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Effects of Low-Dose Ipilimumab Formulation on the Prescription Volume and Drug Costs in Japan

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Background: Ipilimumab, a monoclonal antibody that targets cytotoxic T-lymphocyte antigen-4 (CTLA-4), is effective against malignant tumors, including non-small-cell lung cancer. In Japan, ipilimumab was launched in 2015 with only a 50-mg formulation, followed by a 20-mg formulation in November 2021. However, its effects on clinical practice remain unclear. This study evaluated changes in ipilimumab prescription patterns and drug costs following the introduction of the 20-mg formulation. Methods: Clinical data were analyzed using the MDV analyzer® (Medical Data Vision Co., Ltd.). The study population included patients who received ipilimumab between November 2020 and October 2023. The investigated parameters included the number of patients, number of prescriptions, prescribed dose (potency), drug costs, and prescribed formulations. Results: Data from 245 medical institutions included 4,366 patients and 13,805 prescriptions. The prescription rate of the 20-mg formulation increased over 12 months after introduction and stabilized at approximately 40% in the following year. The average prescribed dose per prescription decreased from the 80-mg range before the introduction to the 70-mg range 12 months after the introduction. The average drug cost per prescription decreased from the 800,000-yen range to the 600,000-yen range. Conclusion: The addition of the 20-mg formulation increased its usage and reduced the prescribed dose and drug costs. This reduction was likely due to decreased drug waste. These findings suggest that the introduction of low-dose formulations can contribute to cost savings in clinical practice.

Key words ipilimumab, low-dose standard, drug cost, medical economics

INTRODUCTION

Cancer treatment in Japan has significantly progressed with the advent of molecularly targeted therapies and immune checkpoint inhibitors. However, these drugs are highly expensive, leading to increased drug costs.[1,2] The dosage of many antineoplastic agents is determined based on the patient's body surface area or weight. When the prescribed dosage does not align with the available vial sizes, a leftover drug solution may be generated.[3,4] Under Japan's healthcare system, even if the residual drug is discarded, its cost can still be reimbursed, contributing to rising drug expenditures. Therefore, reducing drug waste by minimizing residuals is crucial. One proposed approach to achieving this is to reassess pharmaceutical packaging and vial sizes.[3,5-6]

Ipilimumab is an antineoplastic agent classified as a human monoclonal antibody that targets human cytotoxic T-lymphocyte antigen-4 (CTLA-4). It was first launched in Japan in August 2015. As of May 2022, it has been approved for the treatment of unresectable malignant melanoma, unresectable or metastatic renal cell carcinoma, unresectable advanced or recurrent colorectal cancer with high-frequency microsatellite instability (MSI-High) that has progressed after cancer chemotherapy, unresectable advanced or recurrent non-small-cell lung cancer (NSCLC), unresectable advanced or recurrent malignant pleural mesothelioma, and unresectable advanced or recurrent esophageal cancer. The dosage per administration is based on body weight. For unresectable malignant melanoma, the recommended dose is 3 mg/kg, whereas, for all other approved indications, the dosage is 1 mg/kg. In cases of adverse reactions, treatment postponement or discontinuation is recommended because no dose reduction guidelines exist.

During its initial launch, ipilimumab was available only in a 50 mg formulation. However, in November 2021, a 20 mg formulation was introduced. The 20 mg formulation contains the same drug solution as the 50 mg formulation but is not approved for use in the United States or Europe. Before the introduction of the 20-mg formulation, the total drug amount prepared during compounding had to be in 50-mg increments, often resulting in leftover drug. However, after the addition of

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the 20-mg formulation, the use of 20- and 50-mg vials allowed for drug preparation in 10-mg increments. Theoretically, this change reduces the amount of residual drugs, potentially decreasing both the prescribed drug amount (including waste) and overall drug costs.

Previous studies investigating the effects of vial size revisions on drug costs have estimated the effects based on administered doses in real-world clinical settings.[3,5-6] However, no study has examined the actual effects of vial size revisions on prescription volume and drug costs in clinical practice. Furthermore, at the time of this study, the 20-mg formulation of ipilimumab had not been approved in the United States or Europe, and information on this formulation remains limited worldwide. In this study, changes in prescription volume and drug costs following the addition of a low-dose formulation of ipilimumab were analyzed using real-world clinical data from multiple healthcare institutions in Japan, obtained from the MDV analyzer® (Medical Data Vision Co., Ltd.).

METHODS

Study Design In this retrospective study, clinical data were analyzed using the MDV analyzer®, a web-based service provided by Medical Data Vision Co., Ltd. for analyzing healthcare databases in Japan. The MDV analyzer® is a free version of a healthcare database analysis platform that includes anonymized inpatient and outpatient claims (receipt) and diagnosis procedure combination data. These data were collected from medical institutions across Japan that consented to the secondary use of data. The anonymization process was performed at the medical institutions using dedicated tools before data registration. The database allows the analysis of various clinical data from April 2010 onward. As of November 2024, the MDV analyzer® contains clinical data from 530 medical institutions, with a cumulative total of 48.95 million patients, including deceased patients. By specifying the target drugs and study period in the MDV analyzer®, researchers can extract the number of patients, number of prescriptions, and other relevant data.

Study Period The study period spanned 36 months, from November 2020 to October 2023, covering 12 months before and 24 months after the introduction of the 20-mg formulation of ipilimumab.

Study Population The study population was limited to medical institutions that, as of June 2024, had continuously provided clinical data to Medical Data Vision Co., Ltd. throughout the period from November 2020 to October 2023. The eligibility criteria were as follows: patients who received ipilimumab at any of the participating institutions during the study period. Duplicate patient counts were avoided when the same patient visited the same institution or multiple departments within that institution. However, if the same patient received treatment at different institutions that contributed data to Medical Data Vision Co., Ltd., they were counted as separate patients.

Study Variables The following variables were analyzed: number of medical institutions, number of patients, number of prescriptions, prescribed vial sizes, prescribed dose (potency), drug costs, and medical departments involved. The target drugs and study period were specified in the MDV analyzer®, and the trends in these variables were examined every three months. The MDV analyzer® is designed to allow analysis by prescribing medical department; therefore, for the top 10 departments with the highest number of prescriptions, these variables were further analyzed separately by department. Regarding drug costs, both the actual claimed drug costs and drug costs adjusted to the April 2022 drug prices for the entire study period were calculated. All results were based on actual claims data. If residual drug volumes were included in the claims, they were also reflected in the prescribed dose and drug cost calculations. The definition of prescription vial sizes was categorized into three groups based on the claims data. If only 20-mg vials were prescribed on the claim date, the prescription was classified as "20-mg vial only." If only 50-mg vials were prescribed, it was classified as "50-mg vial only." If both 20- and 50-mg vials were prescribed together, the prescription was categorized as "combination of 20- and 50-mg vials." Regarding drug pricing, the price per 20-mg vial was 200,703 yen from November 2021 to March 2022 and 170,598 yen from April 2022 to October 2023. The price per 50-mg vial was 493,621 yen from November 2021 to March 2022 and 419,578 yen from April 2022 to October 2023.

Statistical Analysis All study variables were evaluated using descriptive statistical methods.

RESULTS

During the study period, 410 medical institutions provided clinical data to Medical Data Vision Co., Ltd. Among these institutions, 245 had records of prescribing ipilimumab. The study included 4,366 unique patients with 13,805 prescriptions. Figure 1 presents the time-series trends of patient numbers and prescription counts, and Figure 2 presents the trends in prescribed vial sizes and the proportion of 20-mg vial prescriptions. Figure 3 presents the time-series trends in prescribed dose (potency) and drug costs. Following the introduction of the 20-mg formulation, the prescription rate increased over time and eventually stabilized at approximately 40%. The average prescribed dose per prescription was in the 80-mg range before the introduction of the 20-mg formulation; however, it gradually decreased over time, stabilizing in the 70-mg range. Similarly, the average drug cost per prescription was in the 800,000-yen range before the introduction of the 20-mg formulation; however, it decreased over time, eventually stabilizing in the 600,000-yen range.

Table 1 presents the time-series trends of patient numbers, prescription counts, proportion of 20-mg vial prescriptions, prescribed dose (potency), and drug costs for the top 10 medical departments with the highest prescription counts. Throughout the study period, the department with the highest number of patients and prescriptions was respiratory medicine. The proportion of 20-mg vial prescriptions varied according to department, with dermatology having the lowest proportion after the introduction of the 20-mg formulation. Regarding the average prescribed dose (potency), dermatology had the highest average dose during the study period. Although many medical departments exhibited a decrease in the average prescribed dose (potency) after the introduction of the 20-mg formulation, dermatology exhibited little fluctuation. Regarding the average drug cost per prescription, dermatology had the highest costs throughout the study period. However, after the introduction of the 20-mg formulation, the average drug cost was lower across all medical departments.

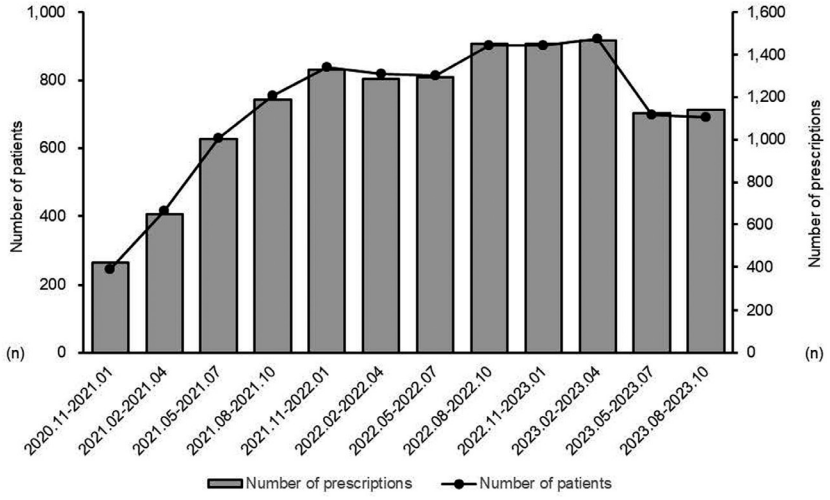

Fig. 1. Temporal Trends in the Number of Patients and Prescriptions.

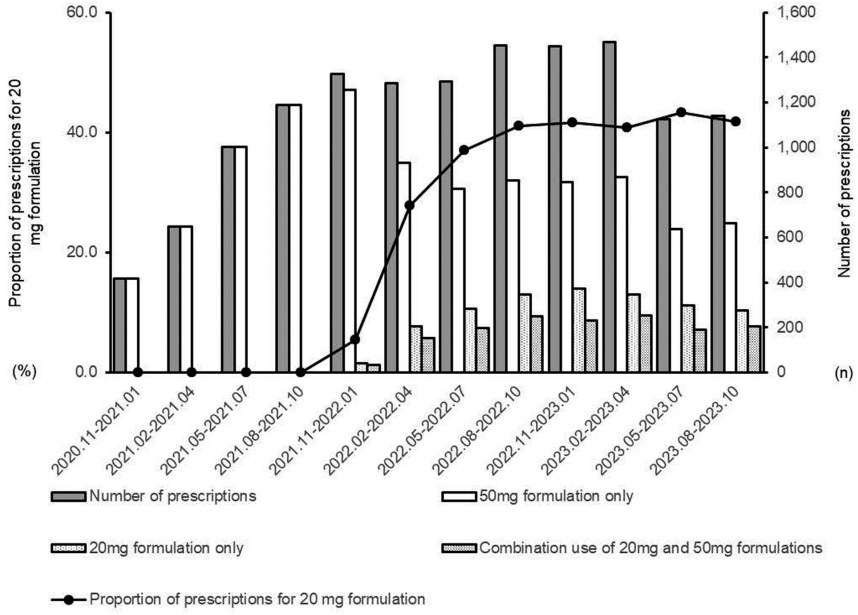

Fig. 2. Temporal Trends in the Number of Prescriptions for Each Formulation and the Proportion of 20-mg Formulation Prescriptions.

DISCUSSION

In this study, the clinical data provided by Medical Data Vision Co., Ltd. were analyzed to investigate the effects of the introduction of a low-dose ipilimumab formulation in real-world clinical practice in Japan. Following the introduction of the 20-mg formulation, its prescription proportion increased over time, whereas the average prescribed dose (potency) and average drug costs gradually decreased. These findings suggest that the introduction of the 20-mg formulation reduced the prescribed dose (potency) and drug costs in actual clinical settings. To the best of our knowledge, this is the first study to examine the effects of the introduction of a low-dose ipilimumab formulation on prescription volume and drug costs across multiple medical institutions in real-world practice.

The number of patients and prescriptions gradually decreased over time, starting in November 2020. Regarding department-specific trends, except for the first three months of the study period, respiratory medicine had the highest number of patients and prescriptions. When combined with other respiratory-related departments, such as thoracic surgery and pulmonology, these accounted for approximately half of all cases. The high proportion of prescriptions in respiratory-related departments suggests that ipilimumab was primarily prescribed for unresectable advanced or recurrent NSCLC, which was approved as an indication in Japan in November 2020. In contrast, ipilimumab has been approved for the treatment of unresectable malignant melanoma since August 2015, and dermatology departments are expected to be the primary prescribers of this indication. However, the number of

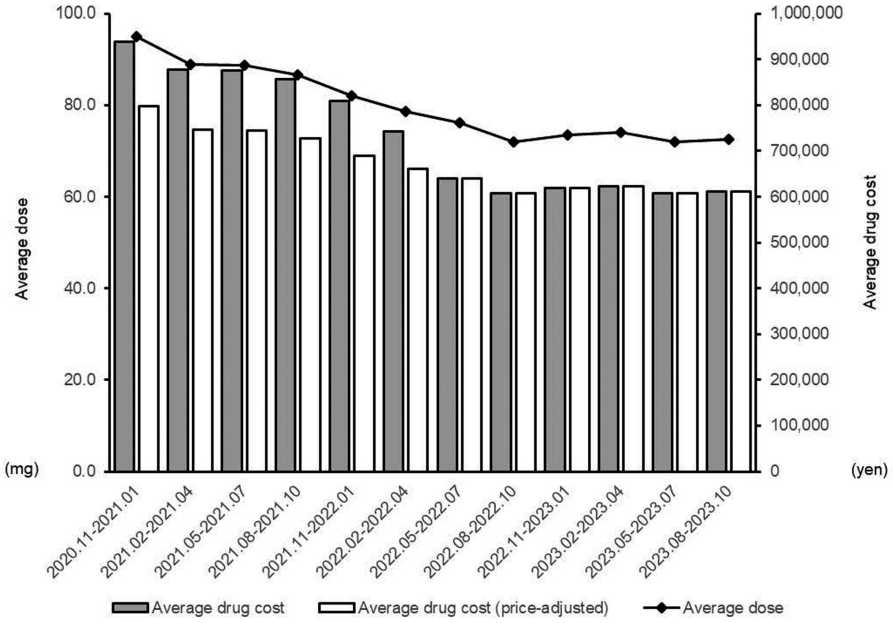

Fig. 3. Temporal Trends in the Average Dosage per Prescription and the Average Drug Costs.

patients and prescriptions in dermatology remained relatively stable throughout the study period. Therefore, these findings may have been influenced by the approval status and timing of additional indications, with a particularly strong impact from respiratory-related departments.

The proportion of prescriptions using the 20-mg formulation gradually increased after its introduction and ultimately stabilized at approximately 40%. Furthermore, the prescribed dose (potency) exhibited a downward trend from November 2020 onward, with a further decrease observed after the introduction of the 20-mg formulation in November 2021, eventually stabilizing in the low 70-mg range. Similarly, the average drug cost per prescription also decreased from November 2020, with a further decrease observed after the introduction of the 20-mg formulation in November 2021, ultimately stabilizing in the low 600,000-yen range. Before the introduction of the 20-mg formulation, the total drug volume was adjusted in 50-mg increments. However, with the introduction of the 20-mg formulation, adjustments in 10-mg increments became possible. For instance, when a dose of 70 mg was required, two vials of the 50-mg formulation (totaling 100 mg) were necessary before the introduction of the 20-mg formulation, resulting in 30 mg of leftover drug solution. In contrast, after the introduction of the 20-mg formulation, the combination of one vial of the 50-mg formulation with one vial of the 20-mg formulation made it possible to achieve exactly 70 mg, eliminating any leftover drug solution. In the Japanese healthcare system, if the leftover drug solution is excluded in the reimbursement claim, the medical institution is liable to incur the cost burden. Because many institutions do not implement vial-sharing practices, it is presumed that the cost of the leftover drug solution is typically included in reimbursement claims from a financial perspective. The study findings suggest that approximately 40% of all prescriptions in Japan required the 20-mg formulation. Moreover, the introduction of the 20-mg formulation likely reduced the total prescribed drug volume (potency), including any leftover drug solution. In addition, there were no new indications approved or existing indications withdrawn for the 20-mg formulation during the period from June 2022 to May 2025. Because trends in the number of patients and prescriptions are presumed to be significantly affected by the approval status of indications, it was inferred that the proportion of prescriptions using the 20-mg formulation was unlikely to fluctuate greatly during this period. In June 2025, however, an additional indication for unresectable hepatocellular carcinoma was approved. This is expected to increase the number of patients and prescriptions in the field of gastroenterology, and as a result, the proportion of prescriptions for the 20-mg formulation may fluctuate in the future. Furthermore, in the present study, the specific reasons why the proportion of prescriptions for the 20-mg formulation remained around 40% could not be investigated. Therefore, further research will be needed to clarify this point.

Regarding drug costs, as of April 2022, the 20-mg formulation had a higher price per mg than the other formulations. However, when administering a potency of 40 mg, prescribing one vial of the 50-mg formulation and including the cost of the 10-mg leftover solution in the claim was more expensive than prescribing two vials of the 20-mg formulation, which eliminated the leftover solution. Therefore, minimizing leftover solution by prescribing the 20-mg formulation is particularly important for ipilimumab. Based on this, the introduction of the 20-mg formulation may have reduced the prescribed drug potency, including the leftover solution, and decreased the average drug cost per prescription. International reports have suggested that the introduction of a 10-mg formulation, in addition to the existing 50- and 200-mg formulations (the latter is not available in Japan), can further reduce the leftover solution and consequently lower drug costs. Similar findings have been reported for other drugs, in which the addition of low-dose formulations was associated with cost savings. Although the 20-mg formulation introduced in Japan

Table 1. Temporal Trends According to Medical Department

1-1 Temporal Trends in the Number of Patients, Number of Prescriptions, and the Proportion of 20-mg Formulations according to Medical Department

	2020.11-2021.01	2021.02-2021.04	2021.05-2021.07	2021.08-2021.10	2021.11-2022.01	2022.02-2022.04	2022.05-2022.07	2022.08-2022.10	2022.11-2023.01	2023.02-2023.04	2023.05-2023.07	2023.08-2023.10
Number of patients												
Respiratory Medicine	38	152	242	331	351	347	313	339	318	337	226	197
Urology	115	109	100	97	94	86	80	75	69	69	58	63
Internal Medicine	14	28	50	76	105	107	107	108	96	94	64	61
Thoracic Surgery	6	17	52	79	95	110	99	97	107	96	77	62
Pulmonology	8	29	73	77	104	90	88	87	90	80	54	50
Surgery	9	12	23	22	25	19	25	63	61	66	65	87
Oncology	20	25	36	30	27	26	41	38	39	35	28	37
Dermatology	25	21	31	22	16	18	27	23	25	20	15	25
Gastroenterology	2	4	5	3	3	3	14	31	46	61	55	54
Gastrointestinal Surgery	2	3	2	2	4	1	5	19	32	39	32	32
Number of prescriptions												
Respiratory Medicine	42	201	347	482	539	514	469	526	513	508	359	321
Urology	225	201	206	187	181	170	162	156	137	140	114	118
Internal Medicine	22	42	74	122	154	176	158	175	151	150	105	106
Thoracic Surgery	7	24	70	111	139	160	158	153	162	148	114	89
Pulmonology	10	40	98	121	151	138	141	136	134	128	87	89
Surgery	16	17	42	31	47	30	35	95	90	95	96	135
Oncology	36	39	62	48	43	43	71	65	62	58	49	65
Dermatology	40	43	53	38	25	28	51	32	45	32	26	44
Gastroenterology	5	9	13	7	5	4	17	43	69	89	84	82
Gastrointestinal Surgery	3	6	5	5	7	2	5	30	49	64	52	51
Proportion of prescriptions for the 20 mg formulation												
Respiratory Medicine	0.0	0.0	0.0	0.0	5.9	36.4	46.5	50.2	51.3	55.3	59.6	59.5
Urology	0.0	0.0	0.0	0.0	9.4	17.6	29.0	37.8	47.4	41.4	56.1	45.8
Internal Medicine	0.0	0.0	0.0	0.0	6.5	19.3	25.9	35.4	32.5	29.3	28.6	32.1
Thoracic Surgery	0.0	0.0	0.0	0.0	1.4	16.3	37.3	37.9	38.3	37.8	46.5	44.9
Pulmonology	0.0	0.0	0.0	0.0	4.6	25.4	34.0	39.7	38.8	30.5	21.8	27.0
Surgery	0.0	0.0	0.0	0.0	6.4	40.0	28.6	21.1	20.0	25.3	26.0	40.0
Oncology	0.0	0.0	0.0	0.0	0.0	55.8	56.3	49.2	48.4	50.0	36.7	21.5
Dermatology	0.0	0.0	0.0	0.0	0.0	14.3	7.8	31.3	24.4	28.1	23.1	11.4
Gastroenterology	0.0	0.0	0.0	0.0	0.0	0.0	35.3	34.9	29.0	27.0	34.5	37.8
Gastrointestinal Surgery	0.0	0.0	0.0	0.0	0.0	0.0	60.0	50.0	38.8	39.1	30.8	27.5

1-2 Temporal Trends in Average Dose (Potency) and Average Drug Cost

	2020.11-2021.01	2021.02-2021.04	2021.05-2021.07	2021.08-2021.10	2021.11-2022.01	2022.02-2022.04	2022.05-2022.07	2022.08-2022.10	2022.11-2023.01	2023.02-2023.04	2023.05-2023.07	2023.08-2023.10
Average dose (potency)												
Respiratory Medicine	81.7	80.1	80.1	81.6	79.3	71.6	67.5	67.8	67.5	67.3	66.1	66.1
Urology	81.1	80.7	81.9	82.9	80.8	83.8	77.8	75.8	74.1	73.8	74.7	71.3
Internal Medicine	111.4	98.9	93.9	81.8	77.6	75.6	72.0	70.3	71.5	76.6	82.9	74.4
Thoracic Surgery	53.1	69.1	81.3	79.3	77.7	72.9	67.0	64.8	63.3	65.7	61.8	62.2
Pulmonology	84.3	81.0	84.7	79.6	80.3	77.5	72.7	70.0	73.1	73.0	74.6	73.1
Surgery	71.5	76.6	80.0	83.1	78.9	68.3	70.7	64.7	61.7	65.8	64.6	61.4
Oncology	91.7	84.2	87.5	85.4	88.6	81.2	79.4	79.5	67.3	69.1	67.5	73.5
Dermatology	208.8	190.5	180.1	194.7	184.9	201.6	203.7	182.1	202.3	189.6	184.6	195.3
Gastroenterology	120.0	77.8	100.0	150.0	80.0	87.5	64.1	60.5	69.8	67.9	61.3	64.2
Gastrointestinal Surgery	44.0	58.3	90.0	134.0	85.7	100.0	52.0	56.0	67.8	79.1	70.0	69.2
Average drug cost												
Respiratory Medicine	806,154	790,894	790,553	805,114	770,183	582,767	471,400	470,166	468,771	464,582	449,481	441,006
Urology	800,969	796,596	808,067	818,286	748,315	747,811	586,082	510,417	545,986	500,295	524,794	517,839
Internal Medicine	1,099,429	976,664	927,340	807,920	742,093	643,589	540,375	507,775	534,967	572,385	610,121	539,758
Thoracic Surgery	524,649	682,020	802,205	783,034	761,280	642,351	493,014	497,628	485,471	494,208	443,217	440,578
Pulmonology	832,245	799,543	835,932	785,632	777,994	685,760	553,179	531,437	562,176	553,861	613,536	588,974
Surgery	705,878	756,692	789,582	820,717	747,050	564,054	547,698	527,967	486,667	501,188	497,047	442,535
Oncology	904,972	831,308	864,314	843,269	874,742	618,243	546,994	551,959	457,131	450,655	516,419	565,670
Dermatology	2,060,868	1,880,593	1,778,209	1,921,719	1,825,035	1,648,026	1,586,049	1,165,580	1,365,858	1,243,382	1,259,955	1,472,211
Gastroenterology	1,184,690	767,855	987,242	1,480,863	789,794	845,326	510,769	438,254	519,687	513,698	442,277	443,529
Gastrointestinal Surgery	434,386	575,891	888,518	1,322,904	846,207	913,199	440,788	473,925	528,322	609,080	528,061	540,296
Average drug cost (price-adjusted)												
Respiratory Medicine	685,231	672,260	671,970	684,347	654,656	519,783	471,400	470,166	468,771	464,582	449,481	441,006
Urology	680,824	677,107	686,857	695,544	636,068	661,733	586,082	510,417	545,986	500,295	524,794	517,839
Internal Medicine	934,515	830,165	788,240	686,732	630,779	573,209	540,375	507,775	534,967	572,385	610,121	539,758
Thoracic Surgery	445,951	579,717	681,874	665,579	647,088	573,592	493,014	497,628	485,471	494,208	443,217	440,578
Pulmonology	707,409	679,611	710,542	667,788	661,296	607,897	553,179	531,437	562,176	553,861	613,536	588,974
Surgery	599,997	643,188	671,145	697,609	634,993	507,828	547,698	527,967	486,667	501,188	497,047	442,535
Oncology	769,226	706,612	734,668	716,779	743,531	555,604	546,994	551,959	457,131	450,655	516,419	565,670
Dermatology	1,751,738	1,598,504	1,511,478	1,633,461	1,551,281	1,480,921	1,586,049	1,165,580	1,365,858	1,243,382	1,259,955	1,472,211
Gastroenterology	1,006,987	652,677	839,156	1,258,734	671,325	734,262	510,769	438,254	519,687	513,698	442,277	443,529
Gastrointestinal Surgery	369,229	489,508	755,240	1,124,469	719,277	839,156	440,788	473,925	528,322	609,080	528,061	540,296

differs from previously reported formulations, this study confirmed that the addition of a low-dose formulation similarly reduced drug costs. Furthermore, considering that drug price reductions were implemented during the study period, drug costs were also calculated using the April 2021 drug prices for adjustment. The adjusted results demonstrated that drug costs were lower than those before the adjustment, suggesting that the reduction in drug prices also contributed to the overall decrease in costs. Furthermore, previous studies have recommended adjusting the prescribed dose to match the available formulation sizes whenever the discrepancy between the required dose and formulation size is minimal, thereby avoiding leftover solution.[7-9] The introduction of the 20-mg formulation likely further minimized discrepancies between the prescribed doses and available formulations, reducing instances of leftover solution and consequently the average drug costs.

In the analysis based on medical specialty, respiratory medicine had the highest number of patients and prescriptions during the study period. After the introduction of the 20-mg formulation, the proportion of prescriptions for the 20-mg formulation in respiratory medicine increased over time, ultimately stabilizing in the 50% range. The average prescribed dose (potency) was 81.6 mg immediately before the introduction of the 20-mg formulation but gradually decreased after that, eventually stabilizing in the 60-mg range. In contrast, dermatology had the lowest proportion of 20-mg prescriptions after the introduction of the 20-mg formulation. Although the proportion increased following its introduction, it remained within the 10%–20% range by the end of the study period. The average prescribed dose (potency) in dermatology was 194.7 mg immediately before the introduction of the 20-mg formulation and did not significantly change afterward, ultimately stabilizing in the 180–190-mg range.

Regarding the dosage per administration for each disease, the dosage for "unresectable, advanced, or recurrent NSCLC" is 1 mg/kg of body weight, whereas, for "unresectable malignant melanoma," it is 3 mg/kg of body weight. For the 50-mg formulation, when administered at a dosage of 3 mg/kg, the total drug volume corresponds to a body weight of 16.7 kg, whereas when administered at a dosage of 1 mg/kg, it corresponds to a body weight of 50 kg. Before the introduction of the 20-mg formulation, the discrepancy between the total drug volume required for preparation and the actual administered dose, in terms of body weight, was within 16.7 kg for a dosage of 3 mg/kg and within 50 kg for a dosage of 1 mg/kg. After the introduction of the 20-mg formulation, the drug volume could be adjusted in 10-mg increments during preparation. Consequently, the discrepancy could be reduced to within 3.3 kg for a dosage of 3 mg/kg and within 10 kg for a dosage of 1 mg/kg. The resultant difference in the extent of the discrepancy before and after the introduction of the 20-mg formulation was 13.4 kg for a dosage of 3 mg/kg and 40 kg for a dosage of 1 mg/kg, with the smaller discrepancy observed in the 3-mg/kg dosage. Furthermore, within the same body weight range, the higher the dosage per kilogram of body weight, the wider the applicable body weight range for the 50-mg formulation alone. Based on these findings, the differences in the proportion of prescriptions involving the 20-mg formulation and the variations in the prescribed dosage (potency) were presumably influenced by the differences in the dosage per kilogram of body weight. Furthermore, from November 2020 onward, during the study period, the number of patients and prescriptions in respiratory-related departments increased, suggesting a higher proportion of prescriptions using a dosage of 1 mg/kg of body weight. This increase in the proportion of prescriptions at a dosage of 1 mg/kg is further presumed to have influenced the observed changes in the average prescribed dosage (potency) and drug cost.

This study has several limitations that should be considered. First, the results were based solely on claims data submitted by the participating medical institutions. Consequently, detailed information on the patients and medical institutions were unavailable. Specific factors that could not be verified included patient body weight, actual administered dose, target disease, billing practices of each medical institution (e.g., whether discarded residual volumes were billed or if split dosing was implemented to bill based on actual usage), product formulations adopted, and timing of their adoption. In addition, the extent to which factors such as updates to treatment guidelines or changes in reimbursement policies influenced prescribing practices could not be investigated. Furthermore, the assumption in this study was that there were no differences in patient characteristics, including body weight, before and after the introduction of the 20-mg formulation; that the target diseases were inferred based on the medical department; and that the drug was administered according to the indications, dosage, and administration guidelines specified in the package insert. Furthermore, because of the specifications of the system used in this study, data were extracted only from medical institutions that provided clinical data throughout the study period. Although determining the total number of prescriptions for each period was possible, examining the distribution of doses per prescription was not feasible. Therefore, the analysis was limited to the use of the mean dose per prescription, calculated from the total dose and the number of prescriptions, without including the median or detailed distribution analysis. Additionally, the MDV analyzer® database covers claims data from approximately 30% of DPC hospitals in Japan; therefore, it does not include data from all DPC hospitals, nor does it contain data from non-DPC hospitals. Future studies should consider these factors for a more comprehensive evaluation.

In this study, the effects of the introduction of a low-dose formulation of ipilimumab on prescription volume and drug costs in real-world clinical practice in Japan were analyzed using MDV analyzer® data. The results demonstrated that the introduction of the 20-mg formulation reduced the average drug cost per prescription, which was presumed to be due to a reduction in the amount of discarded residual drug. In the Japanese healthcare system, the occurrence of residual drug is recognized as a significant factor that increases drug costs. These findings suggest that the introduction of low-dose formulations could reduce residual drug and lower drug costs under the current Japanese healthcare system. Furthermore, the low-dose formulation of ipilimumab has not been approved in the United States or Europe, and real-world data on its use remain limited globally. The results of this study may serve as a valuable source of information for pharmaceutical development aimed at promoting the efficient use of medicines and reducing drug costs on a global scale.

Ethical Approval This retrospective study used a database managed by Medical Data Vision Co., Ltd. (Tokyo, Japan). The data were anonymized and provided without any direct involvement with the patients. Therefore, ethical approval from an Institutional Review Board and informed

consent from patients were not required.

Conflict of interest The authors declare no conflict of interest.

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