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A Study on the Description of Anticancer Drug Combination Therapy in the Package Insert in Japan

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Background: Approved anticancer drug combinations are classified into the following groups: broader than (broad label), the same as (same label), or smaller than (narrow label) the series of combination regimens investigated in clinical studies. The present research attempted to elucidate the characteristics of the broad/narrow label to clarify what types of combination regimens are given these labels. Methods: All anticancer drugs approved in Japan between April 2006 and March 2020 and their review reports were selected from the Pharmaceuticals and Medical Devices Agency (PMDA) website. The differences in the number of regimens in clinical trials given each label were investigated using Tukey's test. Multinomial logistic regression analysis was also conducted to examine the factors influencing each category. Results and Discussion: There were significant differences in the numbers of regimens among the labels. The factors that significantly contributed to labeling could not be identified. However, key features were identified. If there were multiple clinically comparable regimens and a clinical trial was conducted to evaluate the clinical benefit of adding new anticancer agents to one of the major regimens, there was a high probability of receiving a broad label. A narrow label may be granted if a regimen considered clinically comparable despite possessing a different mechanism of action does not exhibit clinical benefits in phase III studies. Conclusion: The present study revealed the PMDA stance for reviewing the clinical data of anticancer combination therapies submitted by sponsors in their totality to allow physicians to provide patient-centric, evidence-based, optimized cancer care to patients.

Key words Japan, package insert, oncology, regulatory science, clinical development, PMDA

INTRODUCTION

Drugs represent a major form of cancer treatments, consisting of cytotoxic anticancer agents, endocrine agents, molecular targeted drugs, and immune checkpoint inhibitors. Recent advances in molecular biology have elucidated the mechanisms by which anticancer drugs exert their antitumor effects, lead to cell death, and cause drug resistance. Pharmacotherapy is expected to evolve further concerning the treatment of cancers, and new therapeutic strategies are expected to be developed, permitting a shift from empirical administration to a personalized approach to medicine.[1)]

Currently, the effect of single anticancer agents in most tumors is limited. Combination therapy is used to achieve the maximal therapeutic effect. The objectives of combination therapy are to enhance the therapeutic effects of each anticancer drug, broaden the spectrum of anticancer activities in a variety of cancers, and avoid or delay the emergence of drug-resistant cells. The principles of combination regimens include the selection of drugs with proven efficacy against the target tumors, the avoidance of concomitant anticancer drugs that are cross-resistant because of shared mechanisms of action, and the selection of drugs with non-overlapping toxicity to maintain a higher dose intensity. In addition, each anticancer agent should be administered using its ideal dosing schedule, and the interval between anticancer agents should be minimized. Furthermore, careful consideration should be given to the interaction between concomitant anticancer agents. In summary, pharmacokinetic and pharmacodynamic interactions, including the order of administration, should be considered in combination therapy.[1)]

Based on recent advances in life sciences and various findings from clinical trials, immune checkpoint inhibitors have been successfully developed, and they are currently being positioned as established therapies. However, immune checkpoint inhibitors have therapeutic effects in only a limited proportion of patients. It has been reported that some cancer types respond strongly to immune checkpoint inhibitors (hot tumors), whereas others respond poorly (solid tumors) because of differences in the antitumor immune response in the tumor microenvironment.[2)] Therefore, it is difficult to cure cancers with a single immunotherapy.[2)] Recently, as the biology of the

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tumor microenvironment including the surrounding blood vessels, immune cells, fibroblasts, signaling molecules, and extracellular matrix has been clarified,[3–5] clinical trials are being conducted to investigate the efficacy and safety of combinations of immunotherapies or combinations of immunotherapies and existing chemotherapeutics.[6]

As combination therapy becomes a mainstay of cancer treatment, it is necessary to specify the regimen used in combination therapy in the package insert. Without such a provision, for example, concomitant drugs may be used without clinical trial evidence, which may lead to off-label use. In fact, the off-label use of anticancer drugs, particularly molecular targeted drugs, antiangiogenic drugs, and immune checkpoint inhibitors, has been reported to occur in France, which has a similar insurance system as Japan,[7] suggesting the same situation has arisen in Japan. Concomitant drug provisions are based on evidence from clinical trials in the "Dosage and Administration" section of the package insert.[8,9] In addition, to promote the optimal use of innovative drugs with novel mechanisms of action based on the latest scientific perspectives, guidelines are developed in parallel with the review of approval to indicate the requirements, perspectives, and considerations of patients and medical institutions for the use of such drugs.[10] However, the Dosage and Administration section of package inserts does not define combination therapies that have been evaluated for efficacy and safety in clinical trials as summarized in the Common Technical Document at the time of submission for approval. For example, a comparison of the dosage and administration of Avastin for colorectal cancer in the US and Japan shows revealed that only concomitant drugs that have been studied in clinical trials are permitted as approved combination (in this case, in combination of Avastin with intravenous 5-fluorouracil-, fluoropyrimidine/irinotecan-, or fluoropyrimidine/oxaliplatin-based chemotherapy) in the US,[11] whereas concomitant drugs are allowed to be used "in combination with other anticancer agents" and not limited to combination therapies used in clinical trials in Japan,[12] as shown in Fig. 1. A previous study examining the concomitant drug descriptions for anticancer drugs approved in Japan between April 2006 and March 2017 reported that the number of regimens included in the Common Technical Document may be related to the description in the package inserts.[13]

There are several reports on package inserts in Japan. One study examined the timing of package insert revision by categorizing the subject according to drug lag period.[14] A separate study compared the indications of reference labels among the US, Japan, and the European Union.[15] Another study compared package inserts among the US, the United Kingdom, China, South Korea, and Japan concerning information described in the drug–drug interaction section,[16] whereas one study compared pharmacokinetics information among China, Japan, and the US regarding anticancer drugs.[17] A study on the operational aspects of the Japanese package insert[18] and a proposal for improving the package insert based on previous studies[19] have also been reported.

However, no new studies have reviewed in detail the description of anticancer drug combination therapies in the package insert. As mentioned previously, one of the principles of a combination therapy regimen is the selection of drugs with validated efficacy for the target cancer. However, the description in the package inserts does not provide this information. Specifically, some patterns in cases in which multiple concomitant drugs have been evaluated in clinical trials have emerged. First, concomitant drugs are specified beyond the scope of the combinations evaluated in clinical trials. Second, some of the regimens included in clinical trials are specified as concomitant drugs. In the third pattern, the concomitant drugs evaluated in clinical trials are specified as they are. The aforementioned patterns are defined as "broad," "narrow," and "same" labels, respectively, as described in Fig. 2.

To satisfy the need to use anticancer drugs for certain indications that have not been approved in Japan, a committee has been established to expedite the approval of the indications of anticancer drugs needed for combination regimens.[20] The Japanese health insurance system does not cover off-label use even if clinical evidence supports the use of a particular drug. In this context, drugs can be awarded broad or narrow labels, prompting researches to elucidate the "threshold" of each label description focusing on the oncology agent combination therapy because the prescribing behavior of physicians is strictly defined by the label. However, no in-depth studies have investigated which drugs are classified into the three aforementioned patterns, and the characteristics of each pattern are unknown. These data represent important infor-

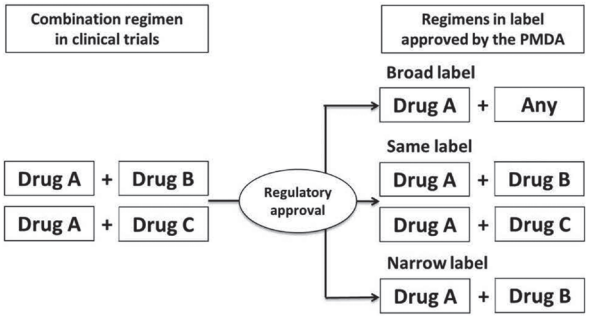

Fig. 2. Groups of the Approval Records: One Example

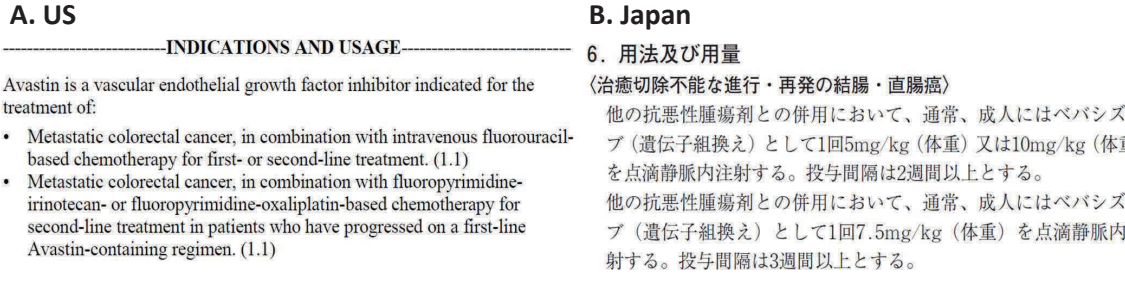

Fig. 1. Avastin® Package Inserts

mation about approved combination therapies that would also provide secure and consistent access to effective anticancer drug combination therapies for Japanese patients with cancer. In particular, it is extremely important to investigate the broad label category because this pattern does not necessarily have an unfavorable aspect given that physicians can prescribe multiple anticancer drugs that have not yet been approved in Japan based on the latest evidence, leading to patient-centered, evidence-based cancer care.

In this study, anticancer drugs approved in Japan between April 2006 and March 2020 were investigated under the condition that the drug was dosed in combination with other anticancer drugs and attempted to elucidate the characteristics of the broad and narrow labels, which is a worthy topic for future consideration in the approval of anticancer combination therapies in Japan.

MATERIALS AND METHODS

Database Used in the Present Study The study drugs were selected from the "List of Approved New Drugs" on the Pharmaceuticals and Medical Devices Agency (PMDA) website[21] for all anticancer agents approved in Japan between April 2006 and March 2020. In total, 186 approved anticancer drugs were selected as the target drugs, excluding those without clinical trial data in the Common Technical Document and those with public knowledge-based applications.

Among the target drugs, we examined the review reports of all drugs on the PMDA website and categorized drugs based on their approval as monotherapies or combination therapies. In this study, we compared the package insert of the drugs approved as adjunctive therapies with the review report and classified them as broad, narrow, or same labels.

A broad label was given to drugs in combination therapies for which the number of regimens that could be prescribed was larger than that of regimens included in the new drug application packages. A narrow label was given to drugs in combination therapies for which the number of regimens that could be prescribed was smaller than that of regimens included in the new drug application packages. A same label was given to drugs in combination therapies for which regimens that could be described were the same series of regimens included in the new drug application packages.

Statistical Analysis The number of regimens assessed in clinical trials included in the Common Technical Document for drugs that were reviewed by the PMDA to evaluate the contribution of each agent to the regimen was investigated, and differences in each category were examined using Tukey's test because this is considered to affect the label description of the combination therapy. The significance of differences between the values of each label category was defined as $p < 0.05$.

A multinomial logistic regression analysis was also conducted to examine the factors influencing each category. The objective variables were broad label (N = 16), narrow label (N = 41), and same label (N = 6), and the following binary variables were used as explanatory variables: type of cancer (solid vs. blood), approval characteristics (new molecular entity vs. indication expansion), company (global vs. Japanese), review category (priority review [yes vs. no], expedited review [yes vs. no], conditional approval [yes vs. no], SAKIGAKE Designation [yes vs. no], orphan drug designation [yes vs. no]). Although the regression analysis used in this study was an exploratory analysis, a certain level of scientific justification was granted because it was based on previous studies in the field of regulatory science focusing on anticancer drugs using logistic regression analysis.[22–25]

Multinomial logistic regression analysis was conducted. The logistic regression can model the probabilities for binary classification problems. When a response variable was categorical, the relationship between the logarithm of the odds and explanatory variables was modeled as follows:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x_1 + \cdots + \beta_i x_i,$$

where p, x, and β are the predicted probability, explanatory variable, and regression coefficient optimized by a maximum likelihood estimation, respectively. This logistic regression approach can be extended to a multiclass classification problem, and the group membership probabilities are given as a log-linear function of x for any class K, including the baseline category, as follows:

$$P(y = k|x) = \frac{exp\left(\beta_0^k + \beta_1^k x_1 + \cdots + \beta_i^k x_i\right)}{\sum_{j=1}^{K} exp\left(\beta_0^j + \beta_1^j x_1 + \cdots + \beta_i^j x_i\right)},$$

where K is the number of classes. New unknown data are classified into group k, in which the obtained probability is the largest.

In this study, a classification model that could discriminate the three label description types (broad, same, and narrow) was established. Multinomial logistic regression analyses were conducted to explore the factors that provided the clearest discrimination.

IRB/Committee Approval Statements This research does not contain any studies with human or animal subjects performed by any of the authors.

RESULTS

Of the 187 analyzed drugs, 63 drugs were listed as combination therapies, and 125 were listed as monotherapies, as shown in Table 1.

The regimen category of clinical trials for each approved therapy is shown in Table 2. Of the drugs examined as part of combination regimens in clinical trials, 16, 41, and 6 drugs were granted broad, same, and narrow labels for combination therapy approvals, respectively, and all monotherapy drug approvals were granted same labels.

The Tukey's test results revealed significant differences in the number of regimens included in the application for approval among the labels, namely 2.0, 1.1, and 3.7 regimens on average for the broad, same, and narrow labels, respectively, as shown in Fig. 3.

Multinomial logistic regression analysis was conducted on the basis of the variables as shown in Table 3, and the results are presented in Table 4. Trends could be confirmed for some variables, but no significant differences were noted.

Because an exploratory multinomial logistic regression analysis did not identify factors that significantly contributed to a broad (or narrow) label designation, the drug names and indications for which the respective labels were granted approval are shown in Table 5 for case analysis of individual drugs. Among 16 drugs granted broad labels, 12 approvals

Table 1. Characteristics of the Study Drugs

A. Approved therapies (all drugs of interest)

Variables	N
Approved therapies	
Monotherapy	125
Combination therapy	63
Type of cancer	
Solid	125
Blood	63
Approval characteristics	
New molecular entity	91
Indication expansion	97
Companies	
Global	106
Japanese	82
Review categories	
Priority review	28
Expedited review	4
Conditional approval	3
SAKIGAKE Designation	4
Orphan drug designation	94
Label categories	
Broad	16
Same	166
Narrow	6

B. Approved therapies (monotherapy)

Variables	N
Type of cancer	
Solid	86
Blood	39
Approval characteristics	
New molecular entity	70
Indication expansion	55
Companies	
Global	72
Japanese	53
Review categories	
Priority review	18
Expedited review	2
Conditional approval	3
SAKIGAKE Designation	4
Orphan drug designation	66
Label categories	
Broad	0
Same	125
Narrow	0

C. Approved therapies (combination therapy)

Variables	N
Type of cancer	
Solid	39
Blood	24
Approval characteristics	
New molecular entity	21
Indication expansion	42
Companies	
Global	34
Japanese	29
Review categories	
Priority review	10
Expedited review	2
Conditional approval	0
SAKIGAKE Designation	0
Orphan drug designation	28
Label categories	
Broad	16
Same	41
Narrow	6

were line extensions. Among six drugs granted narrow labels, four approvals were new molecule entities.

Table 2. Regimen Category of Clinical Trials for Each Approved Therapy

Approved therapies	Regimens in clinical trials		Total
	Monotherapy	Combination therapy	
Monotherapy	100	23*	123
Combination therapy	0	63**	63
Total	100	86	186

* Broad, 0; Same, 123; Narrow; 0.
** Broad, 16; Same, 41; Narrow, 6.

Table 3. Variables for Multinomial Logistic Regression Analysis

Variables	
Label categories	
Same	0
Broad	1
Narrow	2
Approval characteristics	
Indication expansion	0
New molecular entity	1
Type of cancer	
Blood	0
Solid	1
Companies	
Global	0
Japanese	1
Priority review	
No	0
Yes	1
Expedited review	
No	0
Yes	1
Orphan drug designation	
No	0
Yes	1

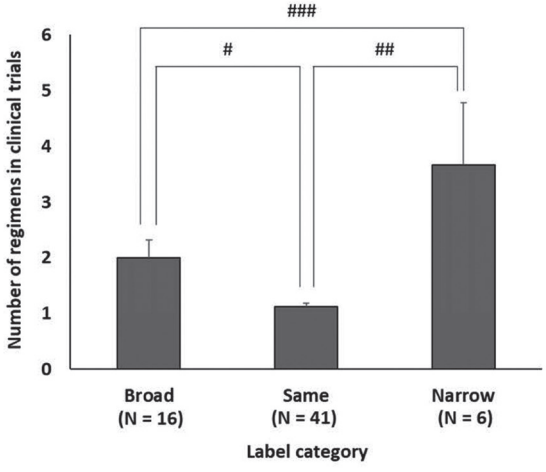

Fig. 3. Number of Regimens in Clinical Trials in Each Label Category

The significance of differences between the groups were determined using one-way ANOVA with Tukey's post hoc test. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$.

DISCUSSION

This present study classified anticancer drugs approved in Japan between April 2006 and March 2020 into three categories: broad, same, and narrow labels. Because the description in the package insert, especially the Dosage and Admin-

Table 4. Results of Multinomial Logistic Regression Analysis

	Partial regression coefficient	Standard error	*p*	Odds ratio	95% confidence interval	
					Lower limit	Upper limit
Broad label						
Approval characteristics	0.066	0.694	0.936	1.057	0.271	4.115
Company	−0.377	0.641	0.557	0.686	0.195	2.412
Type of cancer	−0.107	0.742	0.885	0.898	0.210	3.846
Priority review	0.277	0.970	0.775	1.320	0.197	8.833
Expedited review	−16.992	2005.920	0.993	0.000	0	-
Orphan drug designation	0.295	0.741	0.691	1.343	0.314	5.741
Narrow label						
Approval characteristics	−1.215	0.995	0.222	0.297	0.042	2.087
Company	1.381	1.197	0.248	3.980	0.381	41.546
Type of cancer	−0.346	1.468	0.814	0.707	0.040	12.561
Priority review	−0.285	1.131	0.801	0.752	0.082	6.906
Expedited review	−0.392	0.000	-	0.676	0.676	0.676
Orphan drug designation	1.514	1.464	0.301	4.546	0.258	80.097

Reference; Same Label.

Table 5. Drug Names and Indications

A. Broad Label

Drugs	Approvals
Atezolizumab	·Unresectable advanced or recurrent non-small cell lung cancer
Abemaciclib	·Advanced or metastatic hormone receptor-positive, HER2-negative breast cancer **
Bevacizumab	·Unresectable advanced or recurrent colorectal cancer *, **
	·Unresectable advanced or recurrent colorectal cancer *
	·Non-squamous non-small cell lung cancer
	·Ovarian cancer
	·Advanced or recurrent cervical cancer
Bortezomib	·Multiple myeloma *
	·Multiple myeloma *
	·Mantle cell lymphoma
Daratumumab	·Multiple myeloma
Fulvestrant	·Breast cancer
Mogamulizumab	·CCR4-positive adult T-cell leukemia/lymphoma
Palbociclib	·Unresectable or recurrent breast cancer **
Pertuzumab	·HER2-positive breast cancer **
Rituximab	·CD20-positive chronic lymphocytic leukemia

Approvals were granted for new molecular entities or line extensions.
* Two different approval records exist.
** New molecule entity
HER2, human epidermal growth factor receptor 2

B. Narrow Label

Drugs	Approvals
Aflibercept	·Unresectable advanced or recurrent colorectal cancer *
Bevacizumab	·Unresectable or recurrent breast cancer
Cabazitaxel	·Prostate cancer *
Lapatinib	·Unresectable or recurrent breast cancer with confirmed HER2 overexpression *
Panobinostat	·Relapsed or refractory multiple myeloma *
Ramucirumab	·Unresectable advanced or recurrent colorectal cancer

Approvals were granted for new molecular entities or line extensions.
* New molecule entity
HER2, human epidermal growth factor receptor 2

istration section, is considered to be based on the clinical trial results, the number of regimens submitted at the time of application for approval was initially investigated to identify potential differences in the number of drugs given each label. The inclusion of series of combination regimens with more than two drugs appears to be a reasonable strategy for obtaining approval for combination therapies without restriction in their use in combination with other anticancer drugs for reimbursement. However, more regimens were granted narrow labels than broad labels, necessitating further consideration. Considerations from this perspective will be discussed in detail in the subsequent narrative discussion based on the case analysis.

A multinomial logistic regression analysis based on previous studies was conducted to explore the factors that contributed to each label, and no significant differences were found for any of the variables, suggesting that the PMDA reviews clinical data in new drug applications on a case-by-case basis. However, the number of drugs in each category was small, and the number of variables considered was limited. For example, number of variables was smaller than the standard procedure considering the fact that the adequate number of events per variable was reported as more than 10.[26] Therefore, the case analyses of drugs given broad and narrow labels will be further discussed.

The following is a narrative discussion based on the description of the review report for each drug in each label.[21] The description of the viewpoints of the pharmaceutical companies or PMDA concerning the results of each clinical trial in the review report was mainly discussed referring to the Japanese clinical practice guideline for each cancer type. First, drugs granted broad label were discussed, after which drugs with narrow labels were reviewed. The insights obtained from these narrative discussions have been summarized.

Broad Label Atezolizumab is an antibody medicine approved for the treatment of unresectable advanced or recurrent non-small cell lung cancer. Initially, the drug was approved for use in combination with carboplatin, paclitaxel, and bevacizumab; however, the restrictions on its use in combination were lifted after the drug was demonstrated to be effective in combination with multiple chemotherapies, including platinum anticancer drugs. Although it has a broad label on the package insert, it can be considered to have a same label because the details of the regimen are specified in the Optimal Clinical Use Guidelines, which provide detailed information on the various regimens and specify the most appropriate regimens among the treatment options. This is necessary because several of combination therapies, including platinum anticancer agents, are recommended for the treatment of lung cancer.[27]

Abemaciclib is approved for the treatment of unresectable

or recurrent hormone receptor-positive, HER2-negative breast cancer. This is an example of a broader approval of an endocrine therapy beyond the regimen investigated in a clinical trial. The review was conducted according to the sponsor's list of several drugs that were not concomitantly used with abemaciclib but were considered comparable to the regimens evaluated in clinical trials. It was considered that other endocrine therapies may also be effective because of the mechanism of action of abemaciclib. As a result, the PMDA concluded that the only endocrine therapies that exhibited clinical benefit in combination with abemaciclib were fulvestrant, letrozole, or anastrozole, as investigated in clinical trials, and no clinical trial results demonstrating the clinical benefit of abemaciclib in combination with other endocrine therapies have been reported. Therefore, when administering abemaciclib, it is important to understand the concomitant drugs evaluated in phase III studies and select an appropriate endocrine therapy for combination use. Endocrine treatment is considered a standard choice for patients with estrogen-receptor positive cancers, and several therapeutic regimens are used in patients with breast cancer.[28] Given the accumulation of significant amounts of clinical data, a clinical trial evaluating the combination of abemaciclib with a typical regimen would likely establish a broad label for its combination use with endocrine therapy. A similar discussion occurred for palbociclib, and a broad label was awarded.

Bevacizumab is approved for the treatment of unresectable advanced or recurrent colorectal cancer, unresectable advanced or recurrent non-small cell lung cancer excluding squamous cell carcinoma, ovarian cancer, and advanced or recurrent cervical cancer, all within the scope of its broad label. In the case of colorectal cancer, the PMDA gave the drug a broad label in response to the sponsors' opinion that a regimen should be selected by comprehensively considering its safety profile and the patient's condition as investigated in clinical trials. The mainstay of treatment of colorectal cancer is the combination of multiple anticancer drugs and molecular targeted therapies, and treatment will be continued or changed based on the effects and general condition of the patient.[29] Based on these conditions, a broad label may have been set to allow investigators the choice of therapies for concomitant use. In the case of non-small cell lung cancer, the sponsor argued that the results could be extrapolated to other regimens with comparable efficacy as those reviewed in clinical trials. The PMDA awarded a broad label, stressing that although there is no need to categorically restrict the use of combinations of chemotherapy with other platinum-based anticancer agents, careful attention should be paid to efficacy and safety profiles. This is similar to the situation for atezolizumab. In the case of ovarian cancer, a broad label was given, but it was stressed that this drug should be initiated in combination with carboplatin and paclitaxel, which is considered the standard of care for ovarian cancer[30] and the only combination regimen evaluated in clinical trials. It can be said that this is not actually a broad label. In the case of cervical cancer, a broad label was set with the description that bevacizumab should be initiated in combination with other anticancer agents, including paclitaxel. This is because two regimens that both include paclitaxel are considered the standards of care.[31] In this context, the current label allows physicians to select the optimal regimen between them.

Bortezomib has been approved for the treatment of multiple myeloma and mantle cell lymphoma. In the case of multiple myeloma, the PMDA granted the treatment a broad label based on the opinion that a regimen should be selected on the basis of its safety profile in clinical trials and the patient's condition according to clinical practice guidelines.[32),33] In the case of mantle cell lymphoma, a broad label was also set in the same context. Concerning daratumumab, the same discussion is applied for multiple myeloma.

Fulvestrant has been authorized for the treatment of breast cancer. A clinical benefit is expected only when palbociclib and fulvestrant are concomitantly administered according to the results of clinical trials. Therefore, the PMDA stressed that caution should be exercised in the package insert. Then, concomitant drugs are broadly defined as CDK4/6 inhibitors not limited to palbociclib. The details supporting this decision are not mentioned in the review report.

Mogamulizumab is approved for the treatment of CCR4-positive adult T-cell leukemia/lymphoma, and cancer chemotherapy, including mogamulizumab, has a wide range of concomitant chemotherapy options.[34] The choice should be based on the patient's condition and history of chemotherapy, as mentioned in the clinical outcomes section, further stressing that concomitant chemotherapy should be selected on the basis of clinical trial results.

Pertuzumab is an antibody drug approved for the treatment of unresectable or recurrent breast cancer. A broad label was set with the description that anticancer agents other than trastuzumab for concomitant use with pertuzumab are selected on the basis of the description in the package insert.

Rituximab is approved for the treatment of CD20-positive chronic lymphocytic leukemia. The type of concomitant anticancer agent is described in the package insert, and a broad label was assigned to its concomitant use with a reminder that combination regimens should be selected after careful consideration of the description in the package insert and the latest treatment guidelines.[35]

The inductive derivations from this series of case analyses are summarized. In the case of endocrine therapy in breast cancer and platinum-based combination therapy in lung cancer, multiple regimens are equally effective, and they should be selected by physicians. If a clinical trial is conducted to evaluate the clinical benefit of adding new anticancer agents to one of the major regimens, then there is a high probability that a broad label will be awarded. This deduction is consistent with the smaller number of regimens granted broad labels than given narrow labels.

Narrow Label Aflibercept is indicated for use in combination with FOLFIRI (fluorouracil + levofolinate + irinotecan) as a second-line treatment for patients with advanced or recurrent colorectal cancer that progresses during or after oxaliplatin treatment. The application included two regimens, namely in combination with S-1 and with FOLFIRI, but because the former was evaluated in a phase I study and the latter was examined in a phase III study, it is reasonable to conclude that concomitant use with S-1 alone is not allowed. Therefore, this can be essentially called a same label.

Bevacizumab is approved for the treatment of unresectable or recurrent breast cancer. The application included four regimens: 1. bevacizumab plus paclitaxel, 2. bevacizumab plus taxane antineoplastic agents, 3. chemotherapy including bevacizumab plus anthracycline antineoplastic agents, and 4. bevacizumab plus capecitabine. According to the review report,

the PMDA determined that "the risk-benefit balance of bevacizumab was favorable and clinically meaningful only in combination with bevacizumab and paclitaxel." Therefore, the dosage and administration of bevacizumab was defined as follows: "In combination with paclitaxel, bevacizumab is generally administered to adults at a dose of 10 mg/kg (body weight) by intravenous infusion. The dosing interval should be at least two weeks. In this case, it is appropriate to set it as follows." In addition, the PMDA mentioned in its review report that the clinical efficacy results were inconsistent among the three submitted studies, differences in the magnitude of the benefit of this drug were noted between studies with different combinations of anticancer agents, and the short follow-up period did not provide sufficient data for evaluation. This indicates that even in cancers for which multiple regimens are accepted as the standards of care or even if the results of clinical trials of multiple regimens are included, regimens with immature data or no clear clinical significance are not accepted as combination treatments. The inclusion of multiple difficult-to-interpret trial results only because the clinical benefit of adding a new drug to existing regimens has been confirmed in clinical trials may reduce the quality of the body of evidence and limit the number of regimens that can be used in combination.

Cabazitaxel is indicated for use in combination with prednisolone for the treatment of prostate cancer. The application included two regimens: concomitant use with prednisolone and concomitant use with capecitabine; however, because the former regimen was examined in phase III studies and the latter regimen was examined in phase I/II studies, it is reasonable to conclude that concomitant use with capecitabine is not permitted. Although abiraterone, enzalutamide, and cabazitaxel are possible secondary treatment options,[36] none of them is used in combination with other anticancer agents, and the current label is considered reasonable.

Lapatinib is approved in combination with capecitabine for the treatment of unresectable or recurrent breast cancer in patients with confirmed HER2 overexpression. The application included a multi-dose capecitabine combination regimen; however, the dosage and administration discussed in the Phase III study were defined. In addition, the review report stated, "Given the limited clinical trial results in Japanese patients, it is unavoidable to indicate the concomitant use of capecitabine in the defined dosage with lapatinib." However, if limited to concomitant use with capecitabine, it would be expected that the use of this combination in medical practice would be difficult when new knowledge is gained about concomitant use with antineoplastic agents other than capecitabine. Physicians with sufficient knowledge and experience in cancer chemotherapy are not likely to administer chemotherapy concomitantly with anticancer agents other than capecitabine at this time, but it is also important to provide appropriate information and reminders that concomitant use is recommended only with capecitabine. It is important to note that new information about concomitant use with antineoplastic agents other than capecitabine may make such concomitant therapy difficult to implement in medical practice.

Panobinostat is indicated in combination with bortezomib and dexamethasone for the treatment of relapsed or refractory multiple myeloma. At the time of the application for approval of this drug, concomitant regimens with multiple drugs, including bortezomib and dexamethasone, were included. However, only bortezomib and dexamethasone were evaluated in the pivotal study. Therefore, it is reasonable to limit the drugs that can be used in combination with panobinostat to bortezomib and dexamethasone.

Ramucirumab is indicated in combination with FOLFIRI for the treatment of advanced or recurrent colorectal cancer that is not curatively resectable. At the time of the application, concomitant therapy with FOLFIRI and FOLFOX (fluorouracil, folinic acid, and oxaliplatin) were included. However, concomitant therapy with FOLFIRI was the regimen evaluated in the pivotal study. Therefore, it is reasonable to limit the number of drugs that can be used in combination with ramucirumab to FOLFIRI.

From the case analysis focusing on narrow labels, we can identify some considerations about the inductively inferred information in the case of broad labels. First, the combination regimen will be limited if it is not demonstrated to exhibit clinical benefits in phase III studies even if more than one regimen is included, as noted for bevacizumab. The inclusion of multiple regimens in a clinical trial submitted with an application for approval, rather than narrowing the application to only a representative regimen, could lead to a narrow label. Conversely, in terms of identifying the optimal combination regimen, the inclusion of multiple regimens is scientifically and ethically reasonable. Second, even if there are regimens that are considered clinically comparable, some combination regimens are evaluated on the basis of actual clinical data if the mechanisms of action of the drugs included in the regimen are completely different. In such cases, it is necessary to include all of the regimens in the phase III study. Third, as noted for bevacizumab,-although the decision was made to grant a narrow label, the concomitant use of anticancer drugs should be based on the most up-to-date evidence at the time of the treatment by physicians.

In both cases, it would be desirable to have early-phase Japanese data before initiating a phase III trial of combination therapy. This was clearly described in the lapatinib review report, which found that the clinical trial of lapatinib in combination with capecitabine in Japanese patients was initiated after the new drug application for lapatinib was filed and that the new drug application was inappropriate under the circumstances in which the application was filed because the points made by the PMDA prior to the submission were not addressed. As demonstrated in the case analysis, case-by-case discussion is more important in the development of combination therapy than in the development of monotherapy. Japan has a system that enables access to innovative drugs similarly as the US and Europe,[37] and it is reported that PMDA consultation can shorten the review period.[38] It is important to seek advice from the PMDA at an early stage in the development process regarding the clinical position of any combination therapy under development and the description to be given in the package insert accordingly. In this context, the findings of this study on broad and narrow labels will contribute to the discussion with the PMDA and the planning of clinical development strategies. The label description affects the prescribing behavior of physicians. The present study revealed the PMDA's stance for reviewing the clinical data package of anticancer combination therapy submitted by sponsors in its totality so that physicians can provide patient-centric, evidence-based, optimized cancer care to patients.

The present study had the following limitations. The first is that the sample size was small. Therefore, continuous case analysis should be conducted to obtain more reliable findings. When considering the combination regimen, both the evaluation and reference documents described in the review report were analyzed in the current study. However, the analysis should also be conducted if only the evaluation documents were included or if only the pivotal study in the evaluation documents, in which overall survival or progression-free survival was set as the primary endpoint, was included. Predictive factors represent one of the important things to consider in this regard. It appears that other than those discussed in this study are relevant, and the findings of other studies need to be reviewed to identify these factors. Although the aforementioned limitations and development potential were acknowledged in the present study, the study was considered important because it provided the first findings concerning the description in package inserts, specifically for anticancer combination therapy, which should prompt additional research.

Conclusions The present study revealed the PMDA's stance for reviewing the clinical data package of anticancer combination therapies submitted by sponsors in its totality so that physicians can provide patient-centric, evidence-based, optimized cancer care to patients.

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