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ORIGINAL ARTICLE

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# Lack of correlation between the costs of anticancer drugs and clinical benefits in Japan

Etsuko Satoh[1] | Yasutsuna Sasaki[1] | Ryotaro Ohkuma[1] | Takehiro Takahashi[1] | Yutaro Kubota[1] | Hiroo Ishida[1] | Kazuyuki Hamada[1] | Yuji Kiuchi[2] | Takuya Tsunoda[1]

[1]Division of Medical Oncology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

[2]Department of Pharmacology, Showa University School of Medicine, Tokyo, Japan

**Correspondence**
Yasutsuna Sasaki, Division of Medical Oncology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan.
Email: yasutsuna@med.showa-u.ac.jp

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Both overall survival (OS) and progression-free survival (PFS) are primary endpoints of phase III studies of new anticancer drugs. Medical care expenditures, especially oncology drug prices, are rapidly increasing; however, the impact of oncology drug prices on OS and PFS is unclear. We analyzed the relationship between oncology drug prices and clinical outcomes in Japan. The costs of a full course or 1 year of treatment were estimated on the basis of the latest National Health Insurance Drug Price Standards, and the relationship between costs and improvements in OS or PFS obtained with each drug were analyzed. Cost-effectiveness was compared between new-class drugs and next-in-class drugs. We then developed a simple model for estimating the costs required to prolong OS and PFS by 1 day and used this model to compare cost-effectiveness. Drug costs were not significantly related to treatment outcomes in terms of PFS or OS. There was no significant difference in the median cost between novel drugs and the next-in-class drugs ($P = 0.39$). The oncology drug cost required to prolong PFS by 1 day was more expensive than the drug cost required for prolong OS by 1 day. Prices of oncology drugs should be decided on the basis of actual clinical benefits for cancer patients, and the drug price evaluation process should be disclosed in Japan.

**KEYWORDS**
anticancer drug, clinical benefit, cost-effectiveness, overall survival, progression-free survival

## 1 | INTRODUCTION

Cancer is the main cause of death in developed countries, including Japan. More than half of the Japanese population is given a diagnosis of cancer in their lifetime, and the number of cancer-related deaths is increasing.[1] Medical therapy against advanced or recurrent cancer is the main treatment option for patients with metastatic or recurrent cancer. Although treatment outcomes in response to conventional chemotherapeutic agents seemed to have plateaued in the 20th century, new treatment options such as targeted agents and immune checkpoint inhibitors (ICI) have dramatically improved overall survival (OS) in some types of solid tumors.[2-4] OS, progression-free survival, (PFS), or both are primary endpoints of phase III studies of new oncology drugs.[5] In particular, the prolongation of OS reflects an actual clinical benefit for cancer patients.[5,6] Prolongation of PFS is sometimes used as the primary endpoint in pivotal phase III trials; however, PFS is only a surrogate endpoint and does not always directly reflect clinical benefit of cancer patients.[5]

Owing to the prolongation of OS in patients with many types of cancer, however, medical care expenditures,[7] especially oncology drug prices, are rapidly increasing not only in Japan but also worldwide.[8-11] As an extreme case, the price of nivolumab (Opdivo® Ono Pharmaceutical Co., Ltd., Osaka, Japan), which is currently indicated for melanoma, non-small-cell lung cancer (NSCLC), bladder cancer, head and neck cancer, and Hodgkin's disease, has been set at ¥730 000 per 100 g, with the cost of treatment per patient estimated at ¥35 million per year. A Japanese government panel decided to cut the official price of nivolumab by 50% on the basis of social criticism in November 2016 that the drug was too expensive.[12]

The primary objective of our analysis was to investigate whether OS and PFS are affected by oncology drug prices. In addition, prices were compared between novel drugs and next-in-class drugs in terms of clinical benefits.

## 2 | METHODS

### 2.1 | Data collection

All oncology drugs, including cytotoxic drugs as well as targeting agents and ICI, that were approved by the Japan Pharmaceuticals and Medical Devices Agency (PMDA) on the basis of OS or PFS between April 2006 and December 2015 were included in the analysis. Clinical information on properties such as the prolongation of OS and PFS was obtained from the summary reports of approval for each drug in the PMDA homepage,[13] and actual OS and PFS data were obtained from the published original phase III pivotal studies, except for a comparative phase II study for trabectedin. The latest National Health Insurance Drug Price Standards were used to assess drug prices approved in Japan.[14]

### 2.2 | Data analysis

Relationship between drug prices and clinical outcomes were analyzed in two ways. First, the cost of a full course or 1 year of treatment was estimated on the basis of the latest National Health Insurance Drug Price Standards.[14] The relationship between cost and improvement in OS or PFS was then analyzed for each drug. We also compared the median price per year between drugs with novel mechanisms of action and next-in-class drugs (Table S1). The results were compared with findings previously reported in the USA.[15] Next, the drug costs were compared between experimental and control regimens in pivotal phase III studies. The costs required to prolong OS, PFS, or both, by 1 day, which was defined as the "cost index (CI)", were calculated as follows (Figure 1).

$$\Delta\text{PFS (days)} = [\text{median PFS (days) in experimental treatment arm}] - [\text{median PFS (days) in control treatment arm}].$$

$$\Delta\text{OS (days)} = [\text{median OS (days) in experimental treatment arm}] - [\text{median OS (days) in control treatment arm}].$$

The prices of all prescribed cancer drugs until disease progression in the experimental arm were defined as the prescribed drug price (PDP¥) as follows.

$$CI_{PFS}(¥) = PDP/\Delta PFS, CI_{OS}(¥) = PDP/\Delta OS$$

If a new drug was evaluated in combination with other drugs such as FOLFIRINOX (5-fluorouracil + levofolinate calcium + irinotecan + oxaliplatin) for pancreatic cancer, the total costs of all prescribed drugs were calculated.

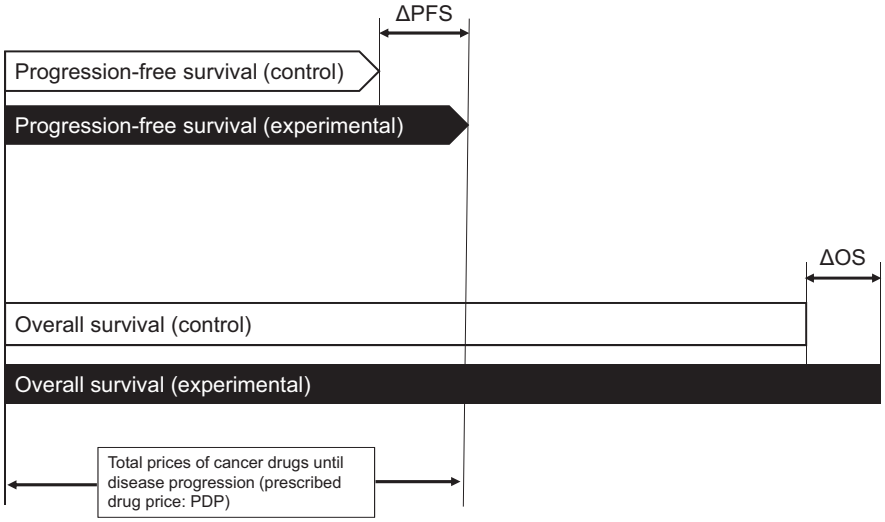


**FIGURE 1** Concept of a simple model for estimating costs required to prolong overall survival (OS) and progression-free survival (PFS) by 1 day

**TABLE 1** Cost required to prolong PFS or OS by 1 day

| Drug | Indication | $CI_{PFS}$ (¥) | Drug | Indication | $CI_{OS}$ (¥) |
|---|---|---|---|---|---|
| Axitinib | RCC | 114 679 | Azacitidine | MDS | 22 687 |
| Afatinib | NSCLC | 29 596 | Abiraterone | PrC | 21 423 |
| Alemtuzumab | CLL | 37 377 | Ipilimumab | MalMel | 66 372 |
| Everolimus | RCC | 50 772 | Eribulin | BC | 23 004 |
| Gefitinib | NSCLC | 19 928 | Erlotinib | NSCLC | 12 240 |
| Sunitinib | RCC | 37 856 | Enzalutamide | PrC | 16 283 |
| Trabectedin | STS | 22 594 | Cetuximab | CRC | 33 474 |
| Pazopanib | STS | 25 406 | Sorafenib | HCC | 37 868 |
| Panitumumab | CRC | 70 687 | Trastuzumab | GC | 24 427 |
| Panobinostat | MuMy | 101 450 | Temsirolimus | RCC | 25 824 |
| Fulvestrant | BC | 27 089 | Trastuzumab emtansine (T-DM1) | BC | 32 635 |
| Pertuzumab | BC | 70 468 | Trifluridine/tipiracil (TAS-102) | CRC | 8909 |
| Bortezomib | MuMy | 42 685 | Nivolumab[a] | NSCLC (Sq) | 110 202 |
| Pomalidomid | MuMy | 94 467 | Nivolumab[a] | NSCLC (Non-Sq) | 79 205 |
| Lapatinib | BC | 36 055 | Bevacizumab | CRC | 28 965 |
| Lenalidomide | MuMy | 67 364 | Vemurafenib | MalMel | 141 929 |
| Lenvatinib | TyC | 28 215 | Ramucirumab | GC | 56 901 |
| | | | Regorafenib | CRC | 21 325 |
| | | | Temozolomid | MalGli | 24 814 |
| | | | Gemcitabine | BC | 12 517 |
| | | | Pemetrexed | MalMeso | 39 441 |
| | | | Doxorubicin HCl liposome (Doxil®)[c] | OC | 120 580 |
| | | | Cabazitaxel | PrC | 23 361 |
| | | | Docetaxel | PrC | 12 581 |
| | | | Topotecan (Nogitecan) | UtCerv | 3950 |
| | | | Nanoparticle albumin-bound paclitaxel (Abraxane®)[d] | PC | 43 751 |
| | | | FOLFIRINOX[b] | PC | 12 659 |

BC, breast cancer; CI, cost index; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; MalGli, malignant glioma; MalMel, malignant melanoma; MalMeso, malignant mesothelioma; MDS, myelodysplastic syndromes; MuMy, multiple myeloma; Non-Sq, non-squamous cell carcinoma; NSCLC, non-small-cell lung cancer; OC, ovarian cancer; OS, overall survival; PC, pancreatic cancer; PFS, progression-free survival; PrC, prostate cancer; RCC, renal cell carcinoma; Sq, squamous cell carcinoma; STS, soft tissue sarcoma; TyC, thyroid cancer; UtCerv, uterine cervical cancer.

[a]Nivolumab is indicated for lung cancer on the basis of two pivotal studies.

[b]FOLFIRINOX regimen (5-fluorouracil, irinotecan, and oxaliplatin) is indicated for pancreatic cancer on the basis of the ACCORD 11 study.

[c]Janssen Pharmaceutical K.K., Tokyo, Japan

[d]Taiho Pharmaceutical Co., Ltd. Tokyo, Japan.

## 2.3 | Statistics

Linear regression analysis was carried out with the use of Statcel4 (OMS Publishing Inc., Tokyo, Japan) and Excel 2013 (Microsoft) software to ascertain the relationships between continuous variables. Mann-Whitney *U* test was used to assess the statistical significance of differences between groups. *P* values <0.05 were considered to indicate statistical significance.

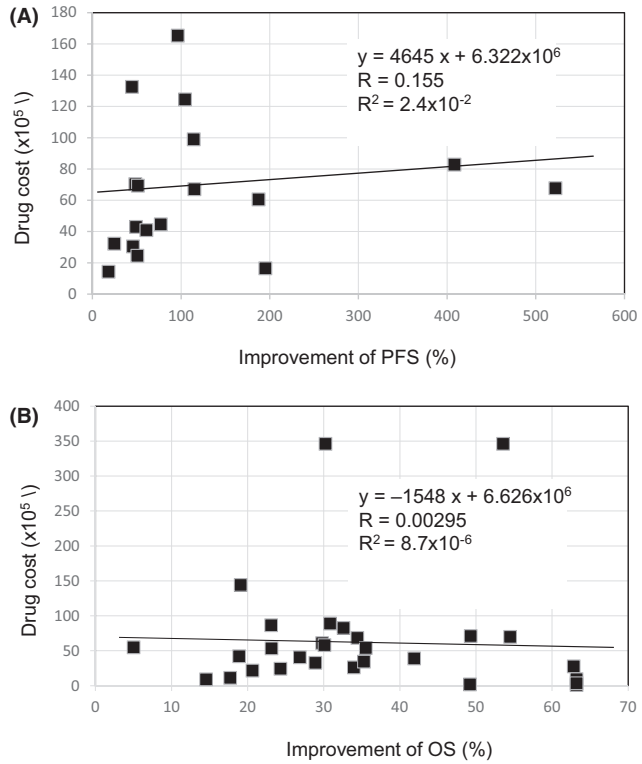


**FIGURE 2** Linear regression analysis of drug price vs. percentage improvement in (A) progression-free survival (PFS) and (B) overall survival (OS). Each point on the graphs represents one drug

## 3 | RESULTS

We studied 45 drugs approved for 70 indications: 17 were approved on the basis of PFS, and 28 were approved on the basis of OS (Table 1); 17 had novel mechanisms, and 28 were next-in-class (Table S1); 14 drugs had more than one indication. Relationships between the percentage improvement in PFS or OS and the cost of a full course or 1 year of treatment were compared. Drug cost was not significantly related to treatment outcomes in terms of PFS or OS (Figure 2). In addition, the median cost did not differ significantly between novel drugs (¥4 453 884) and next-in-class (¥5 635 247) drugs ($P = 0.39$). The cost to prolong PFS and OS for 1 day was compared on the basis of $CI_{PFS}$ and $CI_{OS}$. $CI_{PFS}$ and $CI_{OS}$ differed considerably among the drugs. The lowest $CI_{PFS}$ was ¥19 928 for gefitinib in epidermal growth factor receptor (*EGFR*)-mutated NSCLC and the highest $CI_{PFS}$ was ¥114 679 for axitinib in renal cell carcinoma, which was 5.75-fold more expensive than gefitinib. The lowest $CI_{OS}$ was ¥3950 for topotecan in ovarian cancer, and the highest $CI_{OS}$ was ¥141 929 for vemurafenib in malignant melanoma, which was 35.93-fold more expensive than the cost of topotecan required to prolong OS by 1 day (Table 1). Comparing $CI_{PFS}$ and $CI_{OS}$, $CI_{PFS}$ was higher than $CI_{OS}$ (Table 1 and Figure 3). The costs of antibody drugs required to prolong survival for 1 day tended to be the highest.

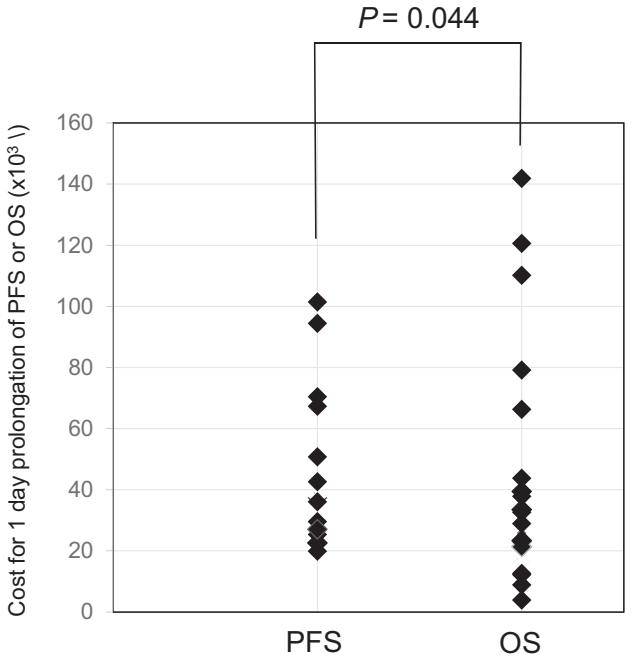


**FIGURE 3** Comparison of the costs required to prolong overall survival (OS) and progression-free survival (PFS) by 1 day

## 4 | DISCUSSION

Clinical benefits of anticancer agents in Japan have shifted from tumor shrinkage to prolongation of overall survival in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). In addition to chemotherapeutic agents, targeting agents and ICI have recently become more expensive. The Ministry of Health, Labour and Welfare (MHLW) published the drug price evaluation criteria in Japan.[16] According to the criteria for calculating drug prices, drugs with a new mechanism of action, drugs that are safer and more effective than similar drugs, and drugs for rare diseases can be priced higher.[16] However, how to decide the prices of new drugs, or how to evaluate "cost-effectiveness" of new drugs, especially expensive oncology drugs, has not been disclosed in Japan.

Since the launch of the ICI nivolumab on the Japanese market, the extremely high price of this drug created a debate on the cost-effectiveness of oncology drugs among patients, oncologists, and the media in Japan. Cost-effectiveness is now one of the most serious problems related to oncology societies worldwide.[9,10,17-19] Mailankody and Prasad reported that there was no significant relationship between cost and percentage improvement in endpoints such as PFS and OS.[15] First, we used the same approach to analyze the relationship between oncology drug prices and clinical endpoints. Our results were consistent with the analysis carried out in the USA, although correlation coefficients were much lower in Japan (PFS, $R^2 = 2.4 \times 10^{-2}$, $R = 0.155$; OS, $R^2 = 8.7 \times 10^{-6}$, $R = 0.00295$) than in the USA (PFS, $R^2 = 0.13167$;

OS, $R^2$ = 0.1649). In both countries, next-in-class drugs are not cheaper than the original drugs. In general, oncologists prescribe anticancer drugs until disease progression, and PFS and OS have been prolonged. In several reports, drug costs were calculated on the basis of the full course or 1 year of treatment.[15,17] However, PFS longer than 1 year is very rare in patients with most solid tumors. Previous studies may therefore have overestimated oncology drug costs.

Many approaches can be used to evaluate the cost-effectiveness of oncology drugs.[10,15,17-20] Next, we proposed a new formula for calculating CI, which indicates the cost of oncology drugs required to prolong PFS and OS by 1 day based on the median PFS. In our analysis, there were huge differences in drug costs required to prolong PFS as well as OS for 1 day. Of note, on comparing median $CI_{PFS}$ with median $CI_{OS}$, $CI_{PFS}$ was found to be higher than $CI_{OS}$. One of the possible explanations is that most of the new drugs approved by PFS belong to targeting agents, which have new mechanisms of action. In addition, decision for the prices of anticancer drugs in Japan may be influenced by the prices in foreign countries especially in the USA. Prolongation of PFS is only a surrogate endpoint for evaluating new oncology drugs as compared with the prolongation of OS, which is more robust and provides more direct evidence of oncology drug efficacy than PFS.[5,6,15] Mengato and Messori compared correlation between incremental cost and survival gain by a similar approach with us in four countries, including Italy, Scandinavia, Japan and the USA.[20] They reported a substantial association between incremental cost and incremental OS for Scandinavia, Japan and Italy. However, the authors accessed data by searching in Pub Med and Google Scholar without obtaining any regulatory information. In addition, they have only analyzed seven drugs that were approved in Japan. Although the authors calculated the relationship between gained overall survival and incremental cost, concluding good correlation in Japan, in this article, we could not find how to calculate the incremental cost in each country.

Approval of bevacizumab in metastatic breast cancer has been withdrawn by the Food and Drug Administration (FDA) in the USA because a pivotal phase III trial concluded that bevacizumab did not prolong OS in this indication.[21,22] In contrast, bevacizumab was approved in Japan at nearly the same time and on the basis of essentially the same data package as that submitted to the FDA in the USA. Many doctors are still prescribing bevacizumab to patients with metastatic breast cancer in Japan. The National Institute for Health and Care Excellence (NICE) in the UK has published a variety of guidelines based not only on clinical evidence, but also on cost-effectiveness.[23] They used quality-adjusted life year (QALYS), which is calculated by estimating the years of life remaining for a patient following a particular treatment or intervention, as a measure of cost-effectiveness. It is extremely important to analyze such cost-effectiveness. Our model of CI uses a simple formula for calculation, but it does not evaluate the quality of life. In addition, if data on median PFS or median OS are not available owing to excellent clinical activity, our model cannot be applied. Survival advantage by ICI is different from chemotherapeutic agents or targeted agents. In general, Kaplan-Meier curves of the control group move to the right by experimental drugs such as chemotherapeutic or targeted agents. However, it is difficult to find long-term survivors in most solid tumors by these agents. Important clinical benefit of ICI shows increasing long-term survivors.[3,4] Prolongation of median PFS or OS does not fully reflect the true clinical benefit of ICI. Similarly, if the risks of events such as recurrence or death are inconsistent over the course of time, our model does not work. Further modifications are necessary to establish standard approaches for evaluating and comparing the cost-effectiveness of oncology drugs on a worldwide basis.

In conclusion, the prices of oncology drugs should be decided on the basis of actual benefits to cancer patients, and the drug price evaluation process should be disclosed in Japan.

## CONFLICTS OF INTEREST

Yasutsuna Sasaki: Honoraria from Chugai Pharmaceutical and Taiho Pharmaceutical. All remaining authors declare no conflicts of interest.

## ORCID

*Yasutsuna Sasaki* http://orcid.org/0000-0002-6712-7116

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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