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ARTICLE

Does Industry-Conducted All-Case Surveillance of Newly Approved Oncology Drugs Contribute to the Revision of Package Inserts in Japan?

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In Japan, the Pharmaceuticals and Medical Devices Agency requires all-case surveillance studies (ACSS) for many novel oncology drugs as a condition for approval. However, this is a major burden on the pharmaceutical industry and clinicians. The objective of this analysis was to investigate whether ACSS can contribute essential new information on severe adverse drug reactions, which are necessary to revise the package inserts of drugs. All oncology drugs for which ACSS were required from January 2006–September 2015 found on the Pharmaceuticals and Medical Devices Agency website were reviewed, and the influence of ACSS on the package insert content was evaluated. Most of the package insert revisions regarding serious treatment-related adverse events were based on spontaneous reports from clinicians. The contribution of ACSS results to the revision of package inserts is limited and comes at the cost of financial resources and labor. An alternative, more efficient adverse-event reporting system is necessary.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ All-case surveillance studies (ACSS) are unique and large postmarketing surveillance studies that are conducted only in Japan; however, limited information is available as to whether ACSS actually provide essential and important information, especially with regard to the revision of package inserts.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ Do industry-conducted ACSS of newly approved oncology drugs contribute to the revision of package inserts in Japan?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The contribution of ACSS results to the revision of package inserts is limited and at a cost of financial and labor resources.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ These results provide new insights into consideration of evaluation of adverse events based on real-world data in the postmarketing phase in Japan. An automated adverse-event reporting system is expected.

Cancer is the main cause of death in developed countries, including Japan. More than half of Japanese people are diagnosed with cancer in their lifetime, and the number of cancer deaths is still increasing.[1] Since the beginning of the 21st century, many new types of oncology drugs, not only chemotherapeutics but also targeted drugs and immune checkpoint inhibitors, have been rapidly introduced and approved in Japan. However, a variety of nonhematological toxicities, including serious adverse drug reactions (ADRs), have been observed in patients who were treated with targeted drugs or immune checkpoint inhibitors.[2,3] In addition, such kinds of serious ADRs are not fully reported before regular approval by a regulatory agency, and the accelerated approval system for oncology products also limits the information on serious ADRs in postmarketing settings.[4,5]

In 1993, the Pharmaceuticals and Medical Devices Agency (PMDA) and Ministry of Health, Labour and Welfare (MHLW) began to request industry-funded all-case surveillance studies (ACSS) for orphan drugs, such as anti-HIV drugs, as a precondition for approval, and required ACSS for irinotecan during the reexamination period as a condition for approval in 1995. ACSS are conducted in Japan to investigate safety and adverse events in all cancer patients to whom most newly approved oncology drugs were prescribed in postmarketing surveillance settings.[6,7] There are several objectives of ACSS, including the prompt management of risk and the collection of information on ADRs, to determine the number of patients who use a drug and to understand the actual conditions of the usage of the drug in the real-world setting. According to an administrative communication, the

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drugs for which ACSS are necessary for are those that meet following conditions: (i) there are only a small number or no cases of domestic study subjects, and (ii) there are concerns about the drug regarding occurrence of serious ADRs.[7]

However, ACSS are a major burden on the pharmaceutical industry and on clinicians because eventually data on thousands of patients must be collected.[8] The pharmaceutical industry must expend large resources, including a workforce

Table 1. The list of all-case surveillance studies for 15 drugs (18 indications)

Brand name (Manufacturer, location, Country)	General name	Indication	Approval date	Planned # of patients	# of patients for safety analysis	Study period	Removal date	Duration for ACSS (yr.)	Final report issued date
Velcade® (Janssen, Tokyo, Japan)	Bortezomib	MM	Oct. 2006	500	1,010	Max. 3 years	Sept. 2011	4.87	Apr. 2014
Avastin® (Chugai, Tokyo, Japan)	Bevacizumab	CRC	Apr. 2007	2,500	2,698	6 months	Sept. 2010	3.38	Dec. 2008
Tarceva® (Chugai, Tokyo, Japan)	Erlotinib	NSCLC	Oct. 2007	3,000	9,909	12 months	Feb. 2012	4.29	Apr. 2013
Nexaver® (Bayer, Osaka, Japan)	Sorafenib	RCC	Jan. 2008	2,000	3,255	12 months	Jun. 2012	4.35	May. 2015[a]
Nexaver® (Bayer, Osaka, Japan)	Sorafenib	HCC	May 2009	4,700	1,608	12 months	Jun. 2015	6.04	Apr. 2015
Sutent® (Pfizer, Tokyo, Japan)	Sunitinib	RCC	Apr. 2008	600	1,671	24 weeks (max. 2 years)	Jul. 2011	3.21	Mar. 2012
Sutent® (Pfizer, Tokyo, Japan)	Sunitinib	GIST	Apr. 2008		470				Mar. 2012
Eurbitux® (Merck, Tokyo, Japan)	Cetuximab	CRC	Jul. 2008	1,800	2,006	—	Sept. 2012	4.13	Nov. 2011
Tasigna® (Novartis, Tokyo, Japan)	Nilotinib	CML[b]	Jan. 2009	—	—	—	Mar. 2014	5.11	—
Sprycel® (BMS, Tokyo, Japan)	Dasatinib	CML[c]	Jan. 2009	800	897	Max. 3 years	Mar. 2015	6.11	Sept. 2015
Doxil® (Janssen, Tokyo, Japan)	Doxorubicin	OC	Apr. 2009	500	2,187	Max. 10 courses or 1 years	Feb. 2014	4.78	Sept. 2015
Tykerb® (Novartis, Tokyo, Japan)	Lapatinib	BreC	Apr. 2009	3,000	4,037	12 months	Oct. 2015	6.45	Oct. 2016
Afinitor® (Novartis, Tokyo, Japan)	Everolimus	RCC	Jan. 2010	1,400	1,710	Max. 12 months	Nov. 2012	2.78	Mar. 2016
Vectibix® (Takeda, Osaka, Japan)	Panitumumab	CRC	Apr. 2010	2,000	3,086	10 months	Jul. 2012	2.21	Mar. 2013
Abraxane® (Taiho, Tokyo, Japan)	Nab-Paclitaxel	BreC	Jul. 2010	300	934	6 courses	Feb. 2013	2.53	Feb. 2013
Treakisym® (SymBio, Tokyo, Japan)	Bendamustine	i-NHL, MCL	Oct. 2010	250	583	18 weeks	Mar. 2013	2.35	Apr. 2013
Tarceva® (Chugai, Tokyo, Japan)	Erlotinib	PC	Jul. 2011	800	843	Max. 28 weeks	Jul. 2015	4.00	Oct. 2014
Gliadel® (Eisai, Tokyo, Japan)	Carmustine	BraC	Sept. 2012	250	558	3 months	Sept. 2015	2.93	Sept. 2015

-: Not available, ACSS, all-case surveillance studies; BraC: brain cancer, BreC: breast cancer, CML: Chronic myelogenous leukemia, CRC: colorectal cancer, GIST: gastro-intestinal stromal tumor, HCC: hepatocellular carcinoma, i-NHL: indolent non-Hodgkin's lymphoma, MCL: mantle cell lymphoma, MM: multiple myeloma, NSCLC: non-small cell lung cancer, OC: ovarian cancer, PC: pancreatic cancer, RCC: renal cell carcinoma, yr.: years.
[a]The indication for Imatinib resistant CML was approved on Jan2009. The indication for CML was approved on DEC2010.
[b]The indication for Imatinib resistant/Philadelphia chromosome-positive CML was approved on Jan2009. The indication for CML was approved on JUN2011.
[c]Report for discussion with PMDA.
Janssen: Janssen Pharmaceutical K.K., Chugai: Chugai Pharmaceutical Co., Ltd., Bayer: Bayer Yakuhin, Ltd., Pfizer: Pfizer Japan Inc., Merck: Merck biopharma, Novartis: Novartis Pharma K.K, BMS: Bristol-Myers Squibb K.K., Takeda: Takeda Pharmaceutical Co., Ltd., Taiho: Taiho Pharmaceutical Co., Ltd., SymBio: SymBio Pharmaceuticals Ltd., Eisai: Eisai Co., Ltd.

and budget. Clinicians also must spend much time in completing case reports. The ACSS system is a unique and large postmarketing surveillance study system that is conducted only in Japan; however, limited information is available as to whether ACSS actually provide essential and important information, especially with regard to the revision of package inserts, at the cost of huge financial recourses and labor. The objective of this analysis was to investigate whether ACSS can contribute essential new information on severe ADRs that necessitates an addition to or a revision of package inserts of oncology drugs.

METHODS

Drugs for this analysis were selected based on the following criteria: (i) anticancer drugs, (ii) drugs approved in Japan with requirement of ACSS from January 2006–September 2015, and (iii) drugs for which the requirement of ACSS had been removed by September 2015. All approved anticancer drugs were selected, including cytotoxic drugs as well as targeted agents and immune checkpoint inhibitors based on a review of the PMDA website.[9] The package inserts of these drugs were investigated, including the revision records and ACSS reports, to evaluate the influence of the results of ACSS on the revision of package inserts. When the revision records or the ACSS reports were not available, the respective pharmaceutical company in Japan was consulted directly.

Novel treatment-related adverse events (trAEs) added to a package insert based on ACSS were defined as follows: (i) the trAEs that were newly included in package inserts until removal of conditional approval of ACSS requirement, (ii) the trAEs that were observed in Japan if the information was available, and (iii) the trAEs that were newly reported in the ACSS if the lists of trAEs that were observed in ACSS were available. The removal date was defined as the date on which the description of ACSS as an approval condition was removed from the package insert. Clinically significant trAEs (CS-trAEs) were defined as trAEs that were included in the "Clinically Significant trAEs" section of the package insert. The data set was analyzed using descriptive statistics, including indication, approval date, planned and registered numbers of patients, study period, removal date, and final report issuance date.

RESULTS

During the surveillance period for this analysis, 147 anticancer drugs (as indication base) were approved on the basis of an PMDA/MHLW review. ACSS were requested by PMDA/MHLW for 52 indications of these drugs. The approval condition of ACSS was removed for 18 indications by September 2015, including 15 drugs that met the selection criteria (**Table 1**). The indications of these drugs covered not only rare cancers such as gastrointestinal stromal tumor and mantle cell lymphoma but also common cancers including colorectal cancer, non-small cell lung cancer, and breast cancer. The planned number of patients per ACSS ranged from 250–4,700. The relationships between the numbers of planned patients and the numbers of actually surveyed patients for safety analysis are shown in **Table 1** and **Figure 1**. For most of the drugs, the number of patients for safety analysis was higher than the planned number of patients. In addition, actual ACSS surveillance durations varied widely, from 2.21–6.11 years (**Table 1**).

The revision of trAEs in package inserts based on ACSS is shown in **Tables 2 and 3** and **Figure 2**. Median (minimum, maximum) of the number of novel trAEs that were included in package inserts based on ACSS was 7 (0, 32). For doxorubicin and carmustine, no novel trAEs from ACSS were included in the package inserts. Median (minimum, maximum) of the number of novel CS-trAEs that were added in package inserts based on ACSS was 1 (0, 21). The ACSS for doxorubicin, lapatinib, nab-paclitaxel, and carmustine provided no novel CS-trAEs to package inserts. The package inserts for only six (bortezomib, bevacizumab, erlotinib, cetuximab, panitumumab, and nab-paclitaxel) of the drugs included incidences of newly observed adverse events, but most of the trAEs and CS-trAEs were reported based not on summary reports of ACSS but on spontaneous reporting by clinicians.

DISCUSSION

The occurrence of postmarketing ADRs is one of the most important public health problems worldwide. Especially for anticancer drugs, not only hematological toxicities but also nonhematological toxicities have become major concerns with both targeted agents and immune checkpoint inhibitors. Postmarketing surveillance for serious ADRs in many countries is primarily based on a spontaneous reporting system (SRS).[10–14] However, whether a voluntary SRS can adequately reveal unreported serious ADRs is controversial. In contrast, the PMDA and MHLW require ACSS especially for selected newly approved drugs, such as

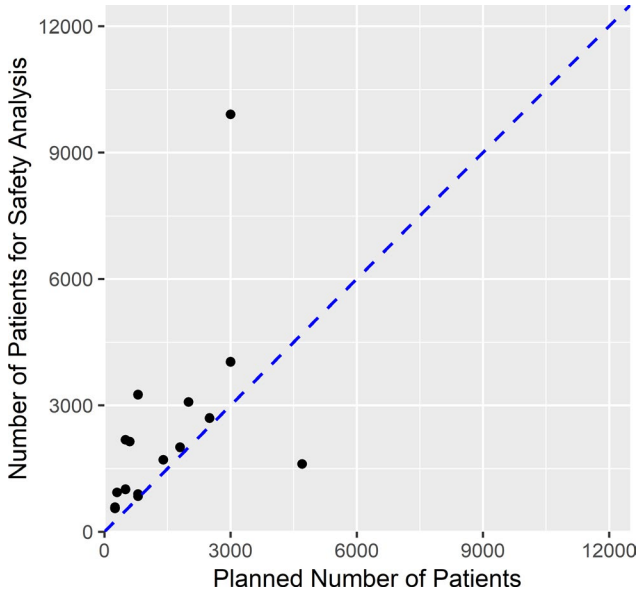

Figure 1 Relationship between the numbers of planned patients and actual patients for safety analysis. Dotted blue line indicates identity.

Table 2. Reflection of novel clinically significant (CS) trAEs and novel trAEs to package insert from all-case surveillance studies

General name	Package Insert Revision Date	Novel CS-trAE	Revised Category from NCS-trAE to CS-trAE	Novel NCS-trAE
Bortezomib	Ver. 4: Sept. 2008	Ileus	—	—
	Ver. 5: Feb. 2010	Reversible posterior leukoencephalopathy syndrome	—	Erythema multiforme, pruritis, impaired urination
	Ver. 6: Sept. 2011[a] Removal of approval condition	—	Hepatic disorder	Hypoglycemia, anxiety, faint, visual disturbance, extra systoles, tachycardia, atrial fibrillation, bradycardia, epistaxis, rhinorrhea, abdominal distension, esophageal reflux
Bevacizumab	Ver. 6: Sept. 2009[a]	Interstitial pneumonia	—	Dizziness, parosmia, periodontitis, stomach discomfort, gastritis, gingival pains, glossitis, tooth loss, elevated fibrinogen, elevated INR, pruritus, urticarias, nail disorder, pain in extremity, arthralgia, rhinorrhea, glucose urine present, increased CRP, injection site reactions, pneumonia, peripheral edema, complications associated with catheter (infections, inflammations, etc.)[a], hot flush, infections, chest pain, cystitis, herpes zoster, infectious enteritis, increased γ-GTP, increased FDP, rash
	Ver. 8: Sept. 2010 Removal of approval condition	—	—	—
Erlotinib	Ver. 4: Jun. 2009	Oculo-mucocutaneous syndrome (Stevens-Johnson syndrome), erythema multiforme, gastrointestinal perforation, corneal perforation	Corneal ulcer	Photosensitivity, skin pigmentation
	Ver. 6: Sept. 2010[a]	Acute kidney injury, gastrointestinal ulceration, gastrointestinal hemorrhage	—	Skin fissures, skin ulcer, subcutaneous hemorrhage, skin vasculitis, eye pruritus, eye discharge, blurred vision, anemia, decreased platelet, dry mouth, gastritis, increased amylase, enterocolitis, esophagitis, heartburn, oropharyngeal pain, dizziness, increased blood pressure
	Ver. 8: Feb. 2012 For NSCLC lifted approval condition	—	—	—
	Ver. 11: Sept. 2013	Severe skin disorder	—	
	Ver. 12: Jul. 2015 For PC Removal of approval condition	—	—	Hand and foot syndrome[a] erythema,[a] hematuria[a]
Sorafenib	Ver. 3: Dec. 2008	Acute lung injury, interstitial pneumonia	—	—
	Ver. 4: Apr. 2009	Oculo-mucocutaneous syndrome (Stevens-Johnson syndrome)	Decreased white blood cell, neutropenia, lymphocytopenia, thrombocytopenia, anemia	Flushing, increased LDH, dysgeusia
	Ver. 6: Sept. 2009	Renal failure (including acute kidney injury)	—	Thyroid hyper function disorders
	Ver. 7: Nov. 2009	Hepatic failure, hepatic encephalopathy	—	
	Ver. 8: Oct. 2010	Tumor hemorrhage, gastrointestinal ulceration, anaphylactic shock symptoms, rhabdomyolysis	—	Radiation recall reaction, hyperkalemia
	Ver. 9: May 2011	Fulminant hepatitis, hemorrhagic enterocolitis, ischemic enterocolitis	—	Dizziness, edema
	Ver. 10: Apr. 2012	Toxic epidermal necrolysis	—	Hypocalcaemia
	Ver. 11: Jun. 2012 For RCC Removal of approval condition	—	—	—
	Ver. 12: Mar. 2013	Nephrotic syndrome, proteinuria	Hyponatremia	Hypokalemia
	Ver. 15: Jun. 2015 For HCC Removal of approval condition	—	—	—
Sunitinib	Ver. 3: Sept. 2009	Gastrointestinal fistulae, disseminated intravascular coagulation syndromes	—	Hypersensitivity
	Ver. 5: Jan. 2011	Cerebral hemorrhage, cerebral infarction	—	—
	Ver. 6: Jul. 2011 Removal of approval condition	Tumor lysis syndrome	—	—

(Continues)

Table 2 (Continued)

General name	Package Insert Revision Date	Novel CS-trAE	Revised Category from NCS-trAE to CS-trAE	Novel NCS-trAE
Cetuximab	Ver. 2: Mar. 2010	Heart failures, severe diarrhea	—	—
	Ver. 4: Sept. 2012[a] Removal of approval condition	—	—	—
Nilotinib	Ver. 5: Jan. 2011	Tumor lysis syndrome	—	—
	Ver. 7: Jul. 2012	Peripheral arterial occlusive disease	—	Hyperkeratosis, oropharyngeal pain
	Ver. 9: Apr. 2013		Hyperglycemia	—
	Ver. 10: Mar. 2014 Removal of approval condition	Cerebral infarction, transient ischemic attack	—	Hypertriglyceridemia
Dasatinib	Ver. 3: Jul. 2010	—	—	Peripheral neuropathies, atrial fibrillation
	Ver. 5: Oct. 2011	Pulmonary arterial hypertension	—	—
	Ver. 7: Mar. 2015 Removal of approval condition	—	—	—
Doxorubicin	Ver. 5: Feb. 2014 Removal of approval condition	—	—	—
Lapatinib	Ver. 5: Oct. 2013	—	—	Gastrointestinal ulceration
	Ver. 6: Sept. 2015 Removal of approval condition	—	—	—
Everolimus	Ver. 2: Mar. 2011	Renal failure, acute respiratory distress syndrome	—	Hypocalcaemia, increased blood bilirubin, nail disorder, acnes, arthralgia, proteinuria, increased γ-GTP, increased ALP
	Ver. 6: Nov. 2012 Removal of approval condition	—	—	—
Panitumumab	Ver. 8: Jul. 2012 Removal of approval condition	—	—	—
	Ver. 10: Mar. 2013[a]	—	Hypomagnesaemia	Dysgeusia, cheilitis, constipation, dermatitis, palmar-plantar erythrodysaesthesia syndrome, eczema, thrombocytopenia, leukopenia, hyperkalemia, malaise, Abnormal hepatic function (AST(GOT), AL-P, LDH, γ-GTP increased, etc.)
Nab-Paclitaxel	Ver. 3: Feb. 2013[a] Removal of approval condition	—	—	Hypoesthesia, muscle spasms, increased potassium, elevated bilirubin, decreased albumin[a] increased blood sugar
Bendamustine	Ver. 2: Apr. 2012	Hepatitis B	—	—
	Ver. 3: Mar. 2013 Removal of approval condition	—	—	—
Carmustine	Ver. 7: Sept. 2015 Removal of approval condition	—	—	—

ALP, Alkaline phosphatase; AST, Asparate amino transferase; CRP, C-reactive protein; CS-trAE, Clinically significant treatment related adverse event; FDP, Fibrinogen degradation products; GOT, Glutamic oxaloacetic transaminase; HCC, Hepatocellular carcinoma; INR, International normalized ratio; LDH, Lactate dehydrogenase; NCS-trAE, Non-clinically significant treatment related adverse event; PI, Package Insert; RCC, Renal cell carcinoma; trAE, Treatment-related adverse event; γ-GTP, γ-glutamyltransferase.
[a]Including numbers of incidence from ACSS in PI.

Table 3. Summary of trAEs and CS-trAEs from all-case surveillance studies for 15 drugs

General name	Including numbers of incidence from ACSS	CS-trAEs	Revised category from NCS-trAE to CS-trAE	NCS-trAEs	Novel trAEs	Novel CS-trAEs
Bortezomib	Yes	2	1	15	17	3
Bevacizumab	Yes	1	0	31	32	1
Erlotinib	Yes	8	1	22	30	9
Sorafenib	No	15	6	10	25	21
Sunitinib	No	5	0	1	6	5
Cetuximab	Yes	2	0	0	2	2
Nilotinib	No	4	1	3	7	5
Dasatinib	No	1	0	2	3	1
Doxorubicin	No	0	0	0	0	0
Lapatinib	No	0	0	1	1	0
Everolimus	No	2	0	8	10	2
Panitumumab	Yes	0	1	11	11	1
Nab-Paclitaxel	Yes	0	0	6	6	0
Bendamustine	No	1	0	0	1	1
Carmustine	No	0	0	0	0	0
	Yes: 6, No: 9	—	—		7 (0, 32)	1 (0, 21)

Median (min, max) for number of trAE.
ACSS, All-case surveillance study, CS-trAE, Clinically significant treatment related adverse event, NCS-trAE, Non-clinically significant treatment related adverse event.

anticancer drugs. However, whether this system is working effectively or not remains unclear. According to the ACSS of cetuximab, the incidence and categories of ADRs were not distinct from previous reports.[15]

In the present investigation, the package inserts for only 6 of the drugs included the incidence of newly observed adverse events out of 18 indications of these drugs and 15 drugs that met the selection criteria, but most of the trAEs and CS-trAEs were reported based not on summary reports of ACSS but on spontaneous reporting by clinicians. The contribution of the ACSS results to the revisions of package inserts is limited, although the framework of ACSS may promote clinicians to conduct intensive reporting of trAEs and CS-trAEs. The present investigation also shows that the incidence rates of both trAEs and CS-trAEs are valuable depending on the drug. In addition, the number of patients per ACSS required by the PMDA fluctuates widely, from 500 to thousands of patients, and is based on no clear rule. Not only the issue of ACSS or SRS but also the sample size of postmarketing surveillance is another important point to detect rare but CS-trAEs or life-threatening trAEs. The PMDA had requested ACSS in 3,000 patients who were treated by erlotinib, and the final number of patients exceeded 9,000. To our knowledge, there is no published guidance to decide the sample size of ACSS by the PMDA. According to a German investigation, postmarketing studies were not improving drug safety surveillance, and the sample sizes are generally too small to allow the detection of rare ADRs.[16] On the basis of "cost performance," the pharmaceutical industry had paid around ¥30,000 to the hospitals per patient, and more than ¥270,000,000 ($24,500,000) in total.

Drug-induced interstitial lung disease was added to the Japanese package insert of sorafenib along with the issuance and distribution of "safety information for acute lung injury/interstitial pneumonia" after approval based on spontaneous reporting by clinicians.[17] Because gefitinib was first approved in Japan for the treatment of non-small cell lung cancer in July 2002, the drug has been used in patients with non-small cell lung cancer. Shortly after the approval of gefitinib, however, it was recognized by many clinicians that the drug could cause severe, occasionally fatal, pulmonary damage and/or interstitial lung disease that could not be predicted during registration trials.[18,19] The PMDA has become concerned about the induction of interstitial lung disease by targeting agents in Japanese cancer patients and has promoted conduction of ACSS

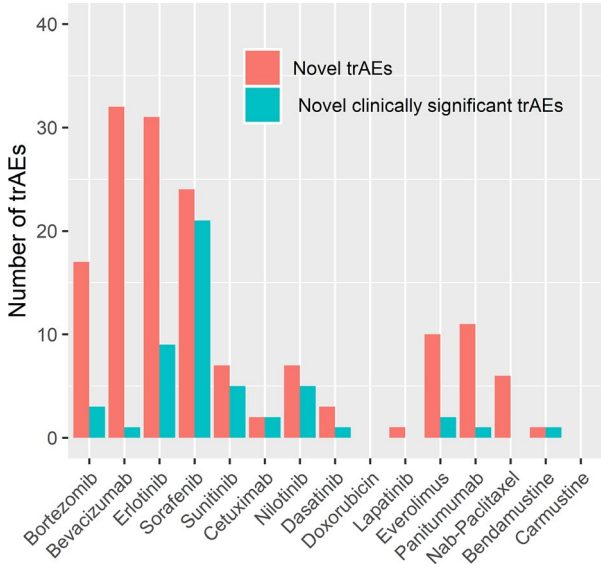

Figure 2 Number of trAEs and clinically significant trAEs from all-case surveillance studies for 15 drugs. trAEs, treatment-related adverse events.

partially because the PMDA did not request ACSS for gefitinib just after approval.

Many serious ADRs may be discovered after a drug receives approval. This suggested a need for continued vigilance and efficient strategies for dissemination of information about ADRs associated with cancer drugs.[20] Healthcare professionals may be more likely to report serious than nonserious adverse drug reactions.[21] One reason a drug may be used for years before risks become evident may be that there is no active drug surveillance system.[22] An automated reporting system is needed to obtain data for a database with an aim for reducing cost and labor.[23] In the United States, Korea, and Japan, the signal detection for adverse events was investigated using databases, including spontaneous adverse event reporting databases.[24–27] The US Food and Drug Administration launched the "Sentinel Initiative" to expand postmarketing safety data analysis,[28] which is still investigational, especially for anticancer drugs. Careful analysis between the costs of creating extremely large databases and obtaining meaningful clinical information must also be conducted.

One of the pitfalls of the present analysis is that ACSS and SRS could not be compared directly; simulations for both postmarketing surveillance systems may contribute additional knowledge to this important issue. Another point is that most of the trAEs and CS-trAEs were reported by SRS on the basis of ACSS framework, and ACSS themselves could not be evaluated in those cases.

In conclusion, most of the revisions regarding serious trAEs in package inserts were based on spontaneous reports from clinicians. The contribution of the ACSS results to the revision of package inserts is limited, although the framework of ACSS may promote clinicians to conduct intensive reporting of trAEs and CS-trAEs. Future investigation is warranted to create an information-rich and cost-effective marketing surveillance system, especially for anticancer drugs.

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Author Contributions. A.S., H.S., and Y.S. wrote the manuscript. A.S., H.S., and Y.S. performed the research. A.S. analyzed the data.

1. Hori, M. *et al.* Cancer incidence and incidence rates in Japan in 2009: a study of 32 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn. J. Clin. Oncol.* **44**, 884–891 (2015).
2. Sandler, A. *et al.* Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. *N. Engl. J. Med.* **355**, 2542–2550 (2006).
3. Herbst, R.S. *et al.* Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* **387**, 1540–1550 (2016).
4. Seruga, B., Sterling, L. & Wang, L. Reporting of serious adverse drug reactions of targeted anticancer agents in pivotal phase III clinical trials. *J. Clin. Oncol.* **29**, 174–185 (2010).
5. Dagher, R., Johnson, J., Williams, G., Keegan, P. & Pazdur, R. Accelerated approval of oncology products: a decade of experience. *J. Natl Cancer Inst.* **96**, 1500–1509 (2004).
6. Ministry of Health, Labour and Welfare. Implementation methods, etc. of early post-marketing phase vigilance for prescription drugs. PFSB/SD Notification No. 0324001 <https://www.pmda.go.jp/files/000209204.pdf> (2006). Accessed March 5, 2019.
7. Ministry of Health, Labour and Welfare. Q & A for all-case surveillance and EPPV for prescription drugs. <https://www.pmda.go.jp/files/000153521.pdf> (2009). Accessed March 5, 2019.
8. Narukawa, M. Research on the situation and implications of the post-marketing all-case surveillance study in Japan—considerations based on a questionnaire survey. *RSMP* **4**, 199–204 (2014).
9. Pharmaceuticals and Medical Devices Agency <https://www.pmda.go.jp>. Accessed March 5, 2019.
10. Therasse, P. *et al.* New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J. Natl Cancer Inst.* **92**, 205–216 (2000).
11. Brewer, T. & Colditz, G.A. Post marketing surveillance and adverse drug reactions; current perspectives and future needs. *JAMA* **281**, 824–829 (1999).
12. Ahmad, S.R. Adverse drug event monitoring at the Food and Drug Administration – your report can make a difference. *J. Gen. Intern. Med.* **18**, 57–61 (2003).
13. Wysowski, D.K. & Swartz, L. Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002: the importance of reporting suspected reactions. *Arch. Intern. Med.* **165**, 1363–1369 (2005).
14. Moore, T.J., Cohen, M.R. & Furberg, C.D. Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. *Arch. Intern. Med.* **167**, 1752–1759 (2007).
15. Ishiguro, M. *et al.* A Japanese post-marketing surveillance of cetuximab (Erbitux) in patients with metastatic colorectal cancer. *Jpn. J. Clin. Oncol.* **42**, 287–294 (2012).
16. Spelsberg, A. *et al.* Contribution of industry funded post-marketing studies to drug safety: survey of notifications submitted to regulatory agencies. *BMJ* **356**, j337 (2017).
17. Horiuchi-Yamamoto, Y. *et al.* Drug-induced lung injury associated with sorafenib: analysis of all-patient post-marketing surveillance in Japan. *Int. J. Clin. Oncol.* **18**, 743–749 (2013).
18. Inoue, A. *et al.* Severe acute interstitial pneumonia and gefitinib. *Lancet* **361**, 137–139 (2003).
19. Ohyanagi, F., Ando, Y., Nagashima, F., Narabayashi, M. & Sasaki, Y. Acute gefitinib-induced pneumonitis. *Int. J. Clin. Oncol.* **9**, 406–409 (2004).
20. Ladewski, L.A. *et al.* Dissemination of information on potentially fatal adverse drug reactions for cancer drugs from 2000 to 2002: first results from the research on adverse drug events and reports project. *J. Clin. Oncol.* **21**, 3859–3866 (2003).
21. Matsuda, S. *et al.* Bias in spontaneous reporting of adverse drug reactions in Japan. *PLoS ONE* **10**, e0126413 (2015).
22. McClellan, M. Drug safety reform at the FDA - pendulum swing or systematic improvement? *N. Eng. J. Med.* **356**, 1700–1703 (2007).
23. Shapiro, S. The role of automated record linkage in the postmarketing surveillance of drug safety: a critique. *Clin. Pharmacol. Ther.* **46**, 371–386 (1989).
24. Park, M.Y. *et al.* A novel algorithm for detection of adverse drug reaction signals using a hospital electronic medical record database. *Pharmacoepidemiol. Drug Saf.* **20**, 598–607 (2011).
25. Xu, R. & Wang, Q. Large-scale combining signals from both biomedical literature and the FDA Adverse Event Reporting System (FAERS) to improve post-marketing drug safety signal detection. *BMC Bioinformatics* **15**, 17 (2014).
26. Xu, R. & Wang, Q. Automatic signal extraction, prioritizing and filtering approaches in detecting post-marketing cardiovascular events associated with targeted cancer drugs from the FDA Adverse Event Reporting System (FAERS). *J. Biomed. Inform.* **47**, 171–177 (2014).

27. Hara, A., Matsumoto, K., Yokoyama, Y. & Kizu, J. Factorial analysis of hepatitis B virus reactivation-induced hepatitis B using JADER. *Biol. Pharm. Bull.* **40**, 782–788 (2017).
28. Robb, M.A. *et al.* The US Food and Drug Administration's sentinel initiative: expanding the horizons of medical product safety. *Pharmacoepidemiol. Drug Saf.* **21**, 9–11 (2012).