A Significant Anticancer Drug Approval Lag Between Japan and the United States Still Exists for Minor Cancers

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Reports have indicated that approval lag for anticancer drugs between Japan and the United States has decreased. However, if this is also true for drugs used to treat minor cancers remains unknown. We analyzed the anticancer drugs approved in Japan from 2006 to 2016 to compare the drug approval lag based on cancer incidence (major vs. minor cancers) between Japan and the United States. The lag of anticancer drugs for minor cancers had not decreased relative to that a decade ago. Recently, development strategies resulting in longer approval lag were used by pharmaceutical companies more often for the development of drugs used to treat minor cancers than for drugs targeting major cancers, leading to significant differences in the approval lag time between drugs for major and minor cancers. Effective measures that expedite the development of drugs targeting minor cancers in Japan should, therefore, be implemented to shorten lag time.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Drug approval lag is defined as the time difference in drug approval between two regions. The Japanese Health Authority has implemented several countermeasures to address this long-standing problem. Recently, lag time has decreased to 9.4 months as of 2014. However, it remained unknown whether the lag time for drugs targeting minor cancers had also been reduced.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ In this study, we analyzed drug approval lag duration by cancer incidence to compare durations for drugs targeting major cancers and those targeting minor cancers.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study has revealed that a significant drug approval lag still exists between Japan and the United States for cancers with an incidence of <6 per 100,000.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The results of the present study revealed a significant delay in the development of drugs targeting minor cancers, and the necessity for expediting the development of these agents in Japan.

Drug approval lag is defined as the duration between when a drug is first approved for use in one region and when it is approved for use in other regions, and has long posed a problem for Japan.[1–6] This lag creates situations in which patient treatment regimens and benefits can differ depending on where an individual resides, posing a serious social problem for lethal diseases, such as cancer.[7,8] The Japanese governmental health authorities, the Ministry of Health, Labour, and Welfare, and the Pharmaceuticals and Medical Devices Agency (PMDA), have implemented several countermeasures to shorten the lag between Japan and the United States.[9] In 2017, they also implemented a conditional early approval system with preliminary clinical evidence for innovative drugs for the treatment of life-threatening diseases.[10]

A recent report has indicated that anticancer drug approval lag has diminished, being 9.4 months in 2014 vs. 37 months in 2001.[11] However, most previous studies relating to anticancer drug approval lag have evaluated all cancer types together, meaning that drug approval lag duration by individual cancer type targeted has not been reported. Therefore, it remains unknown if the lag duration between Japan and the United States has shortened for all cancer types.

Given the considerable time and cost necessary to develop pharmaceutical products, drugs with greater marketability may be prioritized for development. Therefore, the development of drugs for rare cancers (those with an incidence of <6 cases per 100,000 individuals) may be deprioritized compared with that of drugs for

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non-rare cancers. In many cases, anticancer drug development is first initiated outside Japan, with a previous study reporting that 66.7% of anticancer drugs approved for use in Japan between 2001 and 2014 were developed by non-Japanese companies.[12] In the case of drugs targeting rare cancers, non-Japanese companies initiate global studies, whereas their Japanese subsidiaries may not participate in these studies, possibly due to low marketability potential and differences in regulatory systems between countries. Additionally, even the initiation of clinical studies for Japanese patients may be significantly delayed. A recent study noted that drug approval lag durations become considerably longer if Japan cannot or does not participate in a global study, or if Japanese clinical studies were initiated after completion of the final pivotal studies in the United States.[13] This may relate to both low marketability and differences in regulatory systems between Japan and the United States.

Therefore, we aimed to investigate drug approval lag durations between Japan and the United States, specifically targeting drugs for minor cancers. As many anticancer drugs initially receive regulatory approval in the United States,[9,14] we focus only on the drug approval lag between Japan and the United States.

RESULTS

Anticancer drugs investigated

From January 1, 2006, to December 31, 2016, 224 approvals were granted for anticancer drugs in Japan (**Figure 1**). Of these, 116 approvals (New Drug Applications (NDAs): 72; supplemental NDA (sNDAs): 44) were selected for analysis after the following approvals were excluded: approvals for diseases other than cancer indications (diseases other than cancer: 5; supportive effect for other drugs: 1; and supportive or palliative care: 9), approvals for new treatment lines within existing indications (n = 15), approvals not granted for efficacy (n = 20), and approvals not approved in the United States (n = 54) or where approval lag was >30 years (n = 4). Paclitaxel protein-bound particles for injectable suspension (nab-paclitaxel) for breast cancer was approved as an additional dosage form of the existing drug paclitaxel. However, we categorized it as an NDA because the mechanism of action for nab-paclitaxel differs from that of paclitaxel,[15] and nab-paclitaxel has also been considered as an alternative to paclitaxel for breast cancer treatment, as listed in the National Comprehensive Cancer Network guidelines.[16] Regarding the approval of everolimus for renal cell carcinoma, which was submitted as an sNDA, we categorized it as an NDA because this was its first indication for cancer. Regarding the drug approvals analyzed, 53 approvals (NDA: 26; sNDA: 27) were for major cancers (20 types) and 63 approvals (NDA: 46; sNDA: 17) were for minor cancers (32 types; **Tables 1 and 2**).

Regarding development strategy, global studies were used more often for drugs targeting major cancers than for those targeting minor cancers. All pivotal studies for drugs used to treat major cancers were comparative studies, whereas almost half of pivotal studies for drugs targeting minor cancers were noncomparative. We found no differences between drugs targeting major and minor cancers regarding whether the marketing authorization holder was a Japanese or non-Japanese company, or whether the drug was first approved in the United States or Japan.

Drug approval lag duration by cancer incidence (major vs. minor cancers)

Figure 2a shows the drug approval lag between Japan and the United States for anticancer drugs approved in Japan between January 1, 2006, and December 31, 2016. The median drug approval lag for the 116 identified approvals was 949.5 days. The lag for drugs approved from 2012 to 2016 was significantly shorter than for those approved from 2006 to 2011 (median: 752 vs. 1,147 days; P = 0.0082).

Figure 2b depicts the drug approval lag between Japan and the United States by cancer incidence (major vs. minor cancers).

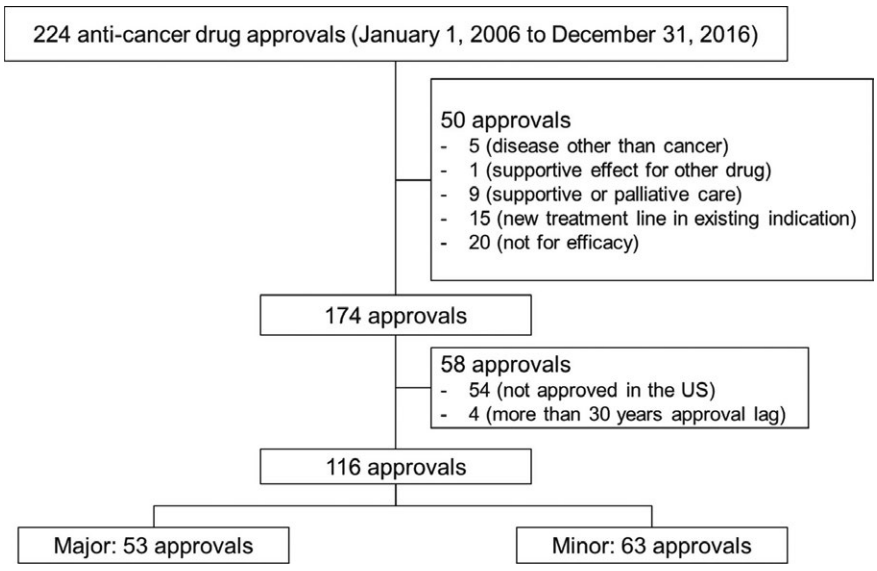

Figure 1 Anticancer drugs approved between January 1, 2006, and December 31, 2016.

Table 1 Summary of analyzed anticancer drugs

	Overall	Major	Minor
Number of approvals	116	53	63
Application category - *n* (%)			
NDA	72 (62)	26 (49)	46 (73)
sNDA	44 (38)	27 (51)	17 (27)
Marketing authorization holder - *n* (%)			
Japanese company	29 (25)	13 (25)	16 (25)
Non-Japanese company	87 (75)	40 (75)	47 (75)
Development strategy - *n* (%)			
Global study	28 (24)	16 (30)	12 (19)
Pre-United States submission BG	25 (22)	12 (23)	13 (21)
Post-United States submission BG	47 (41)	22 (42)	25 (40)
Local study	10 (9)	1 (2)	9 (14)
Japan-excluded study	6 (5)	2 (4)	4 (6)
Pivotal trial design - *n* (%)			
Comparative study	85 (73)	51 (96)	34 (54)
Noncomparative study	27 (23)	0 (0)	27 (43)
No pivotal study	4 (3)	2 (4)	2 (3)

BG, bridging study; NDA, new drug application; sNDA, supplemental new drug application.

The overall lag durations for major and minor cancers were not significantly different (median: 811 vs. 938 days; $P = 0.5798$). Separate analyses for the periods 2006–2011 and 2012–2016 indicated that the major cancer drug approval lag was significantly shortened during 2012–2016 (median: 1,304.5 vs. 395 days; $P = 0.0002$), although no significant difference in lag duration for minor cancers between the two time periods was observed (median: 938 vs. 997.5 days; $P = 0.8967$). Regarding drug approvals occurring in and after 2012, approval lag durations were significantly shorter for drugs targeting major cancers compared with those targeting minor cancers for the period 2012–2016 ($P = 0.0255$), whereas there was no significant difference during the period 2006–2011.

Review time difference by cancer incidence (major vs. minor cancers)

The review time difference between Japan and the United States for minor cancer drugs ($n = 62$, excluding one approval with an unavailable US submission date) was significantly shorter than that for major cancers ($n = 51$, excluding two approvals with unavailable US submission dates) in the overall duration (median: 97.5 vs. 174 days; $P = 0.0017$). There was no significant difference in review time difference between major and minor cancers during the period 2006–2011, whereas the review time difference for minor cancers was significantly shorter than that for major cancer during the period 2012–2016 (median: 70 vs. 114.5 days; $P = 0.0141$).

Table 2 List of cancer types targeted by the analyzed anticancer drugs

Major	Minor
Breast cancer	Acute leukemia
Breast cancer (HER2 overexpressing)	Acute lymphoblastic leukemia
Cervical cancer	ALK-positive NSCLC
Colon cancer	Anaplastic large cell lymphoma
Colorectal cancer	Chronic eosinophilic leukemia (with FIP1L1-PDGFRα fusion kinase)
Colorectal cancer with KRAS wild-type (including EGFR mutation-positive)	Chronic lymphocytic leukemia
Differentiated thyroid carcinoma	Chronic myelogenous leukemia
EGFR mutation-positive NSCLC	Classical Hodgkin's lymphoma
Gastric cancer	Cutaneous T-cell lymphoma
Gastric cancer (HER2 overexpressing)	EGFR T790M mutation-positive NSCLC
Head and neck cancer	Essential thrombocythemia
Hepatic cell carcinoma	Gastrointestinal stromal tumor
NSCLC	Glioblastoma
NSCLC except squamous carcinoma	Hodgkin's lymphoma
NSCLC (PD-L1 positive)	Hypereosinophilic syndrome (with FIP1L1-PDGFRα fusion kinase)
Ovarian cancer	Low-grade B-cell non-Hodgkin's lymphoma
Pancreatic cancer	Malignant pleural mesothelioma
Prostate cancer	Mantle cell lymphoma
Renal cell carcinoma	MDS
Thyroid cancer	MDS associated with a deletion 5q cytogenetic abnormality
	Medullary thyroid cancer
	Melanoma
	Melanoma with BRAF mutation
	Multiple myeloma
	Myelofibrosis
	Neuroendocrine tumor
	Pancreatic neuroendocrine tumor
	Philadelphia chromosome-positive acute lymphoblastic leukemia
	Polycythemia vera
	Soft tissue sarcoma
	T-cell acute lymphoblastic leukemia
	T-cell lymphoblastic lymphoma

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal receptor 2; MDS, myelodysplastic syndrome; NSCLC, nonsmall cell lung cancer; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed cell death ligand 1.

Drug approval lag duration by development strategy

It has been previously noted that development strategy may influence drug approval lag between Japan and the United States.[13,17]

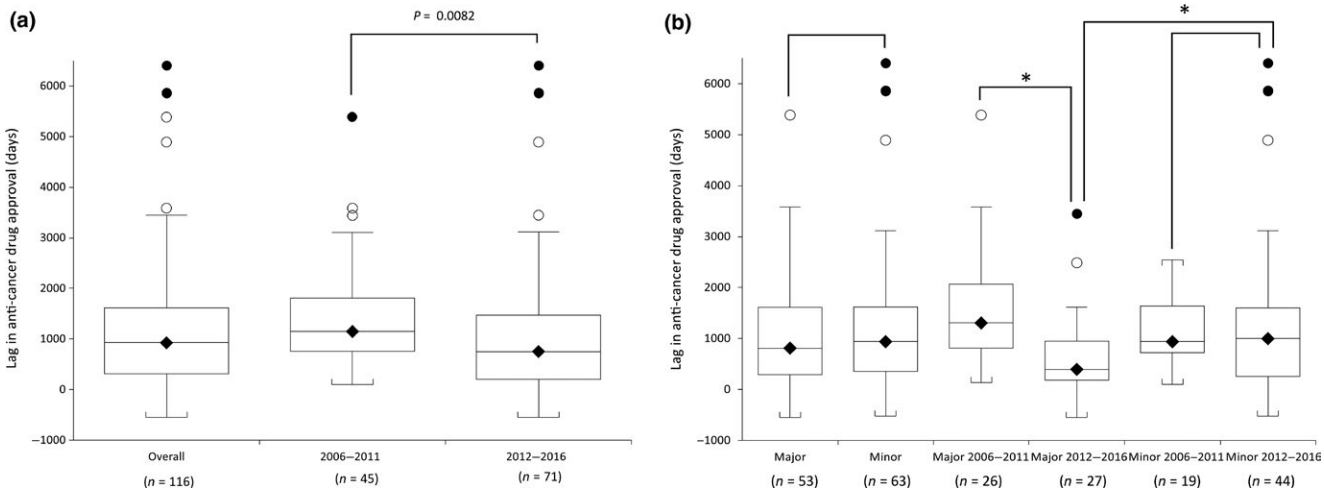

Figure 2 (**a**) Drug approval lag duration between Japan and the United States in 2006–2011 and in 2011–2016. (**b**) Drug approval lag duration between Japan and the United States by cancer incidence. The upper and lower boundaries of the central box indicate the first and third quartiles, respectively, with the median marked with a diamond. Whiskers indicate maximum (upper) and minimum (lower) values, unless an outlier is present, in which case the whiskers indicate the lower or upper quartiles plus (upper) and minus (lower) 1.5 times the interquartile range (IQR), and any data points outside those boundaries are plotted as white circles (mild outlier: 1.5–3 IQR) or black circles (extreme outlier: >3 IQR). Differences between lag durations were evaluated using the Mann–Whitney *U* test. *$P < 0.05$.

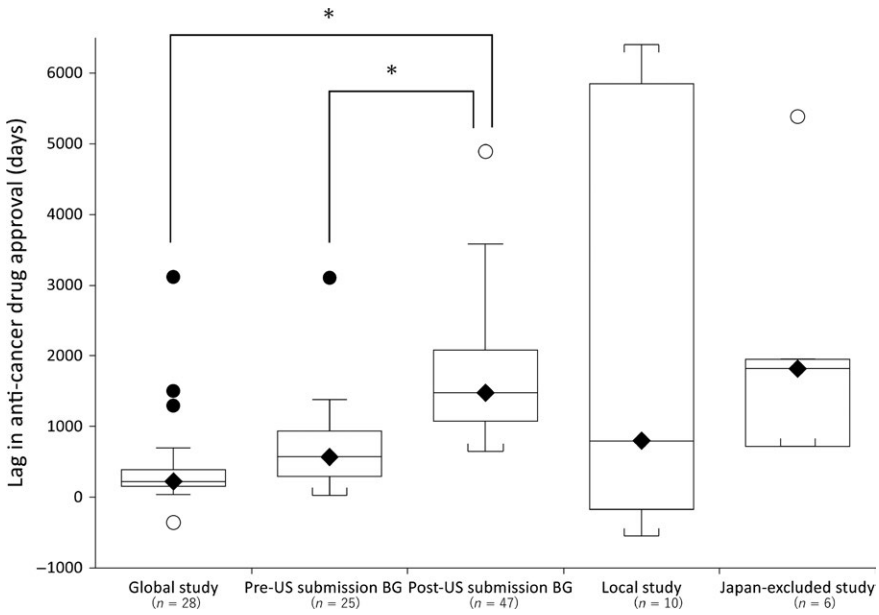

Figure 3 Anticancer drug approval lag duration by development strategy. The upper and lower boundaries of the central box indicate the first and third quartiles, respectively, with the median marked with a diamond. Whiskers indicate maximum (upper) and minimum (lower) values, unless an outlier is present, in which case the whiskers indicate the lower or upper quartiles plus (upper) and minus (lower) 1.5 times the interquartile range (IQR), and any data points outside those boundaries are plotted as white circles (mild outlier: 1.5–3 IQR) or black circles (extreme outlier: >3 IQR). Differences between lag durations were evaluated using the Mann–Whitney *U* test. *$P < 0.05$.

Therefore, we analyzed lag duration by development strategy, which was categorized as a global study, pre-US submission bridging (BG) study, post-US submission BG, local study, or Japan-excluded study for major and minor cancers. Lag duration was shortest for drugs with global study development strategies, and the global study group presented significantly shorter lag times than the post-United States submission BG group (median: 224 vs. 1478 days; $P < 0.0001$; **Figure 3**). The pre-United States submission BG group presented significantly shorter lag durations than the post-United States submission BG group (median: 570 vs. 1478 days; $P < 0.0001$).

Table 3 shows that 12% ($n = 3/26$) of drugs approved during the period 2006–2011 targeting major cancers used global studies during development, whereas this proportion increased to 48% ($n = 13/27$) during the period 2012–2016. Conversely, only 5% ($n = 1/19$) and 25% ($n = 11/44$) of drugs targeting minor cancers approved during the periods 2006–2011 and 2012–2016, respectively, were approved based on global studies. For drugs targeting

Table 3 Development strategy prevalence by cancer incidence (major vs. minor)

	2006–2011			2012–2016		
	Major (*n* = 26)	Minor (*n* = 19)	*P* value	Major (*n* = 27)	Minor (*n* = 44)	*P* value
Development strategy - *n* (%)						
Global study	3 (12)	1 (5)	0.4452	13 (48)	11 (25)	0.1370
Pre-United States submission BG	6 (23)	6 (32)	–	6 (22)	7 (16)	–
Post-United States submission BG	15 (58)	8 (42)	–	7 (26)	17 (39)	–
Local study	0 (0)	2 (11)	–	1 (4)	7 (16)	–
Japan-excluded study	2 (8)	2 (11)	–	0 (0)	2 (5)	–
Development strategy by approval lag - *n* (%)						
Strategy with shorter approval lag	9 (35)	7 (37)	>0.9999	19 (70)	18 (41)	0.0269
Strategy with longer approval lag	17 (65)	12 (63)	–	8 (30)	26 (59)	–

Differences between lag durations for major and minor cancers were evaluated using Fischer's exact test.
BG, bridging study.

major cancers, 23% ($n = 6/26$) of drugs approved during the period 2006–2011 used pre-United States submission BGs during development, with that proportion remaining relatively constant at 22% ($n = 6/27$) during the period 2012–2016. For drugs targeting minor cancers, the proportions were 32% ($n = 6/19$) and 16% ($n = 7/44$) during the periods 2006–2011 and 2012–2016, respectively. The proportion of drugs targeting major cancers approved from 2006 to 2011 that used post-United States submission BG studies was 58% ($n = 15/26$), which declined to 26% ($n = 7/27$) from 2012 to 2016, whereas for minor cancers, the values were 42% ($n = 8/19$) and 39% ($n = 17/44$), respectively.

Local pivotal studies were rarely utilized for drugs targeting major cancers, with only a single case—approved in Japan prior to approval in the United States—among the drugs approved between 2012 and 2016 (and no cases during the period 2006–2011). However, they were more widely implemented for drugs targeting minor cancers, featuring seven approvals (16%) during the period 2012–2016. Furthermore, the drug approval lag for these local studies (median: 1,858 days) was considerably longer than the overall drug approval lag for all drug approvals during the period 2012–2016 (median: 752 days, not significant due to small sample size).

To examine if these differences in drug development strategy between drugs targeting major and minor cancers affected drug approval lag durations, drug approval lag was calculated for each development strategy. Strategies were then categorized as either being a strategy with shorter approval lag (global studies and pre-United States submission BG studies, medians: 224 and 570 days, respectively) or a strategy with longer approval lag (post-United States submission BG studies, local studies, and Japan-excluded studies, medians: 1,478, 800.5, and 1,818.5 days, respectively), based on whether the median drug approval lag was greater or less than 752 days, which was the median drug approval lag for approved drugs during 2012–2016 (**Table 3**).

The proportion of approved drugs targeting major cancers during the period 2012–2016, which utilized strategies with shorter approval lag during development, was twice (70%; $n = 19$) that during the period 2006–2011 (35%; $n = 9$). However, the proportion remained unchanged for approved drugs targeting minor cancers (41%; $n = 18$ and 37%; $n = 7$) during 2012–2016 and 2006–2011, respectively. For drugs approved during the period 2012–2016, a significantly greater proportion of drugs targeting major cancers used strategies with shorter approval lag compared with drugs targeting minor cancers (70% vs. 41%; $P = 0.0269$).

DISCUSSION

Here, we showed that the approval lag duration for drugs targeting minor cancers has not diminished since 2006, indicating that shortening of the overall lag was predominantly caused by drugs targeting major cancers. To our knowledge, this is the first study to investigate anticancer drug approval lag based on cancer incidence. We also revealed that the review time difference by healthcare authorities was significantly shorter for minor cancer drugs than for major cancer drugs. Therefore, we can conclude that the persistent drug approval lag for minor cancers was caused by developmental delays.

Development strategies for agents targeting major cancers have changed relative to those a decade ago. Specifically, the utilization of global studies or pre-United States submission BG studies has increased, contributing to overall reductions in drug approval lag. Kogure *et al.*[13] recently suggested that, to shorten the drug lag, Japanese pharmaceutical companies should utilize a global clinical study or initiate a BG study before completion of the final pivotal study in the United States.

Here, we found that approval lag was significantly shorter for drugs utilizing global study or pre-United States submission BG strategies vs. those using post-United States submission BG strategies. In the context of cancer incidence, anticancer drugs targeting major cancers tended to be the subject of development strategies that could potentially decrease drug approval lag (global study and pre-United States submission BG), whereas most BG studies were conducted for drugs targeting minor cancers only after submission

in the United States. For some drugs targeting minor cancers, Japanese anticancer drug development did not start until long after United States approval, with final approval given based on a small local study or a public knowledge-based application. Therefore, we found that the development of many of anticancer drugs targeting minor cancers has stagnated for a long time. However, the number of minor cancer drugs developed with global studies increased five-fold for the periods 2006–2012 and 2012–2016, with an increasing tendency to utilize global studies for minor cancers.

Since 2007, the Ministry of Health, Labour, and Welfare has encouraged Japanese pharmaceutical companies to join global studies to shorten drug approval lag.[18] Of 53 major and 63 minor cancer drugs, 49 and 52 were approved, respectively, based on multicountry clinical studies, with Japan participating in 16 (33%) and 12 (23%) studies, respectively. Furthermore, between 2012 and 2016, these ratios increased to 52% (13/25) and 32% (11/35), respectively. This shows that the utilization of global studies on minor cancer drugs has increased over time, and can be further promoted by reducing associated hurdles. If joining global studies is not possible, preliminary efficacy studies should be initiated in Japanese patients as soon as possible—at least prior to the United States NDA/BLA/sNDA sBLA. According to a previous report among anticancer drugs approved in 2010 or before in the United States, development of 20 drugs had not commenced in Japan, which is a potential sign of low marketability.[19] It is probably more time-consuming and expensive to conduct clinical studies for minor cancers than for major cancers. Fewer patients can be enrolled per investigational site, and relatively more sites are required in clinical studies for minor cancers, compared with those for major cancers. Site investigators in a particular site may hesitate to participate in clinical studies for minor cancers due to low patient enrollment rates. Additionally, it is recommended that the number of Japanese patients in a global study should be sufficient enough to ensure data consistency between the overall study population and the Japanese subgroup.[18] A Japanese phase I study is usually required before joining a global study.[20] These regulatory requirements may negatively impact patient enrollment and the timeline required for Japan to join a global study.

There are possible ways to seek earlier approval of drugs for minor cancers using smaller studies and fewer study sites, thus making participation in global studies or conducting pre-United States submission BG studies easier. The necessary number of patients in clinical studies can be reduced by utilizing biomarkers that have high prediction efficacy. For example, in one project, investigational sites and pharmaceutical companies collaborated to recruit biomarker-positive patients using blood samples (liquid biopsy) for analysis of comprehensive cancer genome alterations.[21] In terms of study design, a registry study for rare cancers is ongoing in Japan and this may be utilized for more efficient study design or interpretation of study results.[22]

Japan has made various efforts to shorten the drug approval lag between itself and the United States. Presently, a governmental committee (the Evaluation Committee on Unapproved and Off-label Drugs for High Medical Need) has been formed in Japan to request that pharmaceutical companies develop drugs of urgent medical need and that have been approved in other countries. However, this committee covers only drugs previously approved in other countries, limiting its ability to shorten drug approval lag.[23] Pre-existing systems to accelerate review time include priority review and orphan drug designation. However, although the regulatory review time difference between Japan and the United States is significantly shorter for drugs for minor cancers, the drug approval lag is still significant for such cancers. Therefore, until recently, available systems in Japan did not seem to be effective in reducing the duration of drug development for minor cancers. As revealed, 43% of drugs approved for minor cancers between 2006 and 2016 obtained approval based on noncomparative studies. However, until the recent implementation of a regulatory rule (the conditional early approval system[10]), there was no official system enabling drug approval with noncomparative studies. Such approvals seemed to be granted on a case-by-case basis through consultation with the governing health authorities.

The conditional early approval system was implemented in Japan to enable expedited approval of innovative new drugs. It covers only drugs in situations where the available patient population is too small to conduct a comparative study, or when such a study would not be feasible in terms of the time required. It is too early to judge the effect of conditional early approval on accelerating the development of innovative new drugs (including those for minor cancers in Japan), or whether it is widely applicable to the same degree as the United States accelerated approval system or breakthrough-therapy designation system. Nevertheless, the conditional early approval system is expected to increase the number of drugs approved for minor cancers based on noncomparative studies.

Furthermore, parallel consultation with health authorities may be useful for seeking expedited approval based on preliminary clinical evidence. The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) provide parallel scientific advice (PSA) for investigational drugs at the request of the sponsors.[24] If the PMDA can utilize PSA, drug approval may be expedited. As shown here, 54% of approvals for minor cancers were approved based on comparative studies in Japan, whereas some were approved in the United States based on noncomparative studies (data not shown). If the PMDA had known the opinion of the FDA at the time of approval for such drugs, a different approach could have been taken for approval of the corresponding drugs in Japan. If information sharing via PSA is expanded, particularly for innovative drugs under development in or outside of Japan, a development request and the necessary support could be made available for pharmaceutical companies in Japan associated with such drugs.

This study has some limitations. First, it only covered drugs approved in Japan between 2006 and 2016 that have also been approved in the United States, and we did not evaluate drug approval lag durations with other countries or for drugs approved outside this period. Second, we excluded drugs approved for a different treatment line within the same indication, and, thus, could not evaluate time lag for such cases. Third, we tabulated approval numbers by cancer type based on information provided in "*KONO* and *KOKA*" (indications) sections. Therefore, some approvals were counted twice, even if both approvals were obtained based on the same clinical study. Our results may have differed if such cases were

counted as one. Finally, we defined minor cancers based on the Japanese definition of rare cancers (an incidence of <6 cases per 100,000 individuals). Using a different definition may, therefore, alter our results.

Thus, drug approval lag durations tended to decrease for approvals post-2011, mainly due to a shortening of the approval lag times for drugs targeting major cancers, resulting from increased utilization of global studies or pre-United States submission BG development strategies. However, approval lag duration for drugs targeting minor cancers did not change over the 10-year survey period, and, thus, measures expediting the development of drugs to treat minor cancers in Japan should be implemented by all relevant stakeholders involved in drug development.

METHODS

Data sources and collected information

We investigated anticancer drugs approved in Japan between January 1, 2006, and December 31, 2016, including both NDAs and sNDAs. Drugs were identified using the PMDA website (https://www.pmda.go.jp/PmdaSearch/iyakuSearch/), from which information on approval date, approved indication, clinical data package submitted for evaluation, and marketing authorization holder were collected.

Prior to analysis, drugs that had obtained approvals for diseases other than cancers, supportive effects for other drugs, supportive or palliative care, a new treatment line in an existing indication, and nonefficacy indications were excluded. Furthermore, drugs not approved in the United States as of February 17, 2018, and those with lag durations >30 years were also excluded. To obtain United States approval information, we referred to the website of the FDA (https://www.fda.gov/Drugs/default.htm). To calculate drug approval lag time between Japan and the United States, the United States approval date was subtracted from the Japanese date. Therefore, if a drug was initially approved in the United States and then in Japan, a positive value lag time would be generated. In the event of the opposite, a negative value was obtained. Drugs with more than one indication approved on the same date were counted as separate approvals. Furthermore, review time by the corresponding regulatory authority was calculated by subtracting the approval date from the submission date for the Japanese or United States regulatory authority. Review time difference between Japan and the United States was similarly calculated as the drug approval lag.

The clinical studies considered to be the most important for efficacy evaluation for the drug approvals analyzed here were classified as "pivotal studies." These pivotal studies were then each categorized as either a "global study" (a multiregional study in which Japan participated), a "foreign study" (a study conducted outside Japan without Japanese participation), or a "local study" (a study conducted only in Japan). For each of these studies, the study design information (comparative or noncomparative) and the initiation date for the Japanese study for evaluating drug efficacy in Japanese patients, where foreign studies are submitted as pivotal studies for Japan NDA/sNDA (BG), if applicable, were also collected.

Incidence of cancer

Data on the incidence of each cancer in Japan were obtained from a previous publication.[25] For cancers not listed in this publication or those with specific biomarker characteristics, the incidence was estimated using published articles. These exceptions included colorectal cancer with *KRAS* wild type, epidermal growth factor receptor (EGFR) mutation-positive nonsmall cell lung cancer (NSCLC), *EGFR* T790M mutation-positive NSCLC, melanoma with *BRAF* mutation, breast cancer overexpressing human epidermal receptor 2 (HER2), *ALK*-positive NSCLC, anaplastic large cell lymphoma, and programmed cell death-ligand 1-positive NSCLC. Some cancers with specific histologies or biomarker profiles with an incidence <6 per 100,000 individuals prior to selection of histology or biomarkers (e.g., Philadelphia chromosome-positive acute lymphoblastic leukemia, T-cell acute lymphoblastic leukemia, and T-cell lymphoblastic lymphoma) were categorized as minor cancers (as defined below) without identifying their specific incidences. Regarding cetuximab, although approved for *EGFR* mutation-positive colorectal cancer, the associated parameters of the drug were estimated based on colorectal cancer with *KRAS* wild type, because we assumed that the drug was used for these patients.

Drug approval lag by major/minor cancers

To investigate the difference in drug approval lag by cancer incidence, the cancer targeted by each approved drug was categorized by incidence as either major (6 or more cases per 100,000 individuals per year) or minor (<6/100,000). To investigate lag duration by year of drug approval, drugs were divided into two groups: those approved between 2006 and 2011, and those approved between 2012 and 2016.

Drug approval lag by development strategy

Drug development strategies used were categorized as a "global study," "pre-United States submission BG" (a bridging study initiated prior to United States NDA/Biologics License Application (BLA)/sNDA/supplemental BLA (sBLA) submission), "post-United States submission BG" (a bridging study initiated after United States NDA/BLA/sNDA sBLA submission), "local study," or "Japan-excluded study" (public knowledge-based application or foreign study data without a BG), as shown in **Table 4**. We assumed that studies in which only month and year of initiation were available commenced on the first day of the month. If no information on the study initiation date was available, the last available day related to study preparation prior to study initiation was considered as the study initiation date. We defined the United States NDA/BLA/sNDA/sBLA date as the receipt date by the FDA, but if this date was unavailable, the submission date was used. For drugs lacking any application date information, approval date was used instead. In a separate analysis, development strategy was divided into two categories, "strategy with shorter drug approval lag" and "strategy with longer approval lag" to compare differences in lag time based on the development strategy used for major and minor cancers.

Table 4 Definition of clinical studies

Study category	Definition
Global study	Multiregional study in which Japan participated
Pre-United States submission BG	Study for evaluating drug efficacy in Japanese patients (BG) that initiated prior to United States NDA/BLA/sNDA/sBLA, where foreign studies are submitted as pivotal studies for Japan NDA/sNDA
Post-United States submission BG	Study for evaluating drug efficacy in Japanese patients (BG) that initiated after United States NDA/BLA/sNDA/sBLA, where foreign studies are submitted as pivotal studies for Japan NDA/sNDA
Local study	Study that was conducted only in Japan
Japan-excluded study	Study using only public data or foreign study data without a BG

BG, bridging study; BLA, Biologics License; NDA, New Drug Application; sNDA, supplemental New Drug Application; sBLA, supplemental Biologics Application.

Statistical methodology

Drug approval lag between Japan and the United States was described using box-and-whisker plots featuring the 25th percentile, median, and 75th percentile values. Lag duration comparison by cancer incidence (major vs. minor) and year of approval (2006–2011 vs. 2012–2016) was performed using the Mann–Whitney *U* test. Comparison of development strategy proportions utilized for drugs targeting major and minor cancers was performed using Fischer's exact test. All *P* values were based on a two-sided hypotheses, and *P* values < 0.05 were considered statistically significant. For analytical calculations, we used Statsdirect software version 3.1.12 (Statsdirect Ltd.) and R software version 3.4.0.[26]

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CONFLICT OF INTEREST

Kenji Yamashita is an employee of MSD K.K., a subsidiary of Merck, Kenilworth, NJ, USA.

AUTHOR CONTRIBUTIONS

K.Y. wrote the manuscript. K.Y., M.K., and M.N. designed the research. K.Y. performed the research. K.Y., M.K., and M.N. analyzed the data.

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