TDL.ORG TEXAS DIGITAL LIBRARY

Journal of Regulatory Science

http:\\journalofregulatoryscience.org

Journal of Regulatory Science 7 (2019) 1–9

Regulatory Science

Can Rare Cancer Drugs Expect Sales in Japan?: A Prescription Pattern Analysis of Drugs for Chronic Myelogenous Leukemia and Neuroendocrine Tumor

Shoyo Shibata[a,b,*], Emi Noguchi[c,d], Maiko Matsushita[e], Takeshi Suzuki[b], Koken Ozaki[a]

[a]*Graduate School of Business Sciences, University of Tsukuba, 3-29-1 Otsuka, Bunkyo-ku, Tokyo 112-0012, Japan*
[b]*Education Research Center for Pharmaceutical Sciences, Faculty of Pharmacy, Keio University, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan*
[c]*Department of Breast and Medical Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*
[d]*Rare Cancer Center, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*
[e]*Division of Physiology and Therapeutics, Faculty of Pharmacy, Keio University, 1-5-30 Shibakoen, Minato-ku, Tokyo 105-8512, Japan*

Abstract

Despite high unmet medical needs, investment in rare cancer drug development has stagnated, likely because the potential market for such drugs is small. In this context, we hypothesized that rare cancer drugs could achieve a higher sales margin. A dataset was created from publicly available information obtained from the IQVIA Solutions Japan K.K. Pharmaceutical Market database on the website of the Pharmaceuticals and Medical Devices Agency/Ministry of Health, Labour and Welfare of Japan. The total amount of sales and prescription volumes between 2010 and 2016 for drugs whose indications include chronic myelogenous leukemia (CML) and neuroendocrine tumor (NET) were investigated. Regarding drugs for CML, the sales and prescription volumes of imatinib have been decreasing every year, whereas those of dasatinib and nilotinib have been increasing. Regarding drugs for NET, the sales and prescription volumes of sunitinib, everolimus, and streptozocin have been increasing every year. The present study revealed two sales models for the development of rare cancer drugs. First, sales amounts can be assured if clinical positioning with other existing drugs is sufficiently clear. Second, obtaining a label for rare cancers can stimulate drug development for more common cancers. These findings suggest that rare cancer drugs can offer high market value and profit potential; thus, to meet high unmet medical needs, clinical development programs for the development of rare cancer drugs should be promoted.

Keywords: anticancer drug, marketing strategy, health economics, drug development, drug pricing

1. Introduction

Rare cancers account for approximately 22 percent of cancers worldwide, with an incidence of less than 6 per 100,000 persons per year [32]. Because of the lack of scientific and clinical knowledge of the pathology of rare cancers owing to the limited number of cases, patients are often treated in different ways at different sites and are unlikely to receive evidence-based treatment [8]. As a result, patient satisfaction with treatment remains low and prognosis remains poor compared with more common cancers [5]. Despite these high unmet medical needs, rare cancer drug development has stagnated. This stagnation can likely be explained by the following reasons. First, knowledge about rare cancers remains insufficient and the diagnosis is difficult. Second, conventional trial designs often demand large numbers of patients, which is often unfeasible for rare cancers. Third, rare cancer drugs are generally considered to be less profitable than conventional drugs [1].

To address the issue of the wide dispersion of patients with rare cancer, registries for rare cancers have been constructed. For example, the MASTER KEY (Marker Assisted Selective ThErapy in Rare cancers: Knowledge database Establishing registrY) Project was initiated to collect genetic, treatment, and prognostic information actively so that a large-scale, comprehensive database could be established [15]. SCRUM-Japan (the Cancer Genome Screening Project for Individualized Medicine in Japan) was also initiated as a genomic screening project for lung and gastrointestinal cancer [14]. These projects, which are both led by the National Cancer Center, are expected to accelerate the global development of rare cancer drugs through reliable, integrated databases in Japan.

From the regulatory perspective, the Orphan Drug Act was passed in the US in 1983 to facilitate the development of orphan drugs. Orphan Drug Designation will be granted to drugs which treat a serious condition and, if approved, would provide

*Corresponding author: Shoyo Shibata, Phone: +81-3-5400-2496, Email: s1840110@s.tsukuba.ac.jp / shoyo.shibata@keio.jp

a significant improvement in safety or effectiveness and these drugs can receive the priority review; Japan has also established similar regulations. Indeed, the review time for orphan drugs has been shortened significantly compared with non-orphan drugs in Japan [25]. Moreover, the specific characteristics of pivotal studies of orphan drugs have been reported in a non-randomized, non-controlled, Phase II study [11]. A systemic analysis of study designs for rare cancer drug approvals in the US revealed that 69% of approvals were overall response rate as the primary endpoint [4]. In this context, study designs applicable for rare cancer clinical trials have been actively discussed with the aim of achieving efficient clinical development; these include the Umbrella study, Basket study, N-of-1 study, Adaptive design, and Bayesian design [9]. Furthermore, discussions of these innovative trial designs in Japan have been initiated to promote personalized medical care [6].

From the perspective of pharmaceutical product developers, the profitability of such products is considered to be one of the most important factors. Several papers have revealed the characteristics and prognoses of Japanese pharmaceuticals. Japan's unique pricing system indirectly encourages the development of anticancer drugs in Japan, setting higher drug prices than other drugs [21, 22, 23]. In addition, the development of anticancer drugs with novel modes of action has been encouraged at the global level, including in Japan; the Japanese pharmaceutical market rivals the global market, where anticancer drugs are among the most profitable of all therapeutic areas [24, 29, 28]. However, to our knowledge, no systematic empirical study has attempted to address the question of how the development of rare cancer drugs can be profitable. One previous study reported the profitability of orphan drugs in Japan, but the focus of that study was on drugs for neurological diseases [26]. With this background, we hypothesized that rare cancer drugs could achieve a higher sales margin in Japan.

The development of rare cancer drugs in Japan faces three hurdles, the first and second of which have been mitigated by the above countermeasures. However, for the third hurdle, no countermeasures have been taken. Therefore, the primary objective of the present study was to examine whether the development of drugs targeted to treat rare cancers can meet the needs of pharmaceutical companies using the prescription data of selected drugs prescribed to treat rare cancers in Japan between 2010 and 2016.

To the best of our knowledge, no previous studies have used such empirical data on prescription patterns to examine the profitability of drugs for rare cancers in Japan. We believe that the insight obtained from this research by investigating recent prescription patterns could help stimulate drug development for rare cancers by pharmaceutical companies in collaboration with clinicians and academia.

2. Methods

2.1. Database used in the present study

The dataset used in the present study was created from publicly available information obtained from the IQVIA Solutions Japan K.K. Market database. Data regarding the total amount of sales and prescriptions of selected anticancer drugs in Japan between 2010 and 2016 were analyzed. This article does not contain any studies with human or animal subjects performed by any of the authors.

2.2. Selection of rare cancer drugs for this study

The rare cancer drugs selected for analysis in the present study were characterized to evaluate their potential market position in the anticancer drug market in Japan. Drugs for chronic myelogenous leukemia (CML) and neuroendocrine tumor (NET) were selected (Table 1).

The rationale for selection involved drugs for rare cancers that receive relatively long-term pharmacotherapy so that prescription patterns could be investigated periodically. The indications and approval dates for the drugs of interest were selected by referring to the package inserts and interview forms available on the Pharmaceuticals and Medical Devices Agency (PMDA) website [17].

2.3. Prices of selected rare cancer drugs in the present study

The prices of selected rare cancer drugs in the present study were obtained from The Ministry of Health, Labour and Welfare (MHLW) website [12]. It was also used to identify drugs commanding premium pricing.

2.4. Generic medicines of interest investigated in the present study

Next, we aimed to investigate the prescription patterns of generic versions of CML and NET drugs; however, no generic versions of NET drugs were available, so only generic versions of imatinib for CML were selected for analysis.

2.5. Objectives

The primary objective of the present study was to clarify whether the research and development of rare cancer drugs could be profitable for pharmaceutical companies to meet urgent unmet medical needs in Japan, thereby providing direction for future rare cancer drug development by pharmaceutical companies, clinicians, and academia.

3. Results

3.1. Prescription patterns of rare cancer drugs

The prescription patterns of the CML drugs are shown in Figure 1. The prescription pattern of each drug was similar in terms of both sales and prescription volumes. While the sales and prescription volumes of imatinib have been decreasing every year, those of dasatinib and nilotinib have been increasing. No trends could be confirmed for ponatinib as the only data available are for 2016. Dasatinib had the largest market share among the CML drugs.

The prescription patterns of the NET drugs are shown in Figure 2. The prescription pattern of each drug was also similar in terms of both sales and prescription volumes. The sales and

Drug	Indications	Approval Date
Imatinib	Chronic myelogenous leukemia KIT (CD117)-positive gastrointestinal stromal tumor Philadelphia chromosome-positive acute lymphoblastic leukemia FIP1L1-PDGFRα positive; Hypereosinophilic syndrome, Chronic eosinophilic leukemia	21 November, 2001 17 July, 2003 31 January, 2007 22 February, 2012
Dasatinib	Chronic myelogenous leukemia Relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia	21 January, 2009 21 January, 2009
Nilotinib	Chronic myelogenous leukemia in the chronic or transition phase	21 January, 2009
Ponatinib	Chronic myelogenous leukemia resistant or intolerant to prior therapy Relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia	28 September, 2016 28 September, 2016
Sunitinib	Gastrointestinal stromal tumor resistant to imatinib Unresectable or metastatic renal cell carcinoma Pancreatic neuroendocrine tumor	16 April, 2008 16 April, 2008 10 August, 2012
Everolimus	Unresectable or metastatic renal cell carcinoma Neuroendocrine tumor Inoperable or recurrent breast cancer Renal angiomyolipoma with tuberous sclerosis Subependymal giant cell astrocytoma with tuberous sclerosis	20 January, 2010 22 December, 2011 17 March, 2014 21 November, 2012 21 November, 2012
Streptozocin	Gastroenteropancreatic neuroendocrine tumor	26 September, 2014

Table 1: Selected Drugs for Rare Cancers in the Present Study.

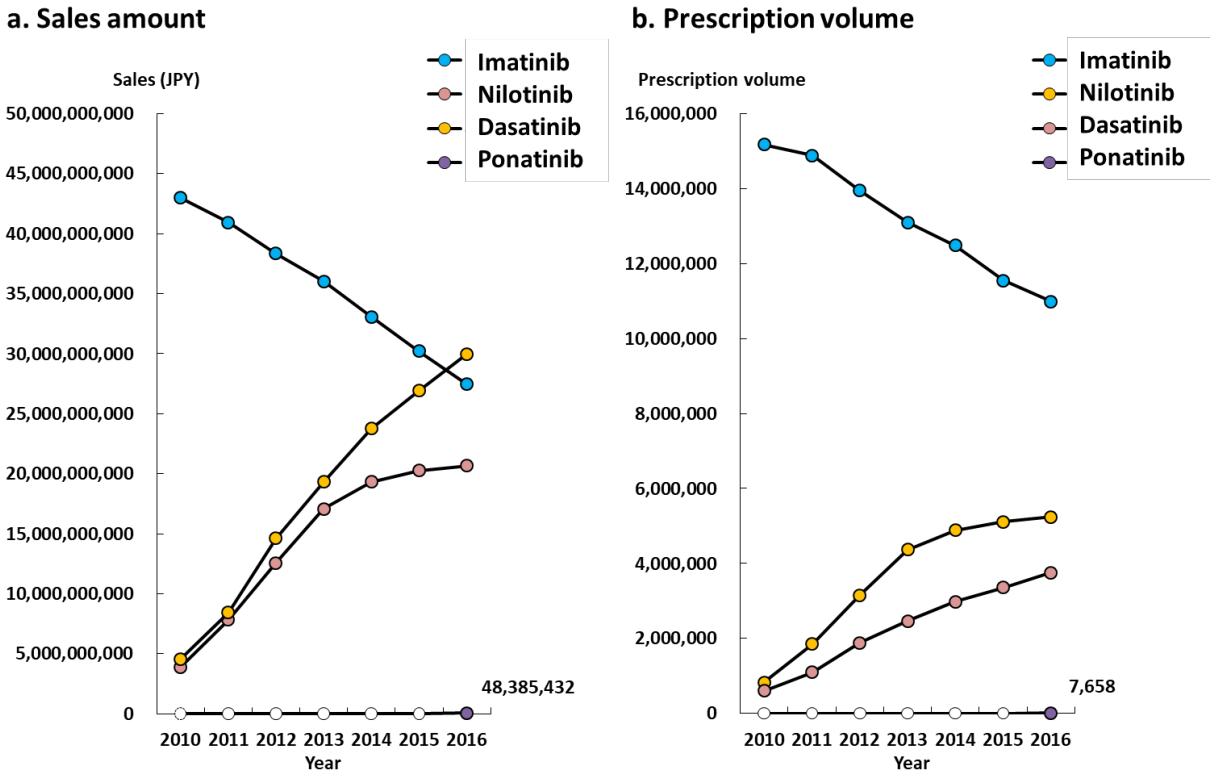

Figure 1: Prescription patterns of drugs for chronic myelogenous leukemia: (a) sales amount; (b) prescription volume. The white circles indicate that no data are available.

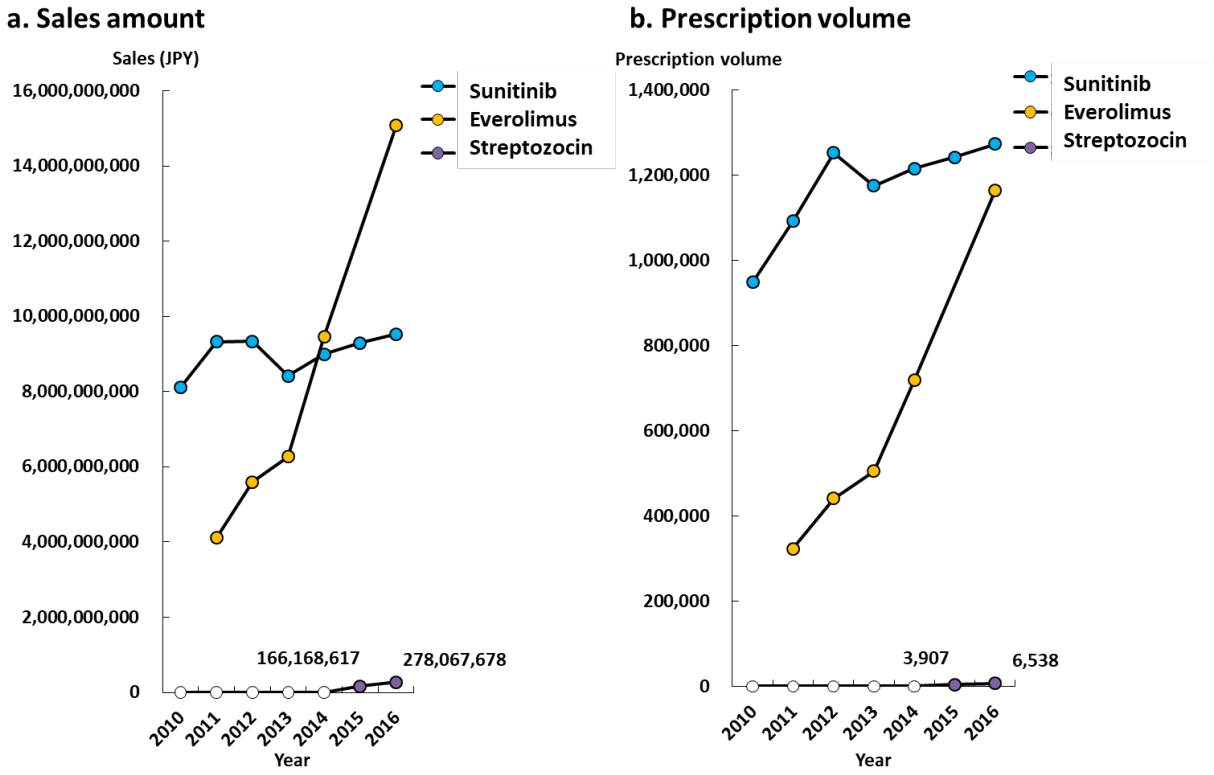

Figure 2: Prescription pattern of drugs for neuroendocrine tumor: (a) sales amount; (b) prescription volume. The white circles indicate that no data are available. For everolimus, the data are not available for 2010 and 2015.

prescription volumes of sunitinib and everolimus have been increasing every year. An increasing trend was also observed for streptozocin, but only over a limited period. Everolimus had the largest market share among the NET drugs.

3.2. Prescription drug trends for generic imatinib medicines

As described above, the only rare cancer drug of interest that had a generic version was imatinib. The prescription patterns of imatinib (original), imatinib (generic), and imatinib (original and generic) are shown in Figure 3. Although the sales and prescription volumes of imatinib (generic) have been increasing since 2013, when the first generic versions were launched, those of imatinib (original) and imatinib (original and generic) have been decreasing.

The numbers of generic imatinib medicines available for CML are shown in Figure 4. The first generic medicines were launched in 2013, and as of 2016, this number had increased to 17.

3.3. Rare cancer drug prices

The rare cancer drug prices are shown in Table 2. Among the CML drugs, dasatinib had the highest price and imatinib the lowest. Compared with 2010 drug prices, those for imatinib and dasatinib in 2016 were lower. On the other hand, those for nilotinib were higher. The rates of change in drug prices from 2010 to 2016 were 88.3%, 88.5%, and 105.0% for imatinib, dasatinib, and nilotinib, respectively. Ponatinib had the second-highest drug price in 2016.

Among the NET drugs, streptozocin had the highest price and sunitinib the lowest. Compared with the drug prices in 2010 for sunitinib and 2011 for everolimus, that for sunitinib in 2016 was lower while that for everolimus was higher. The rates of change in drug prices from 2010 (sunitinib) and 2011 (everolimus) to 2016 were 87.6% and 101.9% for sunitinib and everolimus, respectively.

3.4. Drug prices of generic imatinib medicines

The drug prices of generic imatinib medicines are shown in Table 3. In 2016, the highest price was 1,555 JPY and the lowest was 1,171 JPY, indicating that the prices of generic drugs were set between this range, which was almost half that of imatinib (original).

4. Discussion

The results of the present study demonstrated that rare cancer drugs whose indications focus on CML and NET showed strong sales numbers in Japan. The results also revealed two types of sales models for the development of rare cancer drugs. First, for CML drugs, even though they are "follower" as opposed to "first-in-class" drugs, sales amounts can be assured with clear clinical positioning in regard to other existing drugs

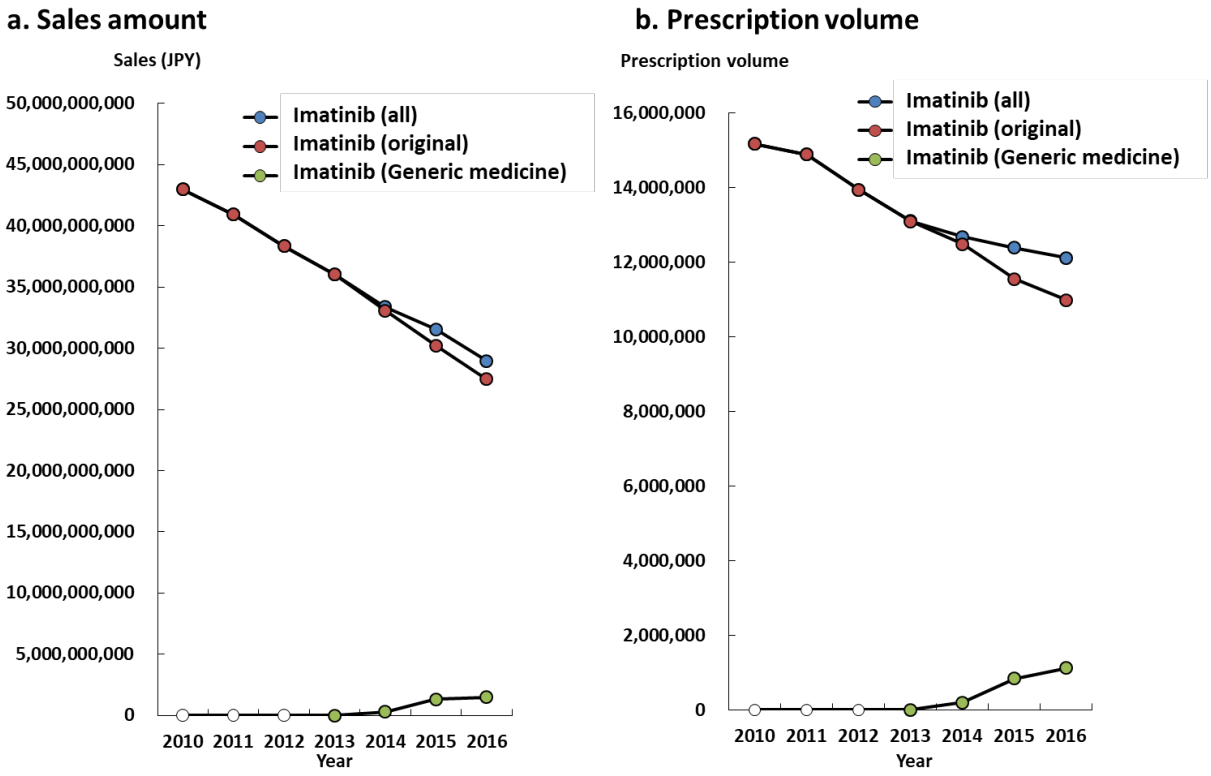

Figure 3: Prescription patterns of imatinib (original), imatinib (generic), and imatinib (original and generic): (a) sales amount; (b) prescription volume. The white circles indicate that no data are available. "Imatinib (all)" indicates imatinib (original and generic).

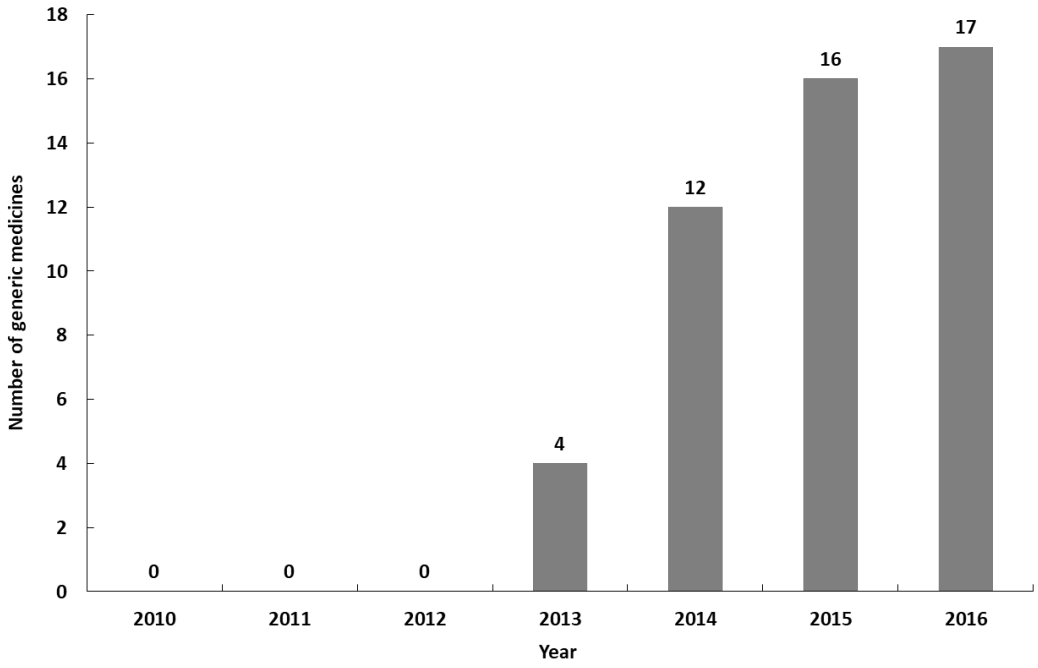

Figure 4: Number of generic imatinib medicines available between 2010 and 2016.

	2010	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Imatinib	2,832	2,749	2,749	2,749	2,648	2,617	2,500
Dasatinib	4,719	4,236	3,984	3,908	3,955	3,964	3,941
Nilotinib	7,602	7,699.6	7,787	7,824	7,967	8,017	7,985
Ponatinib	N/A [a]	N/A	N/A	N/A	N/A	N/A	6,318
Sunitinib	8,546	8,546	7,451	7,162	7,401	7,482	7,482
Everolimus	N/A	12,711	12,678	12,400	13,180	13,547	12,956
Streptozocin	N/A	N/A	N/A	N/A	N/A	42,531	42,531

Table 2: Drug Prices (in JPY) of Selected Drugs for Rare Cancers in the Present Study.

[a]N/A, not available

through well-designed clinical trials. Second, for NET drugs, obtaining the label of a rare cancer drug can stimulate drug development for the more common cancers, resulting in greater sales.

Regarding CML drugs, imatinib is a "first-in-class" drug, whereas dasatinib, nilotinib, and ponatinib were launched as "follower" drugs (Table 1). However, these drugs are all tyrosine kinase inhibitors. Increasing prescription trends were observed for dasatinib, nilotinib, and ponatinib, although it should be noted that the patent for imatinib expired, resulting in greater penetration for generic medicines (Figures 1, 3, and 4). The indications for all of the generic imatinib medicines were for CML and Philadelphia chromosome-positive acute lymphoblastic leukemia [17]. Patients with CML or Philadelphia chromosome-positive acute lymphoblastic leukemia receive long-term therapy, and the prices of the generic versions were almost half that of the original imatinib (Table 3). Therefore, the markets associated with the above two indications are highly competitive. However, the other two indications (gastrointestinal stromal tumor and hypereosinophilic syndrome/chronic eosinophilic leukemia) are dominant for imatinib (original), which has been decreasing in terms of sales and prescription volume. It is notable that nilotinib [34] and ponatinib [35] have been reported to induce stronger clinical responses; they are also used to treat CML that has been resistant or intolerant to prior therapy, which positions them uniquely in relation to imatinib [7, 10]. Dasatinib is structurally diverse from imatinib and is a highly potent inhibitor of BCR-ABL and was also approved for the treatment of imatinib-resistant acute myeloid leukemia [13]. Overall, even for rare cancers, if the clinical positioning can be clearly established, stable sales can be assured.

Regarding the NET drugs, increased sales and prescription volumes were seen for sunitinib, streptozocin, and everolimus after obtaining an indication as a NET drug (Figure 2). Notably, sales and prescription volumes drastically increased for everolimus after obtaining an indication for inoperable or recurrent breast cancer (Figure 2). This "from niche market to mass market" strategy is considered to be one of the most profitable models for rare cancer drug development, because increasingly more investigations have been revealing the molecular biology of cancer, and in accordance with these advances, most of the candidate drugs under clinical development are molecular-targeted drugs, which are unlikely to be affected by the penetration of generic medicines [27, 30].

For rare cancers, indications can be obtained based on early-phase clinical data by the effective use of biomarkers in clinical trials, such as basket and umbrella trials, as genomic medicine advances [15, 18, 19].The utilization of biomarkers can lead to the adequate appraisal of clinical efficacy and safety data in clinical trials, or their use as surrogate markers to evaluate efficacy and safety data, especially in early-phase trials [31]. In addition, using biomarkers to stratify patients can lead to more favorable efficacy and safety. These innovative clinical trial designs can be expected to boost the clinical development of rare cancer drugs.

However, in proposing this sales model, it is necessary to mention the approval of nivolumab in Japan, which has received extensive discussion in regard to the sustainability of the Japanese healthcare system. Because of its high price, which was set when the indication for melanoma was approved, many worry that the use of nivolumab could cause the collapse of the Japanese healthcare system [2]. With their durable response rate, immuno-oncology (IO) agents have transformed cancer therapy, and the number of new clinical trials worldwide in 2017 was reported to be 469 [33], which includes many trials investigating combination therapy with other immune modulators, targeted therapy, chemotherapy, and radiation therapy [20]. In this context, similar financial issues in the Japanese health insurance system may occur after the approval of other IO therapies in Japan. Indeed, it has been reported that cancer therapy can cause "financial toxicity" among cancer patients, although this is the case outside of Japan, where the situation might be different [37]. However, considering the increase in

	2010	2011	2012	2013	2014	2015	2016
GE1	N/A [a]	N/A	N/A	1,842	1,552	1,575	1,284
GE2	N/A	N/A	N/A	1,842	1,555	1,540	1,338
GE3	N/A	N/A	N/A	1,842	1,558	1,540	1,339
GE4	N/A	N/A	N/A	1,842	1,581	1,540	1,256
GE5	N/A	N/A	N/A	N/A	1,661	1,754	1,555
GE6	N/A	N/A	N/A	N/A	1,540	1,540	1,345
GE7	N/A	N/A	N/A	N/A	1,769	1,651	1,359
GE8	N/A	N/A	N/A	N/A	1,540	1,540	1,224
GE9	N/A	N/A	N/A	N/A	1,540	1,540	1,235
GE10	N/A	N/A	N/A	N/A	1,386	1,386	1,216
GE11	N/A	N/A	N/A	N/A	1,386	1,386	1,210
GE12	N/A	N/A	N/A	N/A	1,386	1,386	1,298
GE13	N/A	N/A	N/A	N/A	N/A	1,386	1,309
GE14	N/A	N/A	N/A	N/A	N/A	1,386	1,202
GE15	N/A	N/A	N/A	N/A	N/A	1,429	1,341
GE16	N/A	N/A	N/A	N/A	N/A	1,386	1,171
GE17	N/A	N/A	N/A	N/A	N/A	N/A	1,207

Table 3: Drug Prices (in JPY) of Generic Imatinib Medicines.

[a]N/A, not available

healthcare expenditures, the financial burdens that IO agents may potentially cause to the nation rather than to individual cancer patients in Japan should be considered. Health technology assessment is considered to be one of the solutions for rising healthcare expenditures [16]. Health technology assessment can play a critical role in maintaining a sustainable healthcare system in Japan while ensuring patient access to innovative new drugs.

In summary, future strategies should include efforts to adequately appraise care for rare cancers and refine the health insurance system, while also seeking opportunities to promote the development of rare cancer drugs by stimulating industry-sponsored clinical trials through proper incentive systems. Collectively, the results of the present study are expected to provide important perspectives by informing pharmaceutical companies about the potential profitability of rare cancer drugs, thereby ensuring patients timely access to innovative care for rare cancers.

Notably, two of the four CML drugs (nilotinib and dasatinib) and all three of the NET drugs (sunitinib, everolimus, and streptozocin) received premium rewards in their drug pricing in 2018; this is referred to as "Drug Price Premiums for Promoting the Creation of New Drugs and the Elimination of Off-label Drug Use", and indicates that higher drug prices can be set for rare cancer drugs compared with those for other common cancers. Wakutsu et al. reported that the benefits brought by this premium reward system were considered to be sufficient to encourage pharmaceutical companies to engage in clinical development, in that research and development costs can be recovered at an early stage [36]. However, Wakutsu et al. also stressed that such benefits can be limited, especially for orphan drugs, and suggested that financial support is strongly needed in this disease area to deliver new drugs efficiently [36]. In Japan, drug prices are set by the government and revised every other year. During regular drug price revisions, one of the characteristics associated with price cutting is to have "follower drugs" (the new/generic drugs which have an identical mechanism of

action in the market) on the market [3]. This may also be the case with rare cancer drugs, in which case, it could be a negative factor in terms of their potential development by industry. Indeed, in regard to CML, downward trends in the drug prices of tyrosine kinase inhibitors have been confirmed for imatinib and nilotinib (Table 2). In this context, intensive discussions on drug pricing, together with the balance between the sales of rare cancer drugs and overall healthcare expenditures in Japan, are warranted.

This study did have some limitations. In discussing profitability, the costs associated with research and development and the impact of sales force of each pharmaceutical company must be considered. However, these aspects were not considered in the present study. Furthermore, it is difficult to conclude that the development of rare cancer drugs can be profitable based on only the results obtained from this study since target indications should first be expanded to cover all rare cancers. Moreover, the dataset of the drugs of interest for the present study was not stratified by CML or NET; thus, the prescription data included all indications for each drug. In this context, further research is strongly warranted to estimate adequately the research and development costs for new drugs through mathematical models or proper simulations and investigate the prescription trends of all rare cancer drugs available in Japan while stratifying the data according to each rare cancer indication.

Despite these limitations, by directly testing the sales of rare cancer drugs, even though this was limited to CML and NET drugs, the results of the present study fill a research gap and highlight the potential capabilities of rare cancer drugs to acquire a larger market share and recover the costs of research and development at an early stage.

5. Conclusion

Rare cancer drugs can achieve higher market value and greater sales; therefore, more clinical development should be encouraged in this area to meet urgent unmet medical needs.

6. Declaration of Conflicting Interest

Shoyo Shibata is an employee of Chugai Pharmaceutical Co., Ltd. However, his affiliation with the company did not influence the results or discussion in this paper. Emi Noguchi, Maiko Matsushita, Takeshi Suzuki, and Koken Ozaki have no conflicts of interest to disclose.

7. Disclaimer

This study was presented in part by the authors at the Annual Meeting of the Japanese Society of Medical Oncology held in Kobe, Japan on 20 July 2018. This work was supported in part by Keio Gakuji Academic Development Funds and Ministry of Education, Culture, Sports, Science and Technology (MEXT) Supported Program for the Strategic Research Foundation at Private Universities.

8. Acknowledgement

We are immensely grateful to Yoshimasa Saito (Division of Pharmacotherapeutics, Faculty of Pharmacy, Keio University) for his comments on an earlier versions of the manuscript.

9. Article Information

This article was received December 16, 2018, in revised form February 7, 2019, and made available online February 26, 2019.

10. References

[1] Ashley, D., Thomas, D., Gore, L., Carter, R., Zalcberg, J. R., Omtar, R., & Savulescu, J. (2015). Accepting risk in the acceleration of drug development for rare cancers. *The Lancet Oncology, 16(4)*, e190-e194.

[2] Fukuda, A. & Igarashi, A. (2016). Universal Health Coverage and Cancer Drugs - A Cost-Effectiveness Perspective (in Japanese). *Gan To Kagaku Ryoho, 43(11)*, 1311-1315.

[3] Fukumoto, D., Tsuyuki, A. & Suzuki, T. (2017). Drugs Targeted for Price Cutting in Japan: The Case of Price Revisions Based on the Divergence of Official Versus Delivery Prices. *Therapeutic Innovation & Regulatory Science, 51(5)*, 597-603.

[4] Gaddipati, H., Liu, K., Pariser, A., & Pazdur, R. (2012). Rare Cancer Trial Design: Lessons from FDA Approvals. *Clinical Cancer Research, 18(19)*, 5172-5178.

[5] Gatta, G., Van Der Zwan, J. M., Casali, P. G., Siesling, S., Dei Tos, A. P., Otter, R., . . . Capocaccoa, R. (2011). Rare cancers are not so rare: the rare cancer burden in Europe. *European Journal of Cancer, 47(17),* 2493-2511.

[6] Hirakawa, A., Asano, J., Sato, H., & Teramukai, S. (2018). Master protocol trials in oncology: Review and new trial designs. *Contemporary Clinical Trials Communications, 12*, 1-8.

[7] Kantarjian, H. M., Hochhaus, A., Saglio, G. De Souza, C., Flinn, I. W., Stenke, L., . . . Hughes, T. P. (2011). Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. *The Lancet Oncology,12(9)*, 841-851.

[8] Kawai A. (2015). Rare cancers, the clinical presentation and issues (in Japanese). *Journal of Clinical and Experimental Medicine, 254(9)*, 621-627.

[9] Kawai, A., Goto, T., Shibata, T., Tani, K., Mizutani, S., Nishikawa, A., . . . Ueda, R. (2018). Current state of therapeutic development for rare cancers in Japan, and proposals for improvement. *Cancer Science, 109(5)*, 1731-1737.

[10] Lipton, J. H., Chuah, C., Guerci-Bresler, A., Rosti, G., Simpson, D., Assouline, S., . . . Deininger, M. W. (2016). Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. *The Lancet Oncology, 17(5)*, 612-621.

[11] Maeda, K., Kaneko, M., Narukawa, M., & Arato, T. (2017). Points to consider: efficacy and safety evaluations in the clinical development of ultra-orphan drugs. *Orphanet Journal of Rare Diseases, 12(1)*, 143.

[12] Ministry of Health, Labour and Welfare. Retrieved February 3, 2019 from https://www.mhlw.go.jp/english/

[13] Nakamae, H., Fujisawa, S., Ogura, M., Uchida, T., Onishi, Y., Taniwaki, M., . . . Miyoshi, M. (2017). Dasatinib versus imatinib in Japanese patients with newly diagnosed chronic phase chronic myeloid leukemia: a subanalysis of the DASISION 5-year final report. *International Journal of Hematology, 105(6)*, 792-804.

[14] Ohtsu, A., Goto, K., Yoshino, T., Okamoto, W., & Tsuchihara, K. (2017). Current Status and Future Perspectives of SCRUM-Japan (in Japanese). *Gan To Kagaku Ryoho, 44(8)*, 621-626.

[15] Okuma, H. S., Yonemori, K., Shimizu, T., Yashushi, G., Honma, Y., Morizane, C., . . . Fujiwara, Y. (2018). MASTER KEY project: A basket/umbrella trial for rare cancers in Japan. *Journal of Clinical Oncology, 36:*15_suppl, TPS2598-TPS2598.

[16] Oliver, A. (2003). Health economic evaluation in Japan: a case study of one aspect of health technology assessment. *Health Policy, 63(2)*, 197-204.
[17] Pharmaceutical and Medical Devices Agency. Retrieved February 3, 2019 from https://www.pmda.go.jp/english
[18] Redig, A. J. & Jänne, P. A. (2015). Basket trials and the evolution of clinical trial design in an era of genomic medicine. *Journal of Clinical Oncology, 33(9)*, 975-977.
[19] Renfro, L. A. & Sargent, D. J. (2016). Statistical controversies in clinical research: basket trials, umbrella trials, and other master protocols: a review and examples. *Annals of Oncology, 28(1)*, 34-43.
[20] Rotte, A., Jin, J. Y. & Lemaire, V. (2017). Mechanistic overview of immune checkpoints to support the rational design of their combinations in cancer immunotherapy. *Annals of Oncology, 29(1)*, 71-83.
[21] Shibata, S., Uemura, R., & Suzuki, T. (2016). Factors that Affect the Acquisition of Reward Premiums for Promotion of Innovative Drug Discovery in Japan. *Therapeutic Innovation & Regulatory Science, 50(1)*, 56-65.
[22] Shibata, S., Uemura, R., & Suzuki, T. (2016). Impact of Premium Rewards for the Promotion of Innovative Drug Discovery on the Japanese Pharmaceutical Market: An Analysis by Therapeutic Area. *Therapeutic Innovation & Regulatory Science, 50(1)*, 49-55.
[23] Shibata, S., Uemura, R., & Suzuki, T. (2016). Evaluating the Effectiveness of Repricing for Market Expansion in the Japanese Drug Pricing System. *Therapeutic Innovation & Regulatory Science, 50(6)*, 751-758.
[24] Shibata, S., Uemura, R., & Suzuki, T. (2016). Comparative Analysis Between the Top-Selling Drugs in the Japanese Pharmaceutical Market and Those in the United States, the United Kingdom, France, and Germany. *Therapeutic Innovation & Regulatory Science, 50(2)*, 221-227.
[25] Shibata, S., Uemura, R., Chiba, K., & Suzuki, T. (2016). A comprehensive analysis of factors that contribute to conditional approval and all-case surveillance designations that subsequently lead to shortening of review times in Japan. *Journal of Regulatory Science, 4(1)*, 1-9.
[26] Shibata, S., Kawaguchi, H., Uemura, R., & Suzuki, T. (2016). Emerging Growth of Orphan Drugs for Neurological Diseases in Japan: Potential Benefits for Both Patients and Pharmaceutical Companies. *Journal of Regulatory Science, 4(3)*, 7-13.
[27] Shibata, S., Matsushita, M., Saito, Y., & Suzuki, T. (2017). Optimal Anticancer Drug Profiles for Effective Penetration of the Anti-cancer Drug Market by Generic Drugs in Japan. *Therapeutic Innovation & Regulatory Science, 52(4)*, 442-448.
[28] Shibata, S., Wayama, Y., Tsuyuki, A., Matsushita, M., Chiba, K., Matsuki, E., . . . Suzuki, T. (2017). An empirical study of the prescription pattern of drugs for hematological malignancies in Japan from 20102014. *Biological and Pharmaceutical Bulletin, 40(6)*, 894-901.
[29] Shibata, S. & Suzuki, T. (2018) The pharmaceutical market and drug development prognosis in Japan: Current and future perspectives according to pharmacological classes. *Journal of Generic Medicines, 14(2)*, 70-80.
[30] Shibata, S., Matsushita, M., Saito, Y., & Suzuki, T. (2018). Anticancer Drug Prescription Patterns in Japan: Future Directions in Cancer Therapy. *Therapeutic Innovation & Regulatory Science, 52(6)*, 718-723.
[31] Simon, R. (2017). Critical Review of Umbrella, Basket, and Platform Designs for Oncology Clinical Trials. *Clinical Pharmacology & Therapeutics, 102(6)*, 934-941.
[32] Tamaki, T., Dong, Y., Ohno, Y., Sobue, T., Nishimoto, H. & Shibata, A. (2014). The burden of rare cancer in Japan: application of the RARECARE definition. *Cancer Epidemiology, 38(5)*, 490-495.
[33] Tang, J., Shalabi, A. & Hubbard-Lucey, V. M. (2017). Comprehensive analysis of the clinical immuno-oncology landscape. *Annals of Oncology, 29(1)*, 84-91.
[34] Tojo, A., Usuki, K., Urabe, A., Maeda, Y., Kobayashi, Y., Jinnai, I., . . . Naoe, T. (2009). A Phase I/II study of nilotinib in Japanese patients with imatinib-resistant or-intolerant Ph+ CML or relapsed/refractory Ph+ ALL. *International Journal of Hematology, 89(5)*, 679-688.
[35] Tojo, A., Kyo, T., Yamamoto, K., Nakamae, H., Takahashi, N., Kobayashi, Y., . . . Ohyashiki, K. (2017). Ponatinib in Japanese patients with Philadelphia chromosome-positive leukemia, a phase 1/2 study. *International Journal of Hematology, 106(3)*, 385-397.
[36] Wakutsu, N. & Nakamura, H. (2015). Analyzing the Benefits from New NHI Drug Pricing System in Japan: Factor Decomposition and Simulation (in Japanese). *Iryo To Shakai, 25(2)*, 205-220.
[37] Zafar, S. Y., Peppercorn, J. M., Schrag, D., Taylor, D. H., Goetzinger, A. M., Zhong, X. & Abernethy, A. P. (2013). The financial toxicity of cancer treatment: a pilot study assessing out-of-pocket expenses and the insured cancer patient's experience. *The Oncologist, 18(4)*, 381-390.