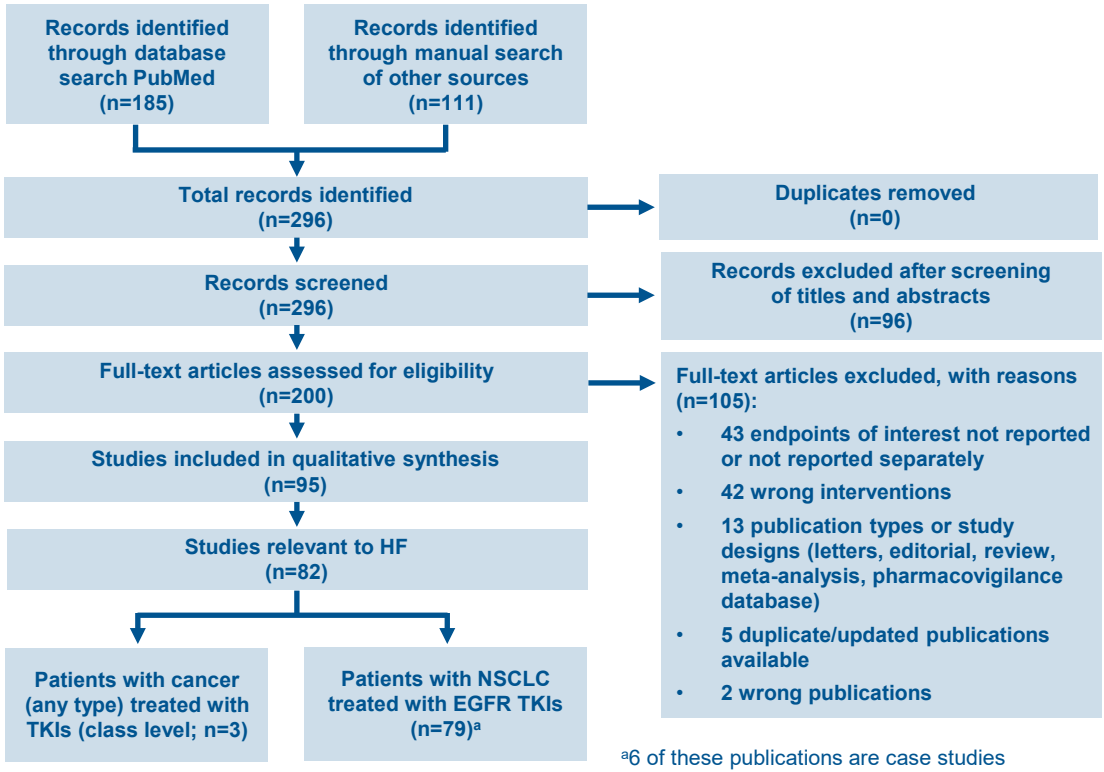
Methods

- A targeted literature review was conducted to determine the incidence and mortality of HF in patients with NSCLC treated with EGFR TKIs
  - Both an electronic search and a manual search were conducted
- Incidence of and mortality due to HF were the outcomes of interest
  - Terminology for HF events included, but was not limited to, cardiac failure, congestive HF, and chronic HF
- Populations assessed were patients with any cancer type treated with TKIs and patients with NSCLC treated with EGFR TKIs
- Specific EGFR TKIs of interest included in the search were afatinib, almonertinib, dacomitinib, erlotinib, gefitinib, icotinib, mobocertinib, olmutinib, osimertinib, and simotinib
- Publication types included single-arm studies, studies with multiple arms of a single drug under examination, comparative studies versus patients with lung cancer treated with prespecified non-TKIs, and case reports

Results

- A total of 296 publications were identified, of which 82 studies met all eligibility criteria and were abstracted for HF incidence or mortality

PRISMA flow diagram for systematic review



[a]6 of these publications are case studies

Results

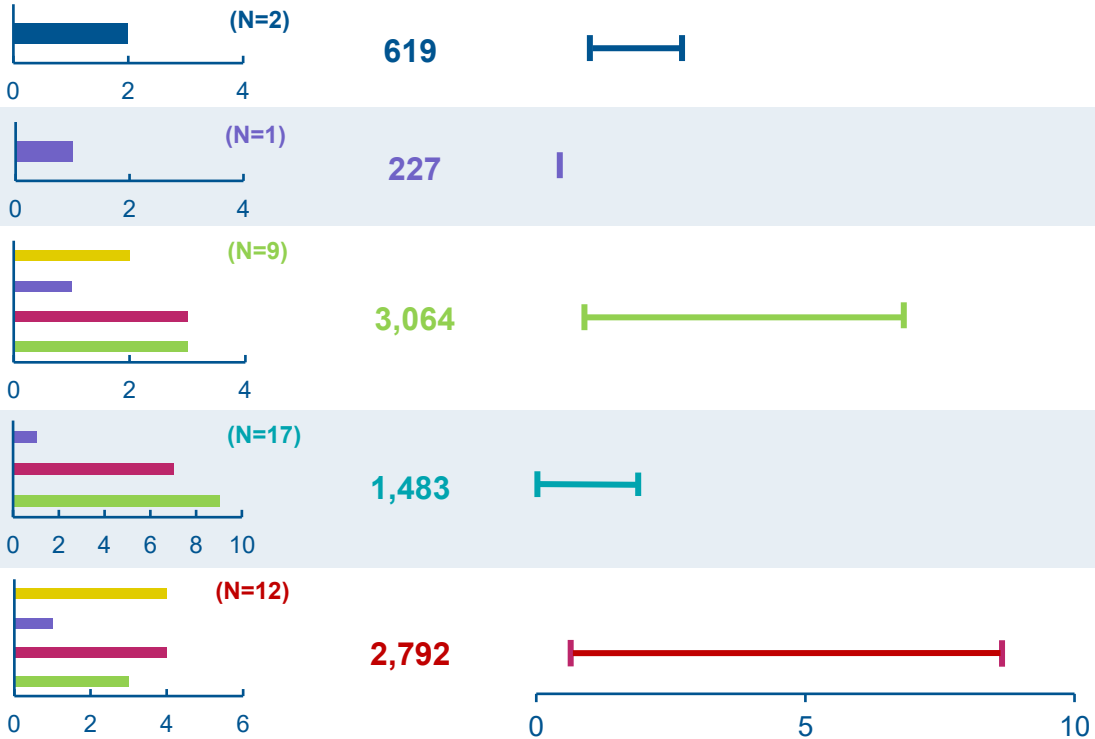
- For patients with any type of cancer treated with TKIs:
  - 3 studies reported data on the incidence of HF
    - No cases of HF were reported from 2 studies and no deaths due to HF were reported
    - In 1 study, incidence of HF or cardiomyopathy was 13 per 1000 person-years; data from 27,992 patients
- For patients with NSCLC treated with EGFR TKIs:
  - 79 articles reported data on the incidence of HF
    - 6 of these articles were case reports including 8 patients with HF
  - Among observational studies and clinical trials,
    - HF incidence ranged from 0% to 8%
    - HF mortality rates ranged from 0% to 4% for the EGFR TKI arms

Results

- Among publications assessing the incidence of HF events in patients with NSCLC by EGFR TKI
  - Publications reporting data on icotinib, mobocertinib, and olmutinib did not report any HF events
  - In most studies evaluating EGFR TKIs in patients with NSCLC, no HF events were observed
- Among publications assessing mortality due to HF in patients with NSCLC by EGFR TKI
  - Publications reporting data on dacomitinib, erlotinib, icotinib, and olmutinib did not report any deaths due to HF

Publications reporting HF incidence and reported rates in patients with NSCLC by EGFR TKI

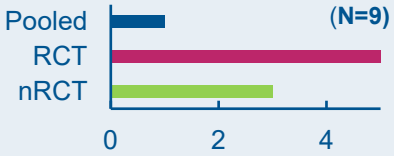
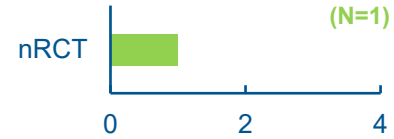
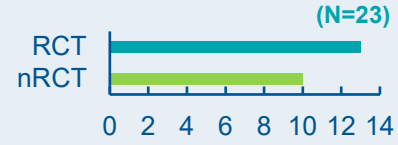
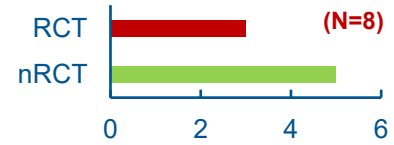
TKI	Publications by type (N)	Total no. of patients	Incidence (% of patients)	Incidence range
Afatinib	RCT (N=2)	619		1%–1.7%[1]
Dacomitinib	RCT (N=1)	227		0.4%[2]
Erlotinib	Case report, Observational, RCT, nRCT (N=9)	3,064		0.9%–5.9%[3–9]
Gefitinib	Observational, RCT, nRCT (N=17)	1,483		0%–1.9%[10–24]
Osimertinib	Case report, Observational, RCT, nRCT (N=12)	2,792		0.7%–8.0%[2,8,25–31]



Note: One publication on mobocertinib reported a mortality due to HF but did not report incidence.

1. Ewer MS, et al. CardioOncol. 2015;1(1):3. 2. Wu YL, et al. Lancet Oncol. 2017;18(11):1454–66. 3. Ehrenstein V, et al. Pharmacoepidemiol Drug Saf. 2021;30(6):758–69. 4. Felip E, et al. Clin Lung Cancer. 2012;13(6):432–41. 5. Schaake EE, et al. J Clin Oncol. 2012;30(22):2731–38. 6. Yamada K, et al. Jpn J Clin Oncol. 2013;43(6):629–35. 7. Pérol M, et al. J Clin Oncol. 2012;30(28):3516–24. 8. Ramalingam SS, et al. N Engl J Med. 2020;382(1):41–50. 9. Shepherd FA, et al. N Engl J Med. 2005;353(2):123–32. 10. Yoshida K, et al. J Thorac Oncol. 2007;2(1):22–8. 11. Asahina H, et al. Br J Cancer. 2006;95(8):998-1004. 12. Asami K, et al. Clin Lung Cancer. 2011;12(6):387–92. 13. Douillard JY, et al. Br J Cancer. 2014;110(1):55–62. 14. Inoue A, et al. J Clin Oncol. 2006;24(21):3340–46. 15. Inoue A, et al. J Clin Oncol. 2009;27(9):1394–1400. 16. Sequist LV, et al. J Clin Oncol. 2008;26(15):2442–49. 17. Sugio K, et al. Lung Cancer. 2009;64(3):314–18. 18. Sunaga N, et al. Lung Cancer. 2007;56(3):383–89. 19. Sutani A, et al. Br J Cancer. 2006;95(11):1483–89. 20. Maemondo M, et al. J Thorac Oncol. 2012;7(9):1417–22. 21. Han JY, et al. J Clin Oncol. 2012;30(10):1122–28. 22. Han B, et al. Int J Cancer. 2017;141(6):1249–56. 23. Zhang L, et al. Lancet Oncol. 2012;13(5):466–75. 24. Takeda K, et al. J Clin Oncol. 2010;28(5):753–60. 25. Kunimasa K, et al. JACC CardioOncol. 2020;2(1):1–10. 26. Goss G, Tsai CM, et al. Lancet Oncol. 2016;17(12):1643–52. 27. Sequist LV, et al. Lancet Oncol. 2020;21(3):373–86. 28. Yu HA, et al. Clin Cancer Res. 2021;27(4):992–1002. 29. Jänne PA, et al. N Engl J Med. 2015;372(18):1689–99. 30. Mok TS, et al. N Engl J Med. 2017;376(7):629–40. 31. Wu YL, et al. N Engl J Med. 2020;383(18):1711–23.

Publications reporting HF mortality and reported rates in patients with NSCLC by EGFR TKI

TKI	Publications by type (N)	Total no. of patients	Incidence (% of patients)	Incidence range
Afatinib		2,210		0.3%–0.9%[1–9]
Mobocertinib		114		0.9%[10]
Gefitinib		2,816		0%–1.9%[11–34]
Osimertinib		1,436		0%–4.0%[a,1,34,35–40]

[a]Combination therapy with ramucirumab may have contributed to the event.

1. Wu YL, et al. Lancet Oncol. 2014;15(2):213–22. 2. de Marinis F, et al. Lung Cancer. 2021;152:127–34. 3. Katakami N, et al. J Clin Oncol. 2013;31(27):3335–41. 4. Yang JC, et al. Lancet Oncol. 2012;13(5):539–48. 5. Park K, et al. Lancet Oncol. 2016;17(5):577–89. 6. Schuler M, et al. Ann Oncol. 2016;27(3):417–23. 7. Miller VA, et al. Lancet Oncol. 2012;13(5):528–38. 8. Sequist LV, et al. J Clin Oncol. 2013;31(27):3327–34. 9. Ewer MS, et al. CardioOncol (London, England). 2015;1(1):3. 10. Zhou C, et al. JAMA Oncol. 2021;7(12):e214761. 11. Asahina H, et al. Br J Cancer. 2006;95(8):998–1004. 12. Asami K, et al. Clin Lung Cancer. 2011;12(6):387–92. 13. Douillard JY, et al. Br J Cancer. 2014;110(1):55–62. 14. Inoue A, et al. J Clin Oncol. 2006;24(21):3340–46. 15. Inoue A, et al. J Clin Oncol. 2009;27(9):1394–1400. 16. Sequist LV, et al. J Clin Oncol. 2008;26(15):2442–49. 17. Sugio K, et al. Lung Cancer. 2009;64(3):314–18. 18. Sunaga N, et al. Lung Cancer. 2007;56(3):383–89. 19. Sutani A, et al. Br J Cancer. 2006;95(11):1483–89. 20. Maemondo M, et al. J Thorac Oncol. 2012;7(9):1417–22. 21. Han JY, et al. J Clin Oncol. 2012;30(10):1122–28. 22. Han B, et al. Int J Cancer. 2017;141(6):1249–56. 23. Zhang L, et al. Lancet Oncol. 2012;13(5):466-475. 24. Takeda K, et al. J Clin Oncol. 2010;28(5):753–60 25. Crinò L, et al. J Clin Oncol. 2008;26(26):4253–60. 26. Park K, et al. Lancet Oncol. 2016;17(5):577–89. 27. Jänne PA, et al. J Clin Oncol. 2012;30(17):2063–69. 28. Kris MG, et al. JAMA. 2003;290(16):2149–58. 29. Lee DH, et al. Clin Cancer Res. 2010;16(4):1307–14. 30. Maemondo M, et al. N Engl J Med. 2010;362(25):2380-2388. 31. Maruyama R, et al. J Clin Oncol. 2008;26(26):4244–52. 32. Mitsudomi T, et al. Lancet Oncol. 2010;11(2):121–28. 33. Shi Y, et al. Lancet Oncol. 2013;14(10):953–61. 34. Ramalingam SS, et al. N Engl J Med. 2020;382(1):41–50. 35. Goss G, et al. Lancet Oncol. 2016;17(12):1643–52. 36. Yu HA, et al. Clin Cancer Res. 2021;27(4):992–1002. 37. Jänne PA, et al. N Engl J Med. 2015;372(18):1689–99. 38. Mok TS, et al. Engl J Med. 2017;376(7):629–40. 39. Oxnard GR, et al. Ann Oncol. 2020;31(4):507–16. 40. Yoh K, et al. Target Oncol. 2021;16(3):339–55.

Incidence of HF and mortality due to HF reported in US prescribing information

Drug	Reported HF rate	Reported HF mortality rate
Afatinib[1]	Not reported	Not reported
Dacomitinib[2]	Not reported	Not reported
Erlotinib[3]	Not reported	Not reported
Gefitinib[4]	Not reported	Not reported
Mobocertinib (n=256)[5]	Pooled safety population: HF: 2.7% (grade 3: 1.2%; grade 4: 0.4%; 1 fatal case)	Pooled safety population: HF death 0.4%
Osimertinib (N=1479)[6]	Across clinical trials Cardiomyopathy[a]: 3%	Across clinical trials Cardiomyopathy[a]: 0.1%

[a]Cardiomyopathy is defined as cardiac failure, chronic cardiac failure, congestive heart failure, pulmonary edema, or decreased ejection fraction.
Note: Almonertinib and icotinib are approved in China, and there is no US prescribing information; olmutinib development was discontinued in 2018; simotinib was in development at time of review. When multiple trials were reported in the US prescribing information, pooled safety information was reported in this table.

1. Gilotrif [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2022. 2. Vizimpro [package insert]. New York, NY: Pfizer Inc.; 2020. 3. Tarceva [package insert]. Northbrook, IL: OSI Pharmaceuticals, LLC; 2016. 4. Iressa [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021. 5. Exkivity [package insert]. Lexington, MA: Takeda Pharmaceuticals America, Inc.; 2023. 6. Tagrisso [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals; 2023.

Limitations

- Notable strengths of this report include:
  - Use of a prespecified protocol, search criteria, and abstraction sheet, as well as the wide breadth of literature evaluated
  - Being the first systematic review to investigate the incidence of and mortality due to HF associated with EGFR TKIs
- Limitations and challenges in identifying relevant data for this report include:
  - Only covered publications in the English language
  - Treatment guidelines and drug availability vary by region, complicating comparisons among studies
  - Some measures of incidence may actually reflect prevalence, incident events, or worsening of events but not an incident condition
  - Possible misclassification of events
  - Follow-up time varied across studies and even within different treatment arms of a single study
  - Different outcome definitions/criteria and different versions of the National Cancer Institute's Common Terminology Criteria for Adverse Events were used across studies

Conclusions

- In patients with cancer treated with TKIs at the class level, no HF events were observed in 2 of the 3 studies reporting the incidence of HF
- For patients with NSCLC treated with EGFR TKIs, in most studies, HF events and instances of HF mortality were not observed
- Healthcare providers should monitor patients for signs of cardiotoxicity, specifically related to HF, consistent with the prescribing information for EGFR TKIs
- Future directions include the development of standardized definitions of HF-related events and methods to improve monitoring for HF in patients with cancer

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Disclosures

BK: Employment with Takeda. **BC:** Employment with Takeda. **KI:** Consulted on this project through CERobs Consulting, LLC; Takeda Pharmaceuticals contracted with CERobs Consulting, LLC, a consulting firm with focus on real-world evidence, outcomes research, epidemiology, and clinical outcome assessments, including patient-reported outcomes. **KR:** Consulted on this project through a collaboration between the University of North Carolina at Chapel Hill and CERobs Consulting, LLC; Takeda Pharmaceuticals contracted with CERobs Consulting, LLC, a consulting firm with focus on real-world evidence, outcomes research, epidemiology, and clinical outcome assessments, including patient-reported outcomes. **NRO:** Consulted on this project through a collaboration between the University of North Carolina at Chapel Hill and CERobs Consulting, LLC; Takeda Pharmaceuticals contracted with CERobs Consulting, LLC, a consulting firm with focus on real-world evidence, outcomes research, epidemiology, and clinical outcome assessments, including patient-reported outcomes. **WS:** Employment with Takeda. **EF:** Employment with Takeda.

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