Evaluation of lung adverse events with trastuzumab using the Japanese pharmacovigilance database

Yuko Kanbayashi (✉ yuko.kambayashi@ompu.ac.jp)
Osaka Medical and Pharmaceutical University: Osaka Ika Yakka Daigaku

Mayako Uchida
Doshisha Women's College of Liberal Arts: Doshisha Joshi Daigaku

Misui Kashiwagi
Doshisha Women's College of Liberal Arts: Doshisha Joshi Daigaku

Hitomi Akiba
Doshisha Women's College of Liberal Arts: Doshisha Joshi Daigaku

Tadashi Shimizu
Hyogo College of Medicine: Hyogo Ika Daigaku

Research Article

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Abstract
The present study aimed to determine the risk of trastuzumab-induced lung toxicity, time to onset, and post hoc outcomes using the Japanese Adverse Drug Event Report database. We analysed data for the period between April 2004 and March 2021. Data on lung toxicities were extracted, and relative risk of adverse events (AEs) was estimated using the reporting odds ratio. We analysed 1,772,494 reports and identified 4,362 reports of AEs caused by trastuzumab. Of these, 693 lung toxicities were reportedly associated with trastuzumab. Signals were detected for seven lung toxicities: interstitial lung disease, pulmonary oedema, pleural effusion, lung disorder, acute pulmonary oedema, pulmonary fibrosis, and radiation pneumonitis. Among these, interstitial lung disease was the most frequently reported (61.8%). A histogram of times to onset showed occurrence from 1 to 105 days, but some cases of interstitial lung disease occurred even more than one year after the start of administration. The AEs showing the highest fatality rates were interstitial lung disease, pulmonary fibrosis, and radiation pneumonitis. This study focused on lung toxicities caused by trastuzumab as post-marketing AEs. Some cases could potentially involve serious outcomes; therefore, patients should be monitored for signs of the onset of these AEs not only at the start of administration, but also over an extended period, especially for interstitial lung disease.

Introduction
Trastuzumab is a monoclonal antibody against human epidermal growth factor receptor 2 (HER2) (also known as ERBB2 [receptor tyrosine-protein kinase2]) [1]. Combination chemotherapy with trastuzumab improves the survival of patients with several metastatic carcinomas [1–6]. In Japan, trastuzumab has been approved for the treatment of advanced solid tumours, including breast cancer, gastric cancer, colorectal cancer, and salivary gland cancer. Trastuzumab has been used in combination with chemotherapy and has been reported to prolong both overall and progression-free survival in clinical trials [1–6]. However, trastuzumab can cause a variety of adverse events (AEs). Among these, cardiac disorder is the most common serious AE, and others include infusion reaction and interstitial pneumonia/pulmonary disorder [7–10]. Cardiac impairment has been reported in previous studies as a mostly reversible AE [11, 12]. In contrast, lung-specific AEs attributable to trastuzumab have received little attention in clinical trials, despite their potentially life-threatening potential. Furthermore, even though trastuzumab has been widely used in patients since its launch, detailed information on lung-specific AEs from post-marketing monitoring has not been reported. Inadequate management of AEs may force discontinuation of trastuzumab treatment until the events can be controlled, which may in turn incur disadvantages to the patient, such as decreased efficacy. We therefore conducted this study to examine times to onset, incidence rates, and outcomes of trastuzumab-induced AEs associated with lung toxicity in patients with cancer, based on information obtained from the spontaneous reporting system in the Japanese Adverse Drug Event Report (JADER) database of the Pharmaceuticals and Medical Devices Agency (PMDA).
Methods

Data source

Healthcare professionals and pharmaceutical companies send AE reports to the PMDA. Information was obtained from the JADER database [13–16] on the PMDA website (http://www.pmda.go.jp), which includes AE cases. All data from the JADER database were fully anonymised by the regulatory authority before we accessed them. All methods were thus performed in accordance with the relevant guidelines and regulations. We analysed AE reports recorded between April 2004 and March 2021. The data structure of the JADER consists of four datasets: patient demographic information (DEMO); drug information (DRUG); AEs (REAC); and medical history (HIST). AEs in the JADER database are coded according to the preferred terminology of the Medical Dictionary for Regulatory Activities/Japanese, version 24.1 (www.pmrj.jp/jmo/php/indexj.php).

We first removed duplicate cases from the DRUG and REAC tables using the methods described by Hirooka and Yamada [16]. We then used the identification number of each AE case to merge corresponding case data from the DRUG, REAC, and DEMO tables. The contributions of medications to AEs were classified as “suspected medicine,” “concomitant medicine,” and “interaction.” Only those cases classified as “suspected medicine” were extracted.

To investigate the associations between trastuzumab and lung AEs, we analysed the JADER database, which contains spontaneous AE reports submitted to the PMDA.

Statistical analyses

Data on lung AEs with more than five reported cases were extracted, and the relative risk of AEs was estimated using the reporting odds ratio (ROR). ROR is frequently used in the spontaneous reporting database as an indicator of the relative risk of AEs. We used the analysis data table and constructed 2 × 2 tables based on two classifications: presence or absence of “lung AEs”; and presence or absence of suspected trastuzumab use. The ROR was calculated by dividing the reported rate of AEs attributable to trastuzumab by the reported rate of the same AEs attributable to all other drugs in the database. The signal of AEs was considered positive if the lower limit of the 95% confidence interval (95%CI) of the ROR was > 1 [18].

The time to onset of AEs was calculated and the number of cases was counted for reports in which the date of onset of AEs, the date of start of administration, and the date of end of administration were described as year/month/day or year/month [5]. The onset time was calculated as "(onset date of AE) - (administration start date) + 0.5" in principle [19]. If there was a period of non-administration for more than one year, the date of first administration of the most recent continuous administration period was used. The time to onset of AEs for analysis was limited to 2 years (730 days). The Weibull distribution is represented by scale parameter α and shape parameter β. The scale parameter α represents the scale of the distribution function, as the quantile in which 63.2% of AEs occur [20]. A large value for this parameter...
indicates a wide distribution, while a small value indicates a narrow distribution. The shape parameter $\beta$ represents the change in hazard over time in the absence of a reference population. Depending on the value of shape parameter $\beta$, an upper limit of the 95%CI for $\beta < 1$ indicates that the hazard increases initially, then decreases (early failure type). Conversely, a $\beta$ value containing 1 or almost 1 and a 95%CI including 1 indicates that the hazard remains constant throughout the exposure period (random failure type), and a lower limit of the 95%CI for $\beta > 1$ indicates that the hazard increases over time (wear-out failure type). All statistical analyses were performed using JMP Pro® version 16.1 (SAS Institute, Cary, NC, USA).

## Results

### Incidence of lung AEs with trastuzumab

We joined the three tables of DRUG (3,875,874 reports), REAC (1,096,193 reports), and DEMO (693,295 patients) by ID number. We removed duplicate data from the DRUG and REAC tables [17]. The causes of ADRs fall into three categories: "suspected drug," "concomitant drug," and "interaction." Of these, all data included in the category of "suspected drug," were extracted and used as the "data table" (1,772,494 reports).

We analysed this data table and obtained 4,362 reports of AEs attributed to trastuzumab. Of these, 693 lung AEs were reportedly associated with trastuzumab (Fig. 1). The patient characteristics are shown in Table 1. Approximately 84.7% of patients were female. According to the age distribution of the study population, pulmonary toxicity occurred frequently among individuals in their 60s (38.4%).
Table 1
Characteristics of patients exhibiting lung adverse events related to trastuzumab

| Variable       | Value (%) |
|----------------|-----------|
| Number of patients | 4362 |
| Sex            |           |
| Male           | 93 (13.4) |
| Female         | 587 (84.7) |
| Unknown        | 13 (1.9)  |
| Age            |           |
| 30s            | 11 (1.6)  |
| 40s            | 53 (7.6)  |
| 50s            | 127 (18.3)|
| 60s            | 266 (38.4)|
| 70s            | 136 (19.6)|
| 80s            | 31 (4.5)  |
| Unknown        | 69 (1.0)  |

Among the types of lung AEs caused by trastuzumab, reported numbers of interstitial lung disease, pneumonia, death, pleural effusion, dyspnoea, lung disorder, respiratory failure, and pulmonary oedema, *Pneumocystis jirovecii* pneumonia and pneumonia aspiration of trastuzumab were 428, 65, 29, 29, 22, 16, 16, 13, 11 and 8, respectively (Table 2). RORs with a lower limit of the 95%CI > 1 comprised interstitial lung disease (3.78, 95%CI 3.42–4.18, p < 0.001), pulmonary oedema (3.06, 95%CI 2.12–4.41, p < 0.001), pleural effusion (2.10, 95%CI 1.22–3.62, p = 0.013), lung disorder (1.89, 95%CI 1.16–3.10, p = 0.015), acute pulmonary oedema (13.53, 95%CI 6.37–28.75, p < 0.001), pulmonary fibrosis (4.53, 95%CI 1.87–10.94, p = 0.006), and radiation pneumonitis (4.05, 95%CI 1.68–9.78, p = 0.009). Signals were thus detected for these seven lung toxicities with five or more cases reported.
Table 2
Numbers of reports and RORs of lung adverse events related to trastuzumab

| Variable                      | Cases (n) | Non-cases (n) | Rate (%) | ROR    | 95%CI           | p-value |
|-------------------------------|-----------|---------------|----------|--------|----------------|---------|
| Interstitial lung disease     | 428       | 3934          | 9.81     | 3.78   | 3.42–4.18      | <0.001  |
| Pneumonia                     | 65        | 4297          | 1.49     | 1.07   | 0.84–1.37      | 0.560   |
| Death                         | 29        | 4333          | 0.66     | 1.38   | 0.96–1.99      | 0.099   |
| Pleural effusion              | 29        | 4333          | 0.66     | 3.06   | 2.12–4.41      | <0.001  |
| Dyspnoea                      | 22        | 4340          | 0.5      | 1.37   | 0.90–2.09      | 0.133   |
| Lung disorder                 | 16        | 4346          | 0.37     | 1.89   | 1.16–3.10      | 0.015   |
| Respiratory failure           | 16        | 4346          | 0.37     | 1.64   | 1.00–2.67      | 0.054   |
| Pulmonary oedema              | 13        | 4349          | 0.30     | 2.10   | 1.22–3.62      | 0.013   |
| *Pneumocystis jirovecii*      | 11        | 4351          | 0.25     | 0.61   | 0.34–1.11      | 0.121   |
| pneumonia                     |           |               |          |        |                |         |
| Pneumonia aspiration          | 8         | 4354          | 0.18     | 0.78   | 0.39–1.56      | 0.636   |
| Pulmonary embolism            | 8         | 4354          | 0.18     | 0.83   | 0.41–1.66      | 0.746   |
| Acute respiratory distress    | 8         | 4354          | 0.18     | 1.55   | 0.77–3.10      | 0.186   |
| syndrome                      |           |               |          |        |                |         |
| Cardio-respiratory arrest     | 8         | 4354          | 0.18     | 1.15   | 0.58–2.31      | 0.570   |
| Acute pulmonary oedema        | 7         | 4355          | 0.16     | 13.53  | 6.37–28.75     | <0.001  |
| Pulmonary fibrosis            | 5         | 4357          | 0.11     | 4.53   | 1.87–10.94     | 0.006   |
| Pneumonitis                   | 5         | 4357          | 0.11     | 0.69   | 0.29–1.66      | 0.573   |

“Cases” indicates the number of reported cases of pulmonary toxicity. ROR, reporting odds ratio; 95%CI, 95% confidence interval. Italicized p-values represent statistically significant results. We used more than five reports for each type of pulmonary toxicity. All analysed data were obtained from the Japanese Adverse Drug Event Report database. The hypothesis tests were two-sided, and statistical significance was set at the level of p < 0.05. P-values were calculated using Fisher's exact test.
| Variable                  | Cases (n) | Non-cases (n) | Rate (%) | ROR  | 95%CI        | p-value |
|--------------------------|-----------|---------------|----------|------|--------------|---------|
| Radiation pneumonitis    | 5         | 4357          | 0.11     | 4.05 | 1.68–9.78    | 0.009   |
| Acute respiratory failure| 5         | 4357          | 0.11     | 1.98 | 0.82–4.77    | 0.113   |
| Pulmonary hypertension   | 5         | 4357          | 0.11     | 2.27 | 0.94–5.47    | 0.073   |

“Cases” indicates the number of reported cases of pulmonary toxicity. ROR, reporting odds ratio; 95%CI, 95% confidence interval. Italicized p-values represent statistically significant results. We used more than five reports for each type of pulmonary toxicity. All analysed data were obtained from the Japanese Adverse Drug Event Report database. The hypothesis tests were two-sided, and statistical significance was set at the level of p < 0.05. P-values were calculated using Fisher’s exact test.

### Time to onset of lung AEs with trastuzumab

Histograms of the times to onset of the seven detected lung AE signals showed that AEs occurred from 1 to 105 days after trastuzumab administration (Fig. 2). Median time to onset was 75 days (interquartile range [IQR] 43–112 days) for interstitial lung disease, 56 days (IQR 55–92 days) for pulmonary oedema, 18 days (IQR 8–85 days) for pleural effusion, 105 days (IQR 92–190 days) for lung disorder, 1 day (IQR 1–31 days) for acute pulmonary oedema, 87 days (IQR 45–129 days) for pulmonary fibrosis, and 85 days (IQR 85–85 days) for radiation pneumonitis caused by trastuzumab. The Weibull distribution of histograms of time to onset showed that the range of 95%CIs for shape parameter β of interstitial lung disease, pleural effusion, and acute pulmonary oedema were β < 1, while other AEs were β > 1 (Table 3).
Table 3
Medians and Weibull parameters of lung adverse events

| Adverse effects            | Case (n) | Median (days) (25–75%) | Scale parameter | Shape parameter |
|----------------------------|----------|------------------------|----------------|----------------|
| Interstitial lung disease  | 249      | 75 (43–112)            | 104.45 (91.06–119.55) | 0.96 (0.88–1.06) |
| Pulmonary oedema           | 11       | 56 (55–92)             | 93.87 (50.97–166.77) | 1.15 (0.69–1.71) |
| Pleural effusion           | 10       | 18 (8–85)              | 54.83 (18.83–148.71) | 0.70 (0.41–1.09) |
| Lung disorder              | 9        | 105 (92–190)           | 185.39 (110.89–299.80) | 1.56 (0.87–2.46) |
| Acute pulmonary oedema     | 7        | 1 (1–31)               | 9.50 (0.66–116.04) | 0.35 (0.18–0.56) |
| Pulmonary fibrosis         | 4        | 87 (45–129)            | 98.30 (52.29–179.76) | 2.26 (0.85–4.70) |
| Radiation pneumonitis      | 1        | 85 (85–85)             | -              | -              |

“Cases” indicate the number of reported cases of pulmonary toxicity. 95%CI, 95% confidence interval. Detected pulmonary toxicity signals were analysed to determine the time to onset.

Outcomes after occurrence of AEs

The percentages of outcomes (recovery, remission, not recovered, with sequelae, death, unclear) after the onset of seven AEs are shown in Fig. 3. Fatal outcomes were observed for interstitial lung disease, pleural effusion, pulmonary oedema, pulmonary fibrosis, and radiation pneumonitis.

Discussion

This study focused on lung toxicities caused by trastuzumab, and those AEs for which signals were detected were interstitial lung disease, pulmonary oedema, pleural effusion, lung disorder, acute pulmonary oedema, pulmonary fibrosis, and radiation pneumonitis.

Among these, interstitial lung disease was the most frequently reported (61.8%, 428/693) and fatal cases were also reported. The Weibull distribution showed that the incidence of interstitial lung disease developed early after trastuzumab administration. Interstitial lung disease caused by trastuzumab has been reported in clinical trials [21–23] and the results of the present study are consistent with the clinical findings. In previous studies, interstitial lung disease has shown a high mortality rate if untreated, and early diagnosis and treatment are known to significantly reduce mortality [24, 25]. In this study, although the incidence of interstitial lung disease did not increase in a dose-dependent manner, continuous
monitoring is recommended throughout the entire treatment period, as some cases were observed during long-term treatment. On the other hand, the risk of developing interstitial lung disease is less than that of Fam-trastuzumab deruxtecan, a novel antibody-drug conjugate that combines trastuzumab with a topoisomerase I inhibitor [26]. However, since the interstitial lung disease caused by trastuzumab is often associated with fatal outcomes, clinicians should pay close attention to its development.

Of the seven AEs for which signals were detected, fatal outcomes were observed in five. Of these, fatal cases of pleural effusion, pulmonary oedema, pulmonary fibrosis, and radiation pneumonitis were observed for interstitial lung disease. Both pleural effusion and interstitial lung disease occur early after trastuzumab administration. Among the reported cases, median time to the onset of pleural effusion was 18 days. Clinicians should be alert to the development of pleural effusion, particularly in the initial stages of trastuzumab administration. The incidences of pulmonary oedema and pulmonary fibrosis developed in a dose-dependent manner. Similarly, continuous monitoring throughout the entire administration period is recommended.

The results of the present study must be considered in light of some limitations. First, the JADER database is based on self-reported data, which may contribute reporting biases such as over- and underreporting. Second, the lack of comprehensive medical records and medication histories limits the scope of the analysis, as details of the trastuzumab dosage and duration of use remain unknown. Third, we could not rule out the possibility that AEs may have been caused by concomitant use of anticancer drugs. Fourth, potential confounding, selection, and information biases cannot be fully excluded from this study. However, the results of this study were based on extracted data representing AEs that the reporting persons considered to be most likely associated with trastuzumab. Thus, our report provides useful information for monitoring AEs of lung toxicity caused by trastuzumab.

In conclusion, we focused on lung toxicities caused by trastuzumab as post-marketing AEs. Interstitial lung disease, pleural effusion, pulmonary oedema, pulmonary fibrosis, and radiation pneumonitis could potentially result in serious outcomes after administration of trastuzumab, and interstitial lung disease in particular still occurred even more than one year after administration. Patients should be monitored for signs of the onset of these AEs not only at the start of administration, but also over an extended period, especially for interstitial lung disease. Clinicians need to be aware of the potential for the development of these AEs for a long period after trastuzumab administration.

**Declarations**

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**Author Contributions**
Yuko Kanbayashi, and Mayako Uchida: Data curation; Writing – original draft; Writing – review and editing. Misui Kashiwagi and Hitomi Akiba: Data curation; Writing – review and editing. Tadashi Shimizu: Conceptualisation; Supervision; Writing – review and editing.

Data availability statement

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval

Ethics approval was not sought for this study, given the database-related, observational design without direct involvement of any research subjects. All results were obtained from data openly available online from the PMDA website (www.pmda.go.jp). All data from the JADER database were fully anonymised by the relevant regulatory authority before we accessed them. Thus, all methods were performed in accordance with the relevant guidelines and regulations.

Conflict of Interest

All authors declare no conflict of interest.

References

1. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783–92. doi:10.1056/NEJM200103153441101.

2. Eiermann W, International Herceptin Study Group. Trastuzumab combined with chemotherapy for the treatment of HER2-positive metastatic breast cancer: pivotal trial data. Ann Oncol. 2001;12(Suppl 1):57–62.

3. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002;20:719–26. doi:10.1200/JCO.2002.20.3.719.

4. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376:687–97. doi:10.1016/S0140-6736(10)61121-X.

5. Meric-Bernstam F, Hurwitz H, Raghav KPS, McWilliams RR, Fakih M, VanderWalde A, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. Lancet Oncol. 2019;20:518–30. doi:10.1016/S1470-2045(18)30904-5.
6. Takahashi H, Tada Y, Saotome T, Akazawa K, Ojiri H, Fushimi C, et al. Phase II trial of trastuzumab and docetaxel in patients with human epidermal growth factor receptor 2-positive salivary duct carcinoma. J Clin Oncol. 2019;37:125–34. doi:10.1200/JCO.18.00545.

7. Chen T, Xu T, Li Y, Liang C, Chen J, Lu Y, et al. Risk of cardiac dysfunction with trastuzumab in breast cancer patients: a meta-analysis. Cancer Treat Rev. 2011;37:312–20. doi:10.1016/jctrv.2010.09.001.

8. Thompson LM, Eckmann K, Boster BL, Hess KR, Michaud LB, Esteva FJ, et al. Incidence, risk factors, and management of infusion-related reactions in breast cancer patients receiving trastuzumab. Oncologist. 2014;19:228–34. doi:10.1634/theoncologist.2013-0286.

9. Long HD, Lin YE, Zhang JJ, Zhong WZ, Zheng RN. Risk of congestive heart failure in early breast cancer patients undergoing adjuvant treatment with trastuzumab: a meta-analysis. Oncologist. 2016;21:547–54. doi:10.1634/theoncologist.2015-0424.

10. Rossi M, Carioli G, Bonifazi M, Zambelli A, Franchi M, Moja L, et al. Trastuzumab for HER2 + metastatic breast cancer in clinical practice: cardiotoxicity and overall survival. Eur J Cancer. 2016;52:41–9. doi:10.1016/j.ejca.2015.09.012.

11. Carver JR, Shapiro CL, Ng A, Jacobs L, Schwartz C, Virgo KS, et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. J Clin Oncol. 2007;25:3991–4008. doi:10.1200/JCO.2007.10.9777.

12. Pivot X, Suter T, Nabholtz JM, Pierga JY, Espie M, Lortholary A, et al. Cardiac toxicity events in the PHARE trial, an adjuvant trastuzumab randomised phase III study. Eur J Cancer. 2015;51:1660–6. doi:10.1016/j.ejca.2015.05.028.

13. Uchida M, Kondo Y, Suzuki S, Hosohata K. Evaluation of acute kidney injury associated with anticancer drugs used in gastric cancer in the Japanese Adverse Drug Event Report Database. Ann Pharmacother. 2019;53:1200–6. doi:10.1177/1060028019865870.

14. Sugawara H, Uchida M, Suzuki S, Suga Y, Uesawa Y, Nakagawa T, et al. Analyses of Respiratory Depression Associated with Opioids in Cancer Patients Based on the Japanese Adverse Drug Event Report Database. Biol Pharm Bull. 2019;42:1185–91. doi: 10.1248/bpb.b19-00105.

15. Uchida M, Kawashiri T, Maegawa N, Takano A, Hosohata K, Uesawa Y. Pharmacovigilance Evaluation of Bendamustine-related Skin Disorders using the Japanese Adverse Drug Event Report Database. J Pharm Pharm Sci. 2021;24:16–22. doi:10.18433/jpps31597.

16. Nakao S, Uchida M, Satoki A, Okamoto K, Uesawa Y, Shimizu T. Evaluation of cardiac adverse events associated with carfilzomib using a Japanese real-world database. Oncology. 2022;100:60–4. doi:10.1159/000519687.

17. Hirooka T, Yamada M. Evaluation of risk of adverse reaction using PMDA ‘Adverse Drug Reaction Database. Database SAS User Groups Ronbun-syu; 2012.

18. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf. 2002;11:3–10. doi:10.1002/pds.668.
19. Ando G, Taguchi K, Enoki Y, Yokoyama Y, Kizu J, Matsumoto K. Evaluation of the expression time of ganciclovir-induced adverse events using JADER and FAERS. Biol Pharm Bull. 2019; 42:1799–804. doi: 10.1248/bpb.b19-00156.

20. Sauzet O, Carvajal A, Escudero A, Molokhia M, Cornelius VR. Illustration of the Weibull shape parameter signal detection tool using electronic healthcare record data. Drug Saf. 2013;36:995–1006. doi:10.1007/s40264-013-0061-7.

21. Sugaya A, Ishiguro S, Mitsuhashi S, Abe M, Hashimoto I, Kaburagi T, et al. Interstitial lung disease associated with trastuzumab monotherapy: a report of 3 cases. Mol Clin Oncol. 2017;6:229–32. doi:10.3892/mco.2016.1113.

22. Abulkhair O, El Melouk W. Delayed paclitaxel-trastuzumab-induced interstitial pneumonitis in breast cancer. Case Rep Oncol. 2011;4:186–91. doi:10.1159/000326063.

23. Hackshaw MD, Danysh HE, Singh J, Ritchey ME, Ladner A, Taitt C, et al. Incidence of pneumonitis/interstitial lung disease induced by HER2-targeting therapy for HER2-positive metastatic breast cancer. Breast Cancer Res Treat. 2020;183:23–39. doi:10.1007/s10549-020-05754-8.

24. Teuwen LA, Van den Mooter T, Dirix L. Management of pulmonary toxicity associated with targeted anticancer therapies. Expert Opin Drug Metab Toxicol. 2015;11:1695–707. doi:10.1517/17425255.2015.1080687.

25. Modi S, Saura C, Yamashita T, Park YH, Kim SB, Tamura K, et al. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N Engl J Med. 2020;382:610–21. doi:10.1056/NEJMoa1914510.

26. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med. 2020;382:2419–30. doi:10.1056/NEJMoa2004413.

**Figures**
Figure 1

Process of constructing a data analysis table

Figure 2

Histograms of lung adverse events for: 1) interstitial lung disease; 2) pulmonary oedema; 3) pleural effusion; 4) lung disorder; 5) acute pulmonary oedema; 6) pulmonary fibrosis; and 7) radiation pneumonitis
Figure 3

Percentages of four AEs associated with trastuzumab by outcome