



# Prospective, Multi-Institutional Observational Study of Deterioration in Activities of Daily Living in Elderly Patients After Lung Cancer Surgery

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## ABSTRACT

**Introduction:** To determine the rate of deteriorating activities of daily living (ADL) and to investigate predictive factors in elderly patients undergoing surgery for NSCLC.

**Methods:** Patients with NSCLC aged 75 years or older who underwent curative surgical resection were evaluated using the Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental ADL (TMIG-IADL) and the Japanese version of EuroQol 5-dimensions 5-level (EQ-5D-5L) quality-of-life scale administered at baseline and at 6 months postoperative. The primary end point was the rate of living patients without substantial deterioration of TMIG-IADL, defined as a decline greater than or equal to three points. Multivariable logistic regression was performed to determine risk factors for deteriorating ADL.

**Results:** Between May 2019 and May 2020, 876 of the 986 screened patients enrolled from 47 institutions were eligible and included in the analysis. TMIG-IADL and EQ-5D-5L scores were obtained from 96.0% and 92.6% of the patients, respectively. At 6 months postoperative, 745 patients (85.1%, 95% confidence interval: 82.5%–87.3%) reported no significant ADL deterioration, and 96 of 841 patients (11.4%) with postoperative score data reported significant deterioration. The social domain was the most frequently affected activity. In multivariable analysis, poor performance status, low G8 geriatric screening score, segmentectomy (versus wedge resection), and surgery lasting less than 3 hours were associated with deteriorating ADL. Worsening EQ-5D-5L scores by minimally important difference or more were observed in 22.1% of the patients. Changes in TMIG-IADL and EQ-5D-5L scores were poorly correlated.

**Conclusions:** Approximately 15% of elderly patients with NSCLC experienced significant ADL deterioration at 6 months postoperative.

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**Keywords:** Non-small cell; surgery; Elderly patients; Activities of daily living; Quality of life

## Introduction

Lung cancer is a leading cause of cancer-related deaths in Japan, with more than 75,000 deaths reported in 2020. With the aging of the general population, the incidence of lung cancer is expected to increase, with more elderly patients undergoing surgical resection. According to a survey by the Japanese Society of

Thoracic Surgery,<sup>1</sup> 44,859 patients in Japan underwent surgery for primary lung cancer in 2018 and nearly 60% of these patients were aged 70 years or older. In fact, 6115 of the patients who underwent resection (14%) were 80 years or older, and both the number and proportion continue to increase.

Many studies have investigated the postoperative outcomes of elderly patients with lung cancer. A Japanese study, which included 367 patients aged 80 years and older who underwent surgical resection for clinical stage I lung cancer<sup>2</sup> reported that serious complications occurred in 8.4% of the patients and that the rates of postoperative mortality and 5-year survival were 1.4% and 55.7%, respectively. A recent prospective cohort study by the Japanese Association for Chest Surgery<sup>3</sup> evaluated 895 octogenarians using a comprehensive scoring system for surgical risk and reported a 30-day postoperative mortality rate of 1.0% and a 3-year survival rate of 86.7%. This study<sup>3</sup> also identified several predictive factors for surgical risk and survival. However, most of the previous studies on elderly patients with NSCLC only evaluated postoperative morbidity and mortality<sup>4,5</sup> and overall survival (OS), and not functional outcomes.

Postoperative activities of daily living (ADL) are critically important for both patients and their families. Although the importance of functional outcomes in elderly populations has been reported,<sup>6–10</sup> few studies have evaluated postoperative ADL and quality of life (QOL) despite the notable impact of surgical stress on frailty in elderly patients.<sup>5,11,12</sup>

Whereas the prognosis of patients with lung cancer undergoing surgery has markedly improved, with 5-year OS rates of 90% or more for node-negative NSCLC, comorbidities including second primary cancers account for a significant portion of deaths.<sup>13–15</sup> Treatment for these comorbidities can be compromised by frailty owing to postoperative deterioration of the patient's physical condition.<sup>16</sup>

In elderly patients with lung cancer, therefore, ADL and QOL after surgery are important not only for their care and comfort but also for their prognosis. Without the information on postoperative ADL and QOL, patients and families cannot make well-informed choices for treatment among available options including surgery, radiotherapy, chemotherapy, immunotherapy, and supportive care.<sup>10,17</sup>

We conducted an observational study to evaluate postoperative ADL and QOL in elderly patients aged 75 years and older with NSCLC. We aimed to elucidate the rate of ADL deterioration in elderly patients undergoing surgical treatment for NSCLC and to determine the predictive factors for ADL deterioration. We used the Japanese version of EuroQol 5-dimensions

5-level (EQ-5D-5L),<sup>18,19</sup> a globally validated QOL assessment tool, and the Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental ADL (TMIG-IADL),<sup>20,21</sup> a 13-item validated scale for geriatric ADL and is the only scale of its kind available in Japan.

Here we report the ADL and QOL of patients at 6 months postoperatively, which are the main objectives of the study.

## Materials and Methods

### Eligibility

Figure 1 summarizes the study flow. Patients aged 75 years or older with radiologically suspected clinical stage 0 to III NSCLC were enrolled. Patients with tumors that were determined as amenable to complete resection and were planned to undergo primary surgery were included. The other inclusion criteria were as follows: (1) radical surgery scheduled within 14 days after enrollment; (2) competency to undergo comprehensive geriatric assessments using TMIG-IADL, G8 geriatric screening, Charlson comorbidity index (CCI), and engaged in social situations before surgery; and (3) competency to communicate in written Japanese. Pathologic diagnosis before surgery was not mandatory. Patients with active invasive malignancy with a disease-free period of shorter than 5 years, those with induction treatment or previous chemotherapy, and those with a history of previous surgical lung resection were excluded.

All patients provided written informed consent form before study enrollment. The present study was conducted according to the tenets of the Declaration of Helsinki and approved by the institutional review boards

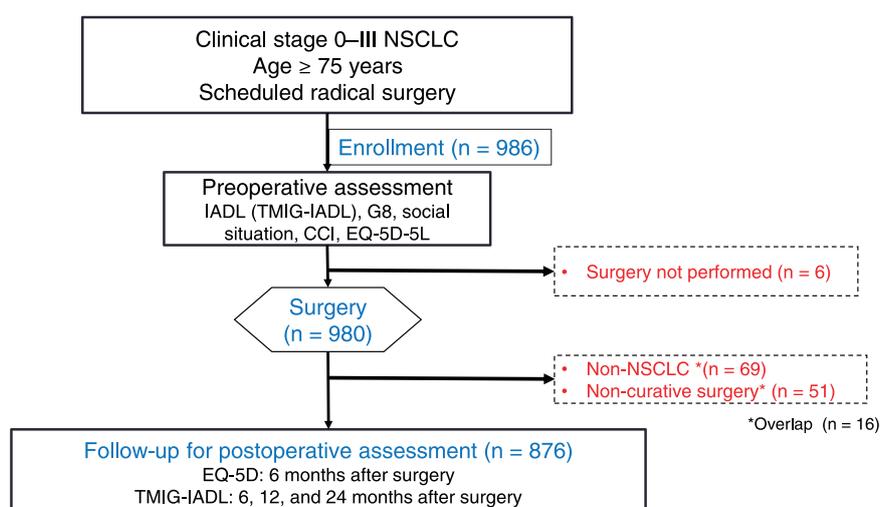
of all participating institutes (Japanese Red Cross Medical Center institutional review board approval number: 2019-973, on April 26, 2019). The study was registered with the UMIN Clinical Trials Registry (UMIN000036796).

### Study Design and Treatment

This was a prospective, multi-institutional observational study conducted by the Lung Cancer Surgical Study Group of Japan Clinical Oncology Group.

Baseline geriatric function assessment before surgery was performed using TMIG-IADL<sup>20,21</sup> (see [Supplementary Table 1A](#) for specific questionnaires and scores) and G8<sup>22</sup> (see [Supplementary Table 1B](#) for specific questionnaires and scores). Baseline information on the social situation, such as habitation, CCI score<sup>23</sup> (see [Supplementary Table 1C](#) for specific conditions and scores), poly-pharmacy status,<sup>24</sup> and Japanese version EQ-5D-5L scores<sup>18,19,25</sup> (see [Supplementary Table 1D](#) for specific questionnaires), were also obtained before surgery. Surgical procedures were not specified in the study protocol. Patients with a final pathologic diagnosis of NSCLC were observed for ADL outcomes. Patients undergoing non-curative surgery and those with neuroendocrine tumors, such as small cell carcinoma, large cell neuroendocrine carcinoma, or carcinoid tumor were excluded from follow-up and subsequent data acquisition.

The EQ-5D-5L questionnaire was administered at 6 months, with responses directly mailed to the research office by the patients, whereas the TMIG-IADL questionnaire was administered by attending physicians at 6, 12, and 24 months to evaluate the long-term surgical impact on ADL. The present study reports the data at postoperative 6 months, which include the primary end point described below.



**Figure 1.** Study flow chart. CCI, Charlson comorbidity index; EQ-5D, EuroQol 5-dimensions; G8, geriatric screening tool; IADL, instrumental activities of daily living; TMIG-IADL, Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living.

## End Points

The primary end point was the rate of patients without ADL deterioration at 6 months after surgery. The TMIG-IADL<sup>20,21</sup> (Supplementary Table 1A) is a 13-item index of competence on three domains and includes five items in instrumental self-maintenance, four items in effectance (defined as effective interaction with one's environment) or intellectual activity, and four items in social role. A higher TMIG-IADL score indicates better capacity for activity. A previous Japanese study<sup>26</sup> revealed that the SD of TMIG-IADL score was 3.0 points in the elderly population; therefore, in the present study, the protocol-specified ADL deterioration was defined as a decline of at least three points in TMIG-IADL score or missing ADL data, because it was presumed that it is likely that most of the missing data actually indicate worsening of the patient's condition. This cutoff was on the basis of the distribution-based method to determine the minimally important difference (MID).<sup>27</sup> A sensitivity analysis with the threshold of "ADL deterioration" with a change in score of two points was also performed; this "criteria-modified" ADL deterioration was defined as TMIG-IADL score deterioration of at least two points or missing data.

Patients with missing postoperative TMIG-IADL data were classified as exhibiting ADL deterioration. The time point of 6 months was determined by consensus of the surgeons on the basis of the consideration that elderly patients were extremely unlikely to achieve functional recovery after 6 months after surgery.

The secondary end points were TMIG-IADL scores at 12 and 24 months, EQ-5D-5L score at 6 months, OS, relapse-free survival (RFS), and rates of serious postoperative complications, defined as greater than or equal to grade 3 within 30 days of surgery according to the Common Terminology Criteria for Adverse Events version 5.0-Japan Clinical Oncology Group criteria.

EQ-5D-5L QOL scores were calculated according to the method by Ikeda et al.<sup>25</sup> The MID was set at 0.061 for the EQ-5D-5L QOL scores, as reported by Shiroiwa et al.<sup>28</sup>

## Statistical Analysis

The calculated sample size was 810 to obtain the half-width of a 95% confidence interval (CI) for the primary end point of within 3.5%. To account for ineligible patients, the planned sample size was set at 1000. A two-sided *p* value of less than 0.05 was considered statistically significant. The rate of patients without TMIG-IADL deterioration and the CI were estimated on the basis of binomial distribution. To determine risk factors for ADL deterioration, univariable and multivariable logistic regression analyses were performed using various demographic and clinical variables (see

Supplementary Table 1E for specific classifications of factors). These variables were used to estimate the rate of patients without ADL deterioration at 6 months. The OS and RFS are estimated using the Kaplan-Meier method.

Exploratory analyses were performed to determine the extent to which the three domains (instrumental self-maintenance, effectance, and social role) were affected in patients with ADL deterioration.

Deterioration of EQ-5D-5L scores by more than the MID and the CI were estimated on the basis of binomial distribution, and the correlation between the changes in EQ-5D-5L and TMIG-IADL scores was evaluated by Spearman's rank coefficient.

All statistical analyses were performed using SAS release 9.4 (SAS Institute, Cary, NC).

## Results

### Study Cohort

A total of 986 patients from 47 institutions were enrolled between May 20, 2019 and May 29, 2020. According to the final pathologic results, 876 patients had NSCLC, underwent complete resection, and were followed up to assess ADL and QOL (Fig. 1).

Table 1 details the study cohort characteristics. A total of 301 (34.4%) and 71 patients (8.1%) were aged 80 to 84 years and 85 years old and above, respectively. The remaining 504 patients (57.5%) were aged 75 to 79 years. Only three patients (0.3%) underwent pneumonectomy. Combined resection, such as pulmonary arterioplasty, bronchoplasty, and costal resection, was performed in 13 patients (1.5%).

The mean plus or minus SD of the baseline TMIG-IADL scores were 11.6 plus or minus 1.8. The SD was smaller than that previously reported in the general population, implying the study population, selected for surgical treatment, might be less heterogeneous in terms of ADL.

### Survival and Postoperative Complications

During a median follow-up of 6.2 months, 14 of the 870 patients with available follow-up data died; the causes were primary lung cancer and other causes in 4 and 10 cases, respectively. Among 868 patients with data on relapse and follow-up, 44 patients died or experienced a relapse. The 6-month OS and RFS rates were 98.7% and 96.0%, respectively.

Grade 3 or higher postoperative complications occurred in 86 of the 876 patients (9.8%) who underwent complete resection. The most frequent complication was pulmonary leakage (3.1%) followed by lung infection (1.4%). Grade 4 postoperative complications occurred in 19 patients (2.2%). There were three deaths (0.3%) during the 30-day postoperative period.

**Table 1.** Baseline Characteristics and Surgical and Pathologic Factors of 876 Patients With NSCLC Who Underwent Complete Resection

Characteristics	Number of Patients (%)			
<b>Sex</b>				
Male	491 (56.1)			
Female	385 (43.9)			
Age (y)		Median: 79	Range: 75-92	Q1-Q3: 77-82
<b>Clinical stage (UICC-TNM eighth classification)</b>				
0	29 (3.3)			
IA1	131 (15.0)			
IA2	254 (29.0)			
IA3	158 (18.0)			
IB	134 (15.3)			
IIA	36 (4.1)			
IIB	96 (11.0)			
IIIA	35 (4.0)			
IIIB	3 (0.3)			
<b>ECOG Performance status</b>				
0	717 (81.8)			
1	152 (17.4)			
2	5 (0.6)			
3	1 (0.1)			
4	1 (0.1)			
<b>Smoking history</b>				
Never	363 (41.4)			
Ever	513 (58.6)			
Smoking years		Median: 43	Range: 0-66	Q1-Q3: 30-54
Number of daily cigarettes		Median: 20	Range: 0-80	Q1-Q3: 15-30
<b>Emphysema</b>				
No	623 (71.1)			
Yes	253 (28.9)			
<b>Interstitial pneumonia</b>				
No	788 (90.0)			
Yes	88 (10.0)			
<b>Number of medications</b>				
0	63 (7.2)			
1-3	255 (29.1)			
4-9	464 (53.0)			
≥ 10	94 (10.7)			
<b>Operation</b>				
Wedge Resection	95 (10.8)			
Segmentectomy	133 (15.2)			
Lobectomy	639 (72.9)			
Bilobectomy	6 (0.7)			
Pneumonectomy	3 (0.3)			
<b>Lymph node dissection</b>				
ND0-1	371 (42.4)			
ND2a or more	505 (57.6)			
<b>Combined resection</b>				
No	863 (98.5)			
Yes	13 (1.5)			
Operation time (min)		Median: 157	Range: 33-524	Q1-Q3: 119-205
<b>Histology</b>				
Adenocarcinoma	678 (77.4)			
Squamous cell carcinoma	169 (19.3)			
Large cell carcinoma	1 (0.1)			
Adenosquamous carcinoma	16 (1.8)			
Others	12 (1.4)			

(continued)

Table 1. Continued

Characteristics	Number of Patients (%)				
Pathologic stage (UICC-TNM Eighth classification)					
0	31 (3.5)				
IA1	171 (19.5)				
IA2	207 (23.6)				
IA3	114 (13.0)				
IB	127 (14.5)				
IIA	45 (5.1)				
IIB	96 (11.0)				
IIIA	74 (8.4)				
IIIB	11 (1.3)				
Postoperative chemotherapy					
None	837 (95.5)				
Tegafur-uracil	30 (3.4)				
Platinum-based	8 (0.9)				
Missing	1 (0.1)				
Postoperative radiotherapy					
None	874 (99.8)				
Yes	1 (0.1)				
Missing	1 (0.1)				
G8 score at enrollment		Mean: 14.0	Median: 14	SD: 1.8	Range: 6.5-17
CCI score		Mean: 0.9	Median: 0	SD: 1.2	Range: 0-8
Baseline TMIG-IADL score		Mean: 11.6	Median: 12	SD: 1.8	Range: 2-13 Q1-Q3: 11-13

CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; G8, geriatric screening tool; N0, no node dissection; ND1, hilar node dissection; ND2, mediastinal node dissection; TMIG-IADL, Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living; Q1, first quartile; Q3, third quartile; UICC, Union for International Cancer Control.

### The TMIG-IADL Data

The TMIG-IADL questionnaire data were not available for 35 patients; the causes were death, incapacitating complications such as brain infarction, and other or unknown reasons in 19, nine, and seven patients, respectively (Fig. 2). Thus, the TMIG-IADL questionnaire data were successfully retrieved from 96.0% (841 of 876) of all patients and 98.1% (841 of 857) of all living patients.

At postoperative 6 months, the TMIG-IADL score changes ranged from  $-13$  to  $+5$ ; the scores worsened (by one point or more) in 306 (36.4%), stable in 350 (41.6%) and improved in 185 (22.0%), respectively, among the 841 patients for whom the scores were retrieved (Fig. 2). There was a statistically significant trend for worsening of the score ( $p < 0.0001$  by Wilcoxon signed rank test), even after excluding dead or incapacitated patients for whom postoperative scores were not available. This trend was observed in almost every strata of sex, age, tumor stage, PS, smoking, operation method, or baseline G8, except for those who underwent wedge resection. A total of 95 patients underwent wedge resection, and their postoperative TMIG-IADL scores were missing/worsened in 31 (32.6%), stable in 41 (43.2%), and improved in 23 (24.2%),

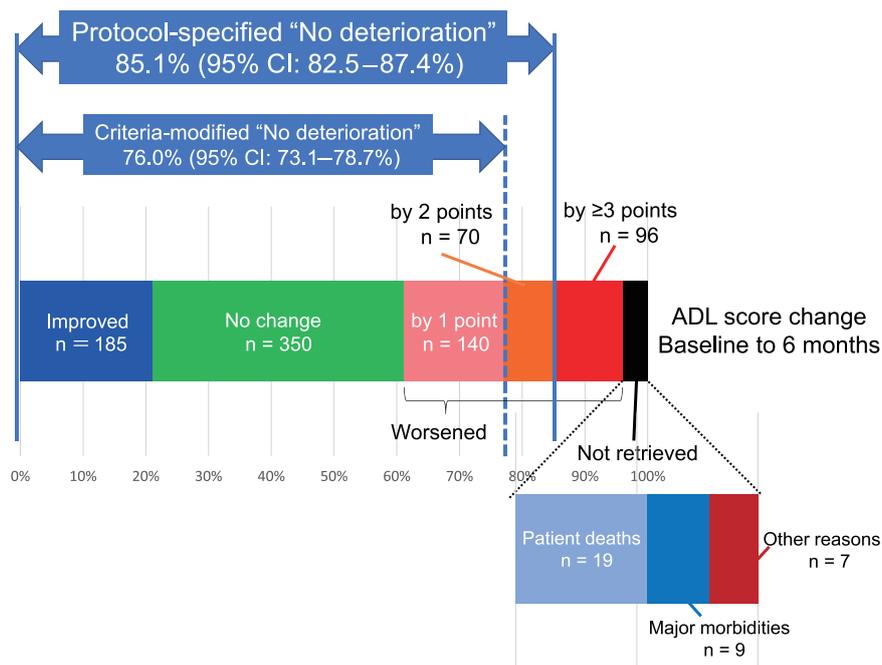
without significant overall change ( $p = 0.18$  by Wilcoxon signed rank test)

### Patients With and Without ADL Deterioration

In 745 of the 876 patients, the TMIG-IADL scores either improved (in 185 patients or 21.1%), did not change (in 350 patients or 40.0%), or worsened by less than or equal to two points (in 210 patients or 24.0%) at postoperative 6 months. TMIG-IADL score deterioration of greater than or equal to three points was observed in 96 patients (11.0%). The rate of patients without protocol-specified ADL deterioration (missing or worsened by  $\geq 3$  points) was 85.1% (95% CI: 82.5%–87.3%) (Fig. 2).

Because the SD of the study population was 1.8, we made a sensitivity analysis with the threshold of “ADL deterioration” changed to two scores. TMIG-IADL score deterioration of greater than or equal to two points was observed in 166 patients (19.7% of the 841 patients), and, including the missing data counted as deterioration, the criteria-modified overall rate of “patients without ADL deterioration” was 76.0% (95% CI: 73.1%–78.7%) (Fig. 2).

The rate of ADL deterioration was higher in patients with grade 3 or higher serious postoperative complications ( $n = 86$ ) than in those without ( $n = 790$ ). The rates



**Figure 2.** Changes of the TMIG-IADL (Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living) scores from baseline to postoperative 6 months. Colored columns represent patients with TMIG-IADL scores improvement, no change, worsening by one point, worsening by two points, or missing postoperatively. Those with missing data are then subclassified according to the reasons: patient deaths, major morbidities and others. The rate of patients without a score worsening by greater than or equal to three points or missing (protocol-specified “no deterioration”) is the primary end point of the study, whereas criteria-modified “no deterioration” means TMIG-IADL score deterioration of greater than or equal to two points or missing data. ADL, activities of daily living; CI, confidence interval.

of patients without ADL deterioration were 61.6% and 87.6% in patients with and without serious postoperative complications, respectively, with an OR of 4.397 (95% CI: 2.711–7.129,  $p < 0.0001$ ) to experience ADL deterioration. Of the 86 patients with grade 3 or higher serious postoperative complications, 21 (24.4%) and 16 (18.6%) reported stable and improved scores, respectively.

### Subset Analysis of Factors Predicting ADL Nondeterioration

The univariable analysis was performed to identify factors associated with ADL nondeterioration at 6 months (Table 2). ADL deterioration was significantly more frequent among male patients, those aged 80 years or older, those with a performance status (PS) (by Eastern Cooperative Oncology Group) score of at least 1, and those with a smoking history of more than 20 years. Patients with emphysema, interstitial pneumonitis, low G8 scores, and high CCI scores were significantly more likely to experience ADL deterioration at 6 months. In addition, those treated with at least four regular medications were more likely to be associated with ADL deterioration at 6 months. There was no clear association of ADL deterioration with

surgical procedures including the extent of lung resection; however, patients undergoing combined resection were significantly more likely to experience ADL deterioration.

Multivariable analysis indicated that only the following four clinical factors were associated with significant ADL deterioration, namely: (1) poor preoperative PS; (2) low G8 score; (3) segmentectomy (versus wedge resection); and (4) surgery lasting shorter than 3 hours (see Supplementary Table 1F for results of the multivariable analysis, which details the four significant factors).

### Changes in Specific ADL Subscales

Among the 841 patients with available data on TMIG-IADL scores at 6 months, a score worsening of at least one point was present in the instrumental self-maintenance, effectance, and social role domains in 16.2%, 17.0%, and 36.4% of the patients, respectively (Table 3). The worsening seemed to be strongest in the social role domain. We considered that this finding might have reflected the coronavirus disease 2019 (COVID-19) pandemic, and performed additional analyses in patients categorized according to the time of enrollment.

**Table 2. Univariable Analyses of Factors Associated With Nondeterioration of ADL by TMIG-IADL at 6 Months After Surgery**

Factor	Classification	Number of Patients	Rate of No Deterioration (95% CI)	OR (95% CI)	p Value
Sex	Male	491	82.7 (79.1-85.9)	1 (reference)	0.0280
	Female	385	88.1 (84.4-91.1)	0.648 (0.440-0.954)	
Age (y)	≤79	504	87.7 (84.5-90.4)	1 (reference)	0.0108
	≥80	372	81.5 (77.1-85.3)	1.624 (1.118-2.357)	
Age (y)	≤84	805	86.0 (83.4-88.3)	1 (reference)	0.0119
	≥85	71	74.7 (62.9-84.2)	2.080 (1.176-3.679)	
Clinical stage	0	29	86.2 (68.3-96.1)	1 (reference)	0.3720 0.8549 0.8667 0.4321 0.2693 0.1787 0.2184
	IA1	131	91.6 (85.5-95.7)	0.573 (0.169-1.946)	
	IA2	254	87.4 (82.7-91.2)	0.901 (0.294 - 2.757)	
	IA3	158	87.3 (81.1-92.1)	0.906 (0.285-2.875)	
	IB	134	79.9 (72.1-86.3)	1.577 (0.506-4.915)	
	IIA	36	94.4 (81.3-99.3)	0.368 (0.062-2.169)	
	IIB	96	74.0 (64.0-82.4)	2.201 (0.697-6.948)	
	IIIA+B	38	73.7 (56.9-86.6)	2.232 (0.621-8.019)	
ECOG Performance status	0	717	87.6 (85.0-89.9)	1 (reference)	<0.0001 0.2191
	1	152	73.7 (65.9-80.5)	2.520 (1.650-3.850)	
	2-4	7	71.4 (29.0-96.3)	2.823 (0.539-14.767)	
Smoking history	Never	363	88.7 (85.0-91.8)	1 (reference)	0.0112
	Ever	513	82.5 (78.9-85.7)	1.671 (1.124-2.485)	
Smoking years	0	364	88.7 (85.0-91.8)	1 (reference)	0.2518 0.0053 0.0127
	1-19	51	94.1 (83.8-98.8)	0.493 (0.147-1.653)	
	20-39	132	78.8 (70.8-85.4)	2.121 (1.250-3.599)	
	≥40	328	82.0 (77.4-86.0)	1.728 (1.124-2.656)	
Respiratory comorbidity	No	588	87.9 (85.0-90.5)	1 (reference)	0.0007
	Yes	288	79.2 (74.0-83.7)	1.916 (1.314-2.795)	
Emphysema	No	623	87.3 (84.5-89.8)	1 (reference)	0.0033
	Yes	253	79.5 (73.9-84.3)	1.781 (1.211-2.620)	
Interstitial pneumonia	No	788	86.3 (83.7-88.6)	1 (reference)	0.0024
	Yes	88	73.9 (63.4-82.7)	2.228 (1.328-3.736)	
Number of medications	0	63	92.1 (82.4-97.4)	1 (reference)	0.5893 0.0721 0.0224
	1-3	255	89.8 (85.4-93.2)	1.317 (0.458-3.578)	
	4-9	464	83.0 (79.2-86.3)	2.380 (0.925-6.124)	
	≥10	94	77.7 (67.9-85.6)	3.337 (1.186-9.388)	
Operation	Wedge Resection	95	88.4 (80.2-94.1)	1 (reference)	0.1441 0.4390 0.7106 0.2899
	Segmentectomy	133	81.2 (73.5-87.5)	1.768 (0.823-3.796)	
	Lobectomy	639	85.5 (82.5-88.1)	1.301 (0.668-2.531)	
	Bilobectomy	6	83.3 (35.9-99.6)	1.527 (0.163-14.305)	
	Pneumonectomy	3	66.7 (9.4-99.2)	3.818 (0.319-46.657)	
Lymph node dissection	ND0-1	371	84.6 (80.6-88.2)	1 (reference)	0.7708
	≥ND2a	505	85.4 (82.0-88.3)	0.946 (0.650-1.376)	
Combined resection	No	863	85.4 (82.9-87.7)	1 (reference)	0.0250
	Yes	13	61.5 (31.6-86.1)	3.656 (1.177-11.353)	
Operation time	<180 min	548	83.8 (80.4-86.8)	1 (reference)	0.1685
	≥180 min	328	87.2 (83.1-90.6)	0.757 (0.510-1.125)	
G8 score at registration	≥15	380	90.5 (87.1-93.3)	1 (reference)	<0.0001
	≤14	495	80.8 (77.1-84.2)	2.269 (1.506-3.149)	
CCI score	0	447	88.8 (85.5-91.6)	1 (reference)	0.0016
	≥1	429	81.1 (77.1-84.7)	1.848 (1.263-2.704)	

ADL, activities of daily living; CCI, Charlson comorbidity index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; G8, geriatric screening tool; ND0, no node dissection; ND1, hilar node dissection; ND2, mediastinal node dissection; TMIG-IADL, Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living.

Among the 230 patients enrolled before September 2019 (for whom the primary end point was evaluated before April 2020, when the first state of emergency for the COVID-19 pandemic was declared in Japan), a score

worsening of greater than or equal to one point at 6 months was detected in the instrumental self-maintenance, effectance, and social role domains in 12.6%, 17.8%, and 30.9% of the patients, respectively.

**Table 3.** Worsening of Scores in Each Specific Item and Domain in the Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living Among Patients Who Responded to Both the Preoperative and Postoperative Surveys (N = 841)

Item	Number of Patients Reporting Score Worsening	% (95% CI)
1. Can you use public transportation (bus or train) by yourself?	73	8.7 (6.9-10.8)
2. Are you able to shop for daily necessities?	42	5.0 (3.6-6.7)
3. Are you able to prepare meals by yourself?	66	7.9 (6.1-9.9)
4. Are you able to pay bills?	37	4.4 (3.1-6.0)
5. Can you handle your own banking?	43	5.1 (3.7-6.8)
Domain: Instrumental self-maintenance (items 1-5) by one point or more	136	16.2 (13.8-18.8)
Domain: Instrumental self-maintenance (items 1-5) by two points or more	60	7.1 (5.5-9.1)
6. Are you able to fill out forms for your pension?	58	6.9 (5.3-8.8)
7. Do you read newspapers?	44	5.2 (3.8-7.0)
8. Do you read books or magazines?	66	7.9 (6.1-9.9)
9. Are you interested in news stories or programs dealing with health?	31	3.7 (2.5-5.2)
Domain: Effectance (items 6-9) by one point or more	143	17.0 (14.5-19.7)
Domain: Effectance (items 6-9) by two points or more	37	4.4 (3.1-6.0)
10. Do you visit the homes of friends?	135	16.1 (13.6-18.7)
11. Are you sometimes called on for advice?	113	13.4 (11.2-15.9)
12. Are you able to visit sick friends?	142	16.9 (14.4-19.6)
13. Do you sometimes initiate conversations with young people?	87	10.3 (8.4-12.6)
Domain: Social role (items 10-13) by one point or more	306	36.4 (33.1-39.7)
Domain: Social role (items 10-13) by two points or more	120	14.3 (12.0-16.8)

CI, confidence interval.

Conversely, a score worsening of greater than or equal to one point at 6 months was detected in the instrumental self-maintenance, effectance, and social role domains in 17.5%, 16.7%, and 38.5% of the 611 patients enrolled after October 2019 (Supplementary Table 1G). The differences between pre and post-COVID-19 score changes were not statistically significant except for social role domain score ( $p = 0.0426$  by chi-square test). Therefore, despite the presence of a certain degree of COVID-19 effect on ADL, this effect was unlikely to be great and the “social role” was the most affected domain in both periods.

### Changes in QOL

The preoperative and postoperative EQ-5D-5L questionnaire data were available for 864 (98.6%) and 821 (93.7%) of the 876 patients, respectively. The score changes could be analyzed in 811 patients (92.6%) who were also included in the primary end point analysis. On the basis of an MID of 0.061 for the EQ-5D-5L score, QOL deterioration (by MID or more) was observed in 179 patients (22.1%), whereas 115 (14.2%) reported QOL worsening by less than MID, 280 (34.5%) reported no change, 85 (10.5%) reported QOL improvement by less than MID, and 152 (18.7%) reported improvement by MID or more. Preoperative poor PS (2–4 versus 0) and smoking history (ever versus never) were significantly

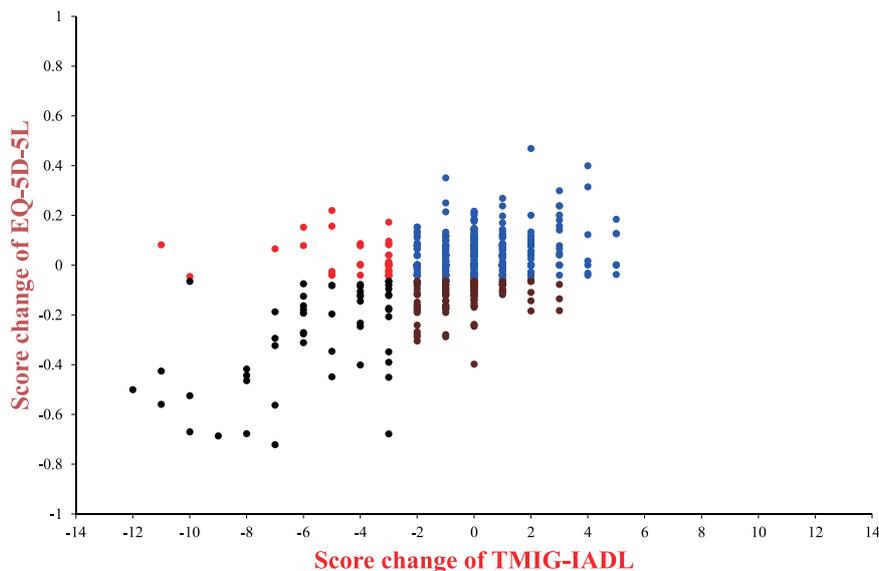
correlated with predetermined (i.e., by MID or more) QOL deterioration at 6 months. QOL score changes were not significantly different between those with and without grade 3 or higher serious postoperative complications, although this comparison is biased because they were limited to patients “fit enough” to fill in postoperative QOL questionnaires.

The correlation analysis including these 811 patients indicated that the changes in TMIG-IADL and EQ-5D-5L scores were poorly correlated (Spearman’s rank correlation coefficient = 0.2884), as illustrated in Figure 3. The kappa coefficient for the agreement between deterioration/nondeterioration of TMIG-IADL (by  $\geq 3$  points) and QOL (by MID of  $\geq 0.061$ ) scores was 0.2655, confirming poor correlation (see Supplementary Table 1H for specific data).

Of the 811 patients with both baseline and postoperative EQ-5D-5L scores, 125 (15.4%) and 154 (19.0%) revealed improvement in Pain/Discomfort item and Anxiety/Depression item, respectively. These patients were more likely to report improved TMIG-IADL or overall QOL scores (Supplementary Table 1I).

### Discussion

In the present study, data on preoperative and postoperative ADL could be obtained from 98.1% of 876 elderly patients undergoing curative surgery for NSCLC



**Figure 3.** Correlation between changes in the TMIG-IADL score and the changes in the EQ-5D-5L score after surgery. Red and black dots represent those with substantial ADL deterioration (TMIG-IADL score worsened by  $\geq 3$  points), whereas brown and black dots represent those with substantial QOL deterioration (EQ-5D-5L score worsened by  $\geq 0.061$  points). TMIG-IADL and EQ-5D-5L scores were poorly correlated (Spearman's rank correlation coefficient = 0.2884). EQ-5D-5L, EuroQol 5-dimensions 5-level; QOL, quality of life; TMIG-IADL, Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living.

who were alive at 6 months. In nine of the 16 alive patients with missing data, the cause of their exclusion was incapacitating complications, which were undoubtedly associated with ADL deterioration as we had anticipated when determining the primary end point of the study. Therefore, data on ADL were only “truly missing” from seven of the 876 patients (<1%). In addition, data on QOL could be obtained from greater than 90% of the patients. Therefore, in the current study, evaluating postoperative ADL and QOL outcomes was feasible despite the disruptive effect of the COVID-19 pandemic during the study period.

With the aging population in Japan, the number of elderly patients with lung cancer, including those undergoing surgical resection, is rapidly increasing.<sup>1,3</sup> Despite improvements in surgical safety and OS,<sup>2,3</sup> data on the impact of surgery on long-term ADL and QOL, which are critically important for patients and families, are limited.<sup>8,10,11</sup> Previous studies have focused on short-term morbidity and mortality of surgical procedures and OS.<sup>2-4</sup> However, aside from survival, the ADL and QOL of patients as cancer survivors should also be evaluated.

In the present study, we confirmed the favorable survival outcomes of surgery in elderly patients with NSCLC, on the basis of surgical mortality and 6-month OS rates of 0.3% and 98.7%, respectively. However, although there was considerable variability in postoperative ADL change, with some suffering from remarkable worsening and others reporting maintained or even improved activities, ADL scores significantly

tended to worsen at postoperative 6 months. Protocol-specified ADL deterioration (defined as a decline of  $\geq 3$  points in TMIG-IADL score or missing ADL data) was not observed in only 85% of the patients, indicating that the remaining 15% of the patients experienced significant functional loss after surgery.

ADL maintenance or recovery was not determined solely by short-term postoperative complications. Although patients who experienced grade 3 or higher surgical complications were statistically significantly more likely to suffer from ADL deterioration, more than 60% achieved ADL recovery at 6 months, with some even reporting “improved” postoperative ADL or QOL. On the other hand, one out of every eight patients without grade 3 or higher postoperative complications experienced significant ADL deterioration. Therefore, operative complications are not a surrogate for long-term functional recovery, and ADL should be evaluated as a distinct end point.

Univariable analyses revealed that male sex, age of at least 80 years, poor PS, smoking history, emphysema, interstitial pneumonia, daily use of multiple medications, low baseline G8 score, high CCI score, and combined resection were associated with postoperative ADL deterioration at 6 months. In multivariable analysis, the following four predictive factors remained significantly associated with ADL deterioration at 6 months: (1) poor preoperative PS; (2) low baseline G8 score; (3) segmentectomy (versus wedge resection); and (4) surgery lasting shorter than 3 hours. The clinical relevance of the

observed association between shorter surgery duration and ADL deterioration remains unclear and could be a statistical anomaly. Or it might be owing to bias that clinically higher-risk patients underwent operation by more experienced surgeons. In any case, it could be concluded that having shorter surgical time would not lead to the maintenance of postoperative ADL. Information on these predictive factors would aid in patient counseling, treatment decision-making, and perioperative care for elderly patients.

Although there were no significant correlations between surgical procedures and ADL deterioration by univariable comparisons, the multivariable analysis did indicate that wedge resection was associated with less ADL deterioration, especially versus segmentectomy. In a recently published Cancer and Leukemia Group B trial,<sup>29</sup> “sublobar” resection was found to be noninferior to lobectomy in early-stage NSCLC, which is compatible with the study by Japan Clinical Oncology Group.<sup>15</sup> However, in this Cancer and Leukemia Group B trial, both wedge resection and segmentectomy were included in the “sublobar resection” group. Given the different effects on ADL, it might be inappropriate to put wedge resection and segmentectomy together as “less invasive” surgical procedures.

Of note, preoperative comprehensive geriatric assessments were significantly associated with short-term surgical complications during the first 30 days in the previous study by the Japanese Association for Chest Surgery.<sup>3</sup> In the present study, we used the simplified G8 assessment,<sup>22</sup> which was also associated with functional outcomes at a longer term of 6 months. On the other hand, age alone did not predict functional outcomes. These results reconfirm the importance of pretreatment assessment using geriatric scales.<sup>3,30,31</sup> The currently ongoing data collection and analyses aim to determine whether patients experience additional ADL deterioration during longer follow-up periods of 12 and 24 months after surgery and to identify predictive factors.

We also collected QOL data using the EQ-5D-5L questionnaire, given that QOL and ADL are not identical. In fact, in the current study, not only the postoperative data retrieval rates were different, but the changes in TMIG-IADL and EQ-5D-5L scores were poorly correlated. QOL deterioration by the MID or more was reported by 22.1% of the patients, which was higher than the rate of patients with ADL deterioration. These results could have reflected the different data collection methods but suggest that ADL and QOL should be separately evaluated despite their comparable importance. Future studies should elucidate whether ADL or QOL has a bigger impact on long-term outcomes in elderly patients undergoing surgery for lung cancer.

The present study has several strengths. This was a multi-institutional prospective study with large cohort size. Previous studies on postoperative patient-reported outcomes (PROs) reported only modest responses. For example, in a European study on the economic burden of patients with resected NSCLC,<sup>32</sup> the authors reported that 306 of the 526 (58%) invited patients completed the survey. In another study by Heiden et al.,<sup>33</sup> which investigated the PROs after NSCLC resection in 334 patients, each of the PRO scores at 6 months could be collected from only half the patients or less. In our study, however, the PRO data retrieval rates were very high for both ADL and QOL, despite the disruptive effect of the COVID-19 pandemic on clinical trials.<sup>34</sup>

On the other hand, we also acknowledge the weaknesses and the limitations of the study. First, as is the case in most surgical observational studies, our patients are selected for curative operation and are undoubtedly “fitter” than the general elderly population. Most of them have a PS of 0, with few comorbidities, and the SD of baseline ADL was smaller. The generalizability of our results to more frail populations, thus, remains unclear. Second, although the cutoff value for the QOL has been set at 0.061 according to a previous report on MID,<sup>28</sup> no data are available regarding the changes in the TMIG-IADL score for clinically relevant ADL deterioration. We embraced the distribution-based method<sup>27</sup> and defined deterioration as a change of one SD in the TMIG-IADL score. Although used in previous studies evaluating the effect of brain radiotherapy cognitive functions,<sup>35–37</sup> this approach could be criticized as arbitrary.

Third, we did not have reference data to determine whether the rate of patients experiencing ADL deterioration of 15% was expected or not. Puts et al.<sup>38</sup> investigated the 6 months postoperative ADL in 112 elderly patients who underwent breast cancer surgery and reported that 21.9% suffered from functioning deterioration, with which no variable was associated. In a larger, the international, multicenter Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery (GOSAFE) study,<sup>39</sup> 945 elderly patients who underwent surgery for various cancers were analyzed for EQ-5D, with worsening and recovered scores at postoperative 3 and 6 months, respectively. No definitions of MID were given in either report. In a study with longer (5-year) follow-up, ADL change was investigated in 239 elderly patients with breast cancer, and Lemij et al.<sup>40</sup> reported that treatment was not associated with physical activities. Although it seemed that our results are not inconsistent with these previous reports, direct comparisons are difficult owing to differences in disease status and evaluation methods. In particular, we cannot precisely differentiate the effect of surgery-induced versus “normal” deterioration process of the aged patients, although it would be unlikely that many

“normal” elderly people suffer from a significant functional loss in 6 months. Comparisons with other modalities, such as radiotherapy, would be greatly informative for treatment selection. Fourth, information on the excluded patients, such as those who underwent non-curative surgery, is missing. In fact, some of the patients might have received effective target-based drugs with no ADL deterioration.

Future oncology trials should adopt a comprehensive approach and include ADL and QOL assessment irrespective of the treatment modalities chosen. There was a significant number of patients who reported improvement of postoperative ADL or QOL; 185 (21.1%) reported TMIG-IADL score improvement, and 152 (18.7%) reported that their QOL was improved by MID or more. This could be attributed to the physical and psychological burden of cancer and the subsequent curative operation leading to “disease-free” status.

In conclusion, our analyses of ADL and QOL in a large cohort of patients from a large number of institutions across Japan revealed that, even in this selected group with limited generalizability, a significant proportion of elderly patients who underwent curative surgical resection for NSCLC experienced ADL deterioration at 6 months after surgery, highlighting the need for further studies elucidating the predictive and contributory factors. The fact that ADL and QOL changes were not uniform, with some reporting improved postoperative ADL/QOL, makes it all the more necessary to have better tools in predicting who will feel better versus worse after surgery.

## CRedit Authorship Contribution Statement

**Hidefumi Takei:** Conceptualization, Investigation, Methodology, Resources, Visualization, Writing - original draft, Writing - review & editing.

**Hideo Kunitoh:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Visualization, Writing - original draft, Writing - review & editing.

**Masashi Wakabayashi:** Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing - review & editing.

**Tomoko Kataoka:** Data curation, Software, Validation, Writing - review & editing.

**Yuta Sekino:** Data curation, Software, Validation, Writing - review & editing.

**Tomonori Mizutani:** Conceptualization, Methodology, Visualization, Writing - review & editing.

**Masahiro Tsuboi:** Investigation, Resources, Writing - review & editing.

**Norihiko Ikeda:** Investigation, Resources, Writing - review & editing.

**Hisao Asamura:** Investigation, Resources, Writing - review & editing.

**Morihito Okada:** Investigation, Resources, Writing - review & editing.

**Makoto Takahama:** Investigation, Resources, Writing - review & editing.

**Yasuhisa Ohde:** Investigation, Resources, Writing - review & editing.

**Jiro Okami:** Investigation, Resources, Writing - review & editing.

**Satoshi Shiono:** Investigation, Resources, Writing - review & editing.

**Keijyu Aokage:** Investigation, Project administration, Resources, Writing - review & editing.

**Shun-ichi Watanabe:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing - original draft, Writing - review & editing.

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## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at [www.jtocrr.org](http://www.jtocrr.org) and at <https://doi.org/10.1016/j.jtocrr.2023.100550>.

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## Original Article

# Real-world treatment trends for patients with advanced prostate cancer and renal cell carcinoma and their cost—a survey in Japan

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## Abstract

**Background:** Advanced (Stage IV) prostate and renal cancer have poor prognosis, and several therapies have been developed, but many are very costly. This study investigated drug regimens used in patients with untreated Stage IV prostate cancer and renal cell carcinoma and calculated the monthly cost of each.

**Methods:** We surveyed first-line drugs administered to patients with untreated Stage IV prostate cancer and renal cancer at Japan Clinical Oncology Group affiliated centers from April 2022 to March 2023. Drug costs were calculated according to drug prices in September 2023. Individual drug costs were calculated or converted to 28-day costs.

**Results:** A total of 700 patients with untreated Stage IV prostate cancer were surveyed. Androgen deprivation therapy + androgen receptor signaling inhibitor was the most common regimen (56%). The cost of androgen deprivation therapy + androgen receptor signaling inhibitor was 10.6–30.8-fold compared with conventional treatments. A total of 137 patients with Stage IV renal cancer were surveyed. Among them, 91% of patients received immune-oncology drug-based regimen. All patients received treatments with a monthly cost of  $\geq 500\,000$  Japanese yen, and 80.4% of patients received treatments with a monthly cost of  $\geq 1$  million Japanese yen, of combination treatments. The cost of immune-oncology drug-based regimen was 1.2–3.1-fold that of TKI alone.

**Conclusion:** To the best of our knowledge, this is the first report of a survey of first-line drug therapy in untreated Stage IV prostate cancer and renal cell carcinoma stratified by age and treatment costs. Our results show that most Japanese patients received state-of-the-art, effective treatments with high financial burden.

**Key words:** renal cell carcinoma, prostate cancer, immune-combination therapy, treatment cost

## Introduction

Japan is facing an unprecedented super-aging society (1). Prostate cancer and renal cell carcinoma (RCC) are the most common urologic cancers among older adults. In Japan, the incidence of prostate cancer is ~15 per 10 000 population, and it was the leading cancer in men in 2019 (2). The average age of patients with prostate cancer is 71.3 years, and the 10-year cancer-specific survival proportion for Stages I–III and IV (14.6% of all patients) are ~90% (good prognosis) and 36.9% (poor prognosis), respectively. By contrast, the average age of patients with RCC is 65.5 years. Similar to prostate cancer, the 10-year cancer-specific survival proportion for Stages I and II and IV (16.2% of all patients) are ~80% (good prognosis) and 7.3% (poor prognosis), respectively (3). Both prostate cancer and RCC have extremely poor prognoses when diagnosed at Stage IV when metastasis has occurred.

The standard treatment for Stage IV prostate cancer was androgen deprivation therapy (ADT) (4). However, metastatic prostate cancer that initially responded to ADT became resistant to ADT and progressed to metastatic castration-resistant prostate cancer within 2–3 years (5). Subsequently, new therapies were developed, and docetaxel, abiraterone, enzalutamide and apalutamide, in combination with ADT, impaired disease progression and improved overall survival (OS) in randomized clinical trials (6–15). This is now the current standard of care.

The standard of care for Stage IV RCC has reached a turning point: inhibitors of the programmed cell death receptor pathway (immune-oncology drug: IO) in combination with a tyrosine kinase inhibitor (TKI) (IO–TKI combination) or in combination with other IO agents (IO–IO combination) were compared with the TKI sunitinib alone. IO–TKI and IO–IO combination therapy showed improved response rates, progression-free survival and OS compared with TKI sunitinib alone (16–26). Thus, with the development of new therapeutic approaches, improvement in prognosis has been achieved, but both TKIs and IOs are expensive treatments.

Although the development of new therapies has improved prognosis, the cost of new drug therapies for cancer treatment has skyrocketed in recent years, which has become a problem worldwide (27–29). For example, high drug costs threaten healthcare budgets and limit funding for other areas such as public investment. In countries that, unlike Japan, do not have universal health insurance, the high cost of prescription drugs can lead to high out-of-pocket costs for individual patients, making drugs unaffordable for those who need them. Recently, higher drug costs have been widely reported across new therapies, particularly for patients with prostate cancer and RCC (30,31). In this study, we surveyed patients with untreated Stage IV prostate cancer and RCC in Japan to determine the currently used drugs. We also calculated the proportion of new treatments in the total drug treatment and the monthly cost per month for each treatment. This study was carried out under the leadership of the Japan Clinical Oncology Group (JCOG) Health Economic Committee.

## Patients and methods

A survey was conducted among physicians at JCOG-affiliated centers regarding the initial drug therapy given to patients with untreated Stage IV prostate cancer and RCC. The patients were first diagnosed with advanced cancer at JCOG institutions between April 2022 and March 2023. The number of patients in different age categories (<75 and ≥75 years) were collected separately. A Google Form questionnaire was used, and no personal patient information was collected; the survey investigated the initial treatment given.

The prostate cancer drug regimens included ADT alone (goserelin, leuprorelin or degarelix), ADT + antiandrogen (bicalutamide or flutamide), ADT + docetaxel and ADT + androgen receptor signaling inhibitor (ARSI; abiraterone, apalutamide or enzalutamide). For RCC drug therapy, the study included patients who received TKI (sunitinib, pazopanib, cabozantinib or sorafenib), IO–IO (nivolumab + ipilimumab) and IO–TKI (pembrolizumab + axitinib, avelumab + axitinib, nivolumab + cabozantinib or pembrolizumab + lenvatinib) regimens.

Drug costs were calculated according to drug prices as of September 2023. For docetaxel, avelumab and ipilimumab doses, a body weight of 59 kg and a body surface area of 1.68 m<sup>2</sup> were used as the standard for Japanese patients. For nivolumab + ipilimumab, the monthly cost was calculated after calculating the 12-month drug cost because the cost of treatment in the first 3 months and beyond varies. We defined high-cost and very high-cost treatments as those that cost ≥500 000 and ≥1 000 000 Japanese yen (JPY) per month, respectively, as per the definition prescribed by the JCOG Health Economics Committee.

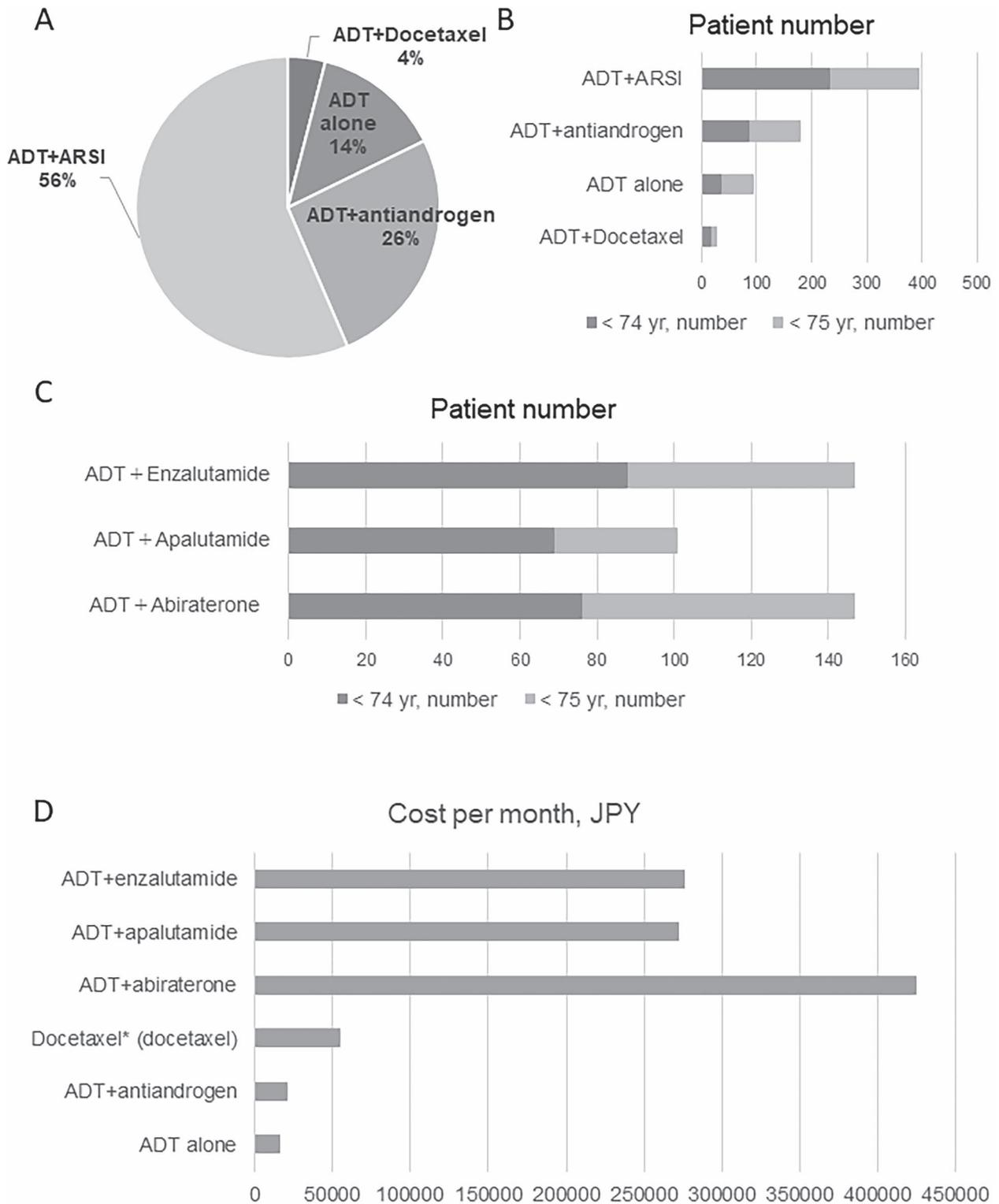
## Results

Among 44 JCOG participating centers, 38 and 36 centers provided information about the drugs they used to treat prostate cancer and RCC, respectively (Supplementary Table 1). A total of 700 patients with untreated Stage IV prostate cancer and 137 patients with Stage IV RCC were surveyed.

The main treatments that were introduced for metastatic hormone-sensitive prostate cancer (mCSPC) stratified by age and cost per month are shown in Fig. 1 and Table 1. ADT + ARSI was the most common (56%) regimen, and ADT + docetaxel was the least common (4.0%). Patients who were ≥75 years old were more likely to be treated with ADT alone than patients <75 years old (18.5% vs. 9.6%). Furthermore, patients ≥75 years old were less likely to be treated with ADT + apalutamide than those <75 years old (9.8% vs. 18.4%). Of note, ADT + ARSI was administered to 56% of all treated patients, with drug costs ranging from 272 874 to 424 746 JPY (Table 1). The cost of ADT + ARSI was 10.6–30.8-fold compared with ADT alone and ADT + antiandrogen, which are conventional treatments. Therefore, although no patients received high-cost treatments according to the definition used by this study, treatment costs for mCSPC have greatly increased. Details of drug costs for prostate cancer are described in Supplementary Table 2.

Table 2 lists the results of clinical trials on primary drug therapy for mCSPC. It summarizes the drug dose, OS, recurrence-free survival, older adult sample size and treatment duration of each clinical trial. The control treatment was ADT alone in all clinical trials except the ENZAMET trial. The LATITUDE trial included patients with high-risk mCSPC, while the other trials included all mCSPC patients. In each trial, >45% of patients were >70 years old and 20–30% were >75 years old. The previously reported median durations of treatment for ADT alone, ADT + antiandrogen, ADT + docetaxel, ADT + abiraterone, ADT + apalutamide and ADT + enzalutamide were 13.8–20.2, 13.8–20.2, 33, 25.8, 39.3 and 40.2 months, respectively (Table 2). ADT + enzalutamide had the longest median treatment duration, and the overall total treatment cost was 11 094 034 JPY. Since no head-to-head trials have compared these three ARSIs, clinicians are faced with the challenging task of choosing the most appropriate treatment for patients with mCSPC.

Figure 2 and Table 3 show the treatments that were used for metastatic renal cancer stratified by age and cost per month: TKI alone, nivolumab + ipilimumab, pembrolizumab + axitinib,



**Figure 1.** (A) Treatment selection for patients with untreated Stage IV prostate cancer. (B) Treatment selection (stratified by age) for patients with untreated Stage IV prostate cancer. (C) Number of patients stratified by age for each of the three ADT + ARSI treatments. (D) Treatment costs of different regimens. ADT, androgen deprivation therapy; ARSI, androgen receptor signaling inhibitor.

avelumab + axitinib, nivolumab + cabozantinib, pembrolizumab + lenvatinib were administered to 8.8, 19.3, 10.8, 9.3, 17.5 and 34.3% of patients. A higher proportion of patients >75 years of age were treated with TKIs alone than patients <75 years of age (13.5 vs.

6.9%). Moreover, patients ≥75 years of age were also more likely to receive avelumab + axitinib than those <75 (6.9 vs. 15.3%). Drug costs ranged from 623 243 to 1 616 042 JPY, all of which were high-cost treatments (>500 000 JPY). Four combination therapies were

**Table 1.** Number of patients by type of treatment, breakdown of patients by age, and monthly drug costs

Treatment	Age, <75 yr	Age, ≥75 yr	Total	Cost per month, JPY
ADT alone	36 (9.6%)	60 (18.5%)	96 (13.7%)	16 383
ADT+ antiandrogen	87 (23.2%)	94 (28.9%)	181 (25.9%)	21 319
ADT+ docetaxel	19 (5.1%)	9 (2.8%)	28 (4.0%)	54 693
ADT+ abiraterone	76 (20.3%)	71 (21.8%)	147 (21.0%)	424 746
ADT+ apalutamide	69 (18.4%)	32 (9.8%)	101 (14.4%)	272 874
ADT+ enzalutamide	88 (23.5%)	59 (18.2%)	147 (21.0%)	275 971
Total	375 (100%)	325 (100%)	700 (100%)	

ADT + ARSI  
(56.4%)

ADT, androgen deprivation therapy.

**Table 2.** Results of pivotal trials investigating hormone therapies for metastatic prostate cancer

	Latitude	Charrrted	Enzamet	Arches	Titan
Author	Fizazi (2017, 2019)	Sweeney (2015) Kyriakopoulos (2018)	Davis (2019) Sweeney (2023)	Armstrong (2019) Armstrong (2022)	Chi (2019, 2021)
New treatment	Abiraterone + ADT	Docetaxel + ADT	Enzalutamide + ADT	Enzalutamide + ADT	Apalutamide + ADT
Dosage	1000 mg	75 mg/m <sup>2</sup>	160 mg	160 mg	240 mg
Control	Placebo + ADT	ADT	NSAA + ADT	Placebo + ADT	Placebo + ADT
Inclusion criteria	High-risk mHSPC Gleason >8 Bone meta >3 Visceral meta	mHSPC	mHSPC	mHSPC	mHSPC
N (total)	1199	790	1125	1150	1152
N (new treatment)	597	397	563	574	525
Age (new treatment), years, median (range)	68 yr (38–89)	64 yr (36–88)	69 yr (63–74)	70 yr (46–92)	69 yr (45–94)
Elderly patients (new treatment), No. (%)	≥75 yr, 123 (20.6%)	≥70 yr, 178 (44.8%)	≥70 yr, 257 (45.6%)	≥75 yr, 170 (29.6%)	≥75 yr, 133 (25.3%)
OS, months, median, New treatment/control	53.3/36.5	57.6/47.2	NR/NR	NR/NR	NR/52.2
	HR 0.66 (95%CI 0.56–0.78)	HR 0.72 (95%CI 0.59–0.89)	HR 0.70 (95%CI 0.58–0.84)	HR 0.66 (95%CI 0.53–0.81)	HR 0.66 (95%CI 0.53–0.79)
PFS, months, median, New treatment/control	33.1/14.7	33.0/19.8	81.0/25.0	49.8/38.9	NR/22.1
	HR 0.46 (95%CI 0.39–0.54)	HR 0.62 (95%CI 0.51–0.75)	HR 0.45 (95%CI 0.39–0.53)	HR 0.63 (95%CI 0.52–0.76)	HR 0.48 (95%CI 0.39–0.60)
Treatment duration, month, median (range)					
New treatment	25.8 (IQR: 12.3–49)	NA	NA	40.2 (range 0.2–58.1)	39.3 (range 0–55.7)
Control	14.4 (IQR: 7.3–25.8)	NA	NA	13.8 (range 0.2–27.6)	20.2 (range 0.1–37.0)

c, clinical; CI, confidence interval; meta, metastasis; HR, hazard ratio; NA, not available; NR, not reached; NSAA, non-steroidal antiandrogen; OS, overall survival; PC, prostate cancer; PFS, progression-free survival; r, radiographic.

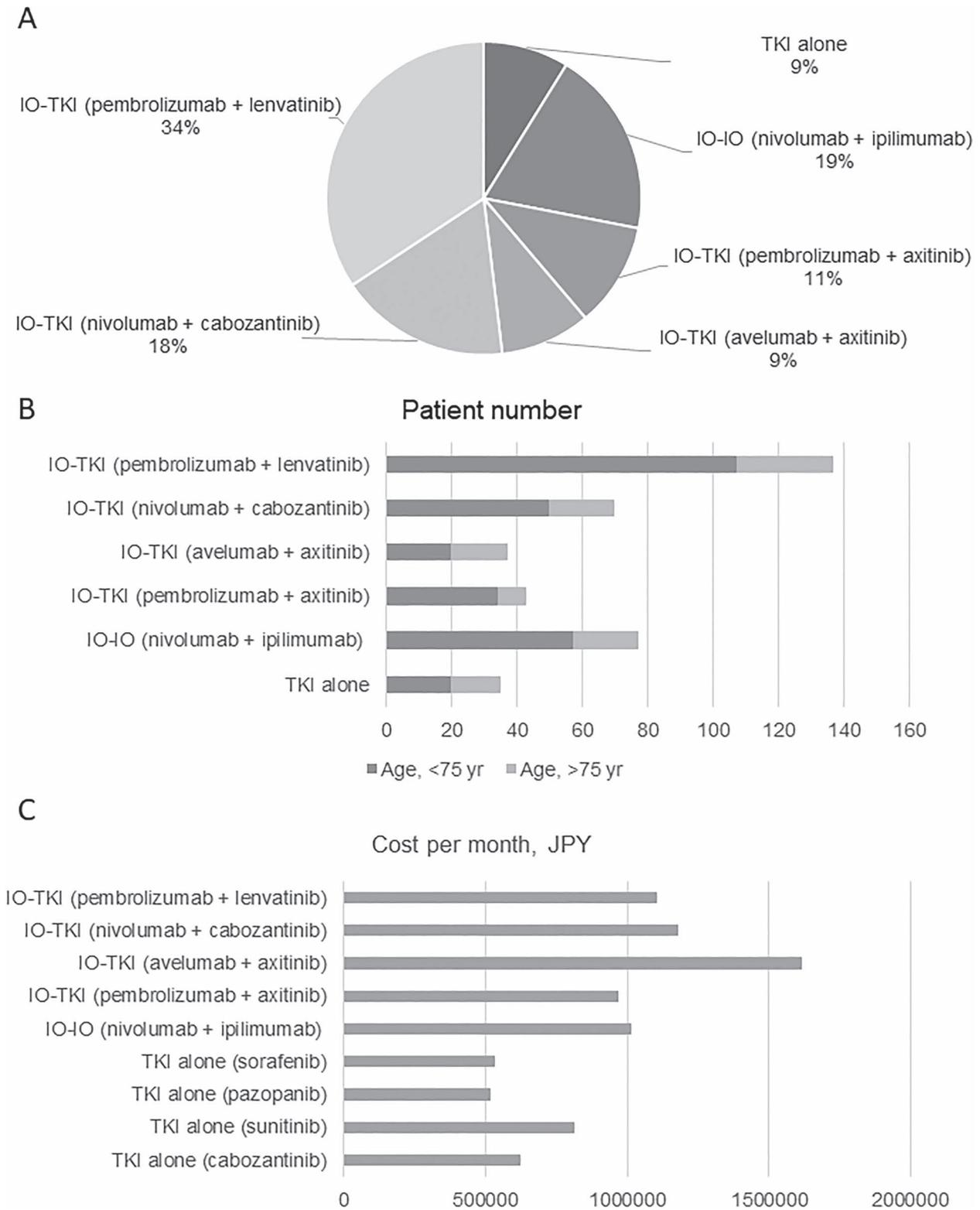
very expensive, costing >1 000 000 JPY/month, and the fifth did not strictly meet the definition of a very high-cost treatment, but was expensive, costing close to 1 000 000 JPY/month. According to the definition of this study, all patients received high-cost treatments as primary therapy for metastatic renal cancer. Furthermore, 80.4% of patients with metastatic renal cancer received very high-cost treatments, with breakdown of 81.3% of <75 years of age and 78.4% of ≥75 years of age. The details of drug costs for RCC are described in [Supplementary Table 3](#).

[Table 4](#) lists the results of clinical trials of metastatic RCC treatments. In all trials, the control was sunitinib alone. Four trials included ~40% of patients aged ≥65 years. In the nivolumab + ipilimumab trial, only 8.2% of the patients were aged ≥75 years. The duration of TKI alone, nivolumab + ipilimumab, pembrolizumab +

axitinib, avelumab + axitinib and nivolumab + cabozantinib and pembrolizumab + lenvatinib treatments were reported as 7.3–11, 7.9, 10.4, 8.6–9.0, 14.3 and 17 months of treatment, respectively ([Table 4](#)). The pembrolizumab + lenvatinib regimen had the longest median treatment duration, and the overall total treatment cost was calculated to be 18 784 677 JPY. The lack of head-to-head trials has made it difficult for clinicians to select the first-line treatment for patients with metastatic RCC.

## Discussion

Until 2015, ADT alone was the common treatment for mCSPC. However, in recent years, novel hormone therapy and chemotherapy drugs have been developed based on ADT, and clinical trials



**Figure 2.** (A) Treatment selection for patients with untreated Stage IV renal cell carcinoma (RCC). (B) Treatment selection stratified by age for patients with untreated Stage IV RCC. TKI, tyrosine kinase inhibitor; IO, immune-oncology drug; JPY, Japanese yen.

have shown their efficacy and safety. The 2023 Japan Urological Association guidelines also weakly recommend the use of ADT + ARSI as a primary hormone therapy for mCSPC (32).

In the current survey, ADT + ARSI was introduced in 56% of patients in Japan. Three ADT + ARSI regimens are available, but the number of patients treated with ADT + apalutamide, which has

**Table 3.** Number of patients by type of treatment, breakdown of patients by age, and monthly drug costs

Treatment	Age, <75 yr	Age, ≥75 yr	Total	Cost per month, JPY
TKI alone	20 (6.9%)	15 (13.5%)	35 (8.8%)	623 243
IO–IO (nivolumab + ipilimumab)	57 (19.8%)	20 (18%)	77 (19.3%)	1 012 535
IO–TKI (pembrolizumab + axitinib)	34 (11.8%)	9 (8.1%)	43 (10.8%)	971 919
IO–TKI (avelumab + axitinib)	20 (6.9%)	17 (15.3%)	37 (9.3%)	1 616 042
IO–TKI (nivolumab + cabozantinib)	50 (17.4%)	20 (18%)	70 (17.5%)	1 181 236
IO–TKI (pembrolizumab + lenvatinib)	107 (37.2%)	30 (27%)	137 (34.3%)	1 104 981

TKI, tyrosine kinase inhibitor; IO, immune-oncology drug; JPY, Japanese yen

**Table 4.** Results of pivotal trials investigating combination therapies for metastatic renal cell carcinoma

	CheckMate 214	JAVELIN Renal 101	KEYNOTE-426	CheckMate 9ER	CLEAR
Author	Motzer (2018, 2019) Albiges (2020)	Motzer (2019) Choueiri (2020)	Rini (2019) Powles (2020)	Choueiri (2021) Motzer (2022)	Motzer (2021) Choueiri (2023)
New treatment	Ipilimumab +Nivolumab	Avelumab + Axitinib	Pembrolizumab +Axitinib	Nivolumab + Cabozantinib	Pembrolizumab +Lenvatinib
Dosage	Nivolumab (3 mg per kilogram), Ipilimumab (1 mg per kilogram)	Avelumab (a dose of 10 mg per kilogram of body weight), axitinib (5 mg twice daily)	Pembrolizumab was (a dose of 200 mg once every 3 weeks), Axitinib (a dose of 5 mg twice daily)	Nivolumab (a dose of 240 mg), cabozantinib (a dose of 40 mg once daily)	Lenvatinib (a dose of 20 mg orally once daily), pembrolizumab (a dose of 200 mg)
Control	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Inclusion criteria	Untreated advanced renal-cell carcinoma with a clear-cell component	Untreated advanced renal-cell carcinoma with a clear-cell component	Untreated advanced renal-cell carcinoma with a clear-cell component	Untreated advanced renal-cell carcinoma with a clear-cell component	Untreated advanced renal-cell carcinoma with a clear-cell component
IMDC risk	Intermediate/poor	All risk	All risk	All risk	All risk
N (total)	847	886	861	651	1069
N (new treatment)	425	442	432	323	355
Age (treatment), years, median (range)	62 yr (26–85)	62 yr (29–83)	62 yr (30–89)	62 yr (29–90)	64 yr (34–88)
Elderly patients (treatment), No. (%)	≥75 yr, 35 (8.2%)	≥65 yr, 171 (38.7%)	≥65 yr, 172 (39.8%)	≥65 yr, 132 (40.9%)	≥65 yr, 161 (45.4%)
OS, months, median New treatment/control	48.1/26.6	NR/NR	NR/35.7	37.7/34.3	NR/NR
	HR 0.65, 95%CI (0.54–0.78)	0.80, 95% CI (0.62–1.03)	HR 0.68, 95%CI (0.55–0.85)	HR 0.70, 95%CI (0.55–0.90)	HR 0.72 95%CI (0.55–0.93)
PFS, months, median New treatment/control	11.2/8.3	13.3/8.0	15.4/11.1	16.6/8.3	23.3/9.2
	HR 0.74 (95%CI 0.62–0.88)	HR 0.69 (95% CI 0.57–0.83)	HR 0.71 (95%CI 0.60–0.84)	HR 0.56 (95%CI 0.46–0.68)	HR 0.42 (95%CI 0.34–0.52)
Treatment duration, month, median (range) New treatment	7.9 (2.1–21.8)	8.6 (0.5–25.3) for avelumab, 9.0 (0.02–24.9) for axitinib	10.4 (0.03–21.2)	14.3 (0.2–27.3)	17.0 (0.1–39.1)
Control	7.8 (3.5–19.6)	7.3 (0.2–23)	7.8 (0.07–20.5)	9.2 (0.8–27.6)	11.0 (0.1–40.0)

been on the insurance list for only a short time, was less than that of the other two regimens. The low percentage of older patients administered ADT + apalutamide may be due to inexperience with administration of this combination therapy. By contrast, 34% of patients receive ADT + ARSI in the USA and Europe (33,34). This indicates that the use of ARSI is more widespread in Japan than in

the West possibly due to Japan's universal health insurance system, which makes the drugs available to many patients even if they are expensive. Although there was no treatment among the initial drug therapies for mCSPC in which the monthly cost exceeded 500 000 JPY, the total cost of ADT + ARSI is likely to be notably higher than other options because of the long treatment period involved.

Patients  $\geq 75$  years used ADT + antiandrogen more frequently than patients  $< 75$  (47.4 vs. 32.8%), whereas ADT + ARSI was used less frequently (49.8 vs. 62.2%). This suggests that clinicians balance efficacy and safety when choosing systemic treatment for mCSPC, considering the patient's age and medical condition. Of note, prospective data are limited due to the lack of enrollment of patients aged  $\geq 75$  years in pivotal clinical trials. However, retrospective real-world data indicate that caution is needed regarding adverse events specific to older adults, such as falls, but appropriately adjusted doses are well tolerated and provide oncologic benefits similar to those observed in younger adults (35–37). Among the three ARSIs, ADT + Abiraterone is  $\sim 1.5$ -fold compared with the other two ARSIs. However, no cost-effectiveness analysis has been performed to evaluate the relative merits of these three ARSIs.

The treatment of metastatic renal cancer has reached a turning point with the development of novel therapies combining immune checkpoint inhibitors and TKIs, resulting in increased therapeutic response rates and survival. The Society for Immunotherapy of Cancer guidelines state that all patients without contraindications to immunotherapy should receive a first-line IO-based regimen (38). Due to the lack of a cost-effectiveness analysis, clinicians need to choose the best IO-based regimen based on evidence from clinical trial data, pathological findings, patient compliance, personal belief and regulatory approval.

In this survey, TKI (only), IO–IO and IO–TKI regimens were administered to 9, 19 and 72% of the patients, respectively. By contrast, a report based on a US database showed that between 2019 and 2022, TKI monotherapy decreased from 33.8 to 8.4%, while IO–IO increased from 52.8 to 57.7% and IO–TKI also increased from 13.3 to 33.9% (39,40). This indicates that the use of immune-combination therapy is more widespread in Japan than in the West due to drug availability, even for RCC drug therapy.

Notably, avelumab + axitinib therapy has the highest cost,  $> 1.5$  million JPY per month, while the costs of the other four immune-combination therapies are  $\sim 1$  million JPY per month. All of the immune-combination therapies are expensive, but there are differences in cost among them; the relative differences between the therapies are small, but the absolute differences are appreciable. The most expensive drug among the TKI monotherapy options was sunitinib, but the monthly drug costs for both TKI monotherapy options exceeded 500 000 JPY. Because conventional TKI therapy is also expensive, the cost ratio of the new therapy compared with conventional therapy for RCC is not as obvious as that of prostate cancer, but the overall cost is larger (41).

While avelumab + axitinib was prescribed the least frequently, it was prescribed the most frequently to the elderly among first-line combined immunotherapies. This may be partly due to the drug characteristics (avelumab is a PDL1 antibody) and safety profile. This combination has the lowest incidence of immune-related adverse events, hence, the increased probability of prescribing it to older adults (20). The most frequently prescribed combined immunotherapy was pembrolizumab + lenvatinib, but the frequency of prescriptions for older adults was low. This is due to the higher incidence of adverse events in prospective studies compared with other immunocomplex therapies (42), resulting in physicians being cautious about administering the therapy.

There are clinical trials that have focused on reducing the cost of expensive drugs. One of them is the low-dose abiraterone trial in which the dose of abiraterone can be reduced by taking it after a meal with non-inferior effect to the standard dose (43,44). Although no Phase III trials have been conducted, the NCCN guidelines suggest taking a quarter of the usual dose of abiraterone with a

low-fat diet as an alternative when circumstances preclude taking the typical dose (45,46). The other clinical trial is related to IO-based treatment. Considering the long-lasting effect of IO-based treatment, discontinuation of IO-based therapy may help reduce side effects and the financial burden of taking these drugs. There are two ongoing prospective trials that aim to confirm the non-inferiority of discontinuation versus continuation of IO-based treatment (47,48).

This study had limitations. First, the survey was conducted over a short period of 1 year at limited JCOG participating centers and did not capture the actual treatment duration. Second, the cost of each treatment was calculated based on 1 year of treatment at the usual dose, and thus, does not consider cases in which the dose was reduced or discontinued in actual practice. However, to the best of our knowledge, this is the first report of a survey of first-line drug regimens for patients with untreated Stage IV prostate cancer and RCC patients in Japan stratified by age and treatment costs. The survey results can be used to plan future health economic studies that examine cost-effectiveness and promote the efficient use of limited resources to ensure better patient outcomes.

## Conclusion

This study reports on prescription preferences and respective drug costs in Japan based on a questionnaire survey of first-line drug therapy for untreated Stage IV prostate cancer and RCC. Most Japanese patients with urologic cancers receive state-of-the-art, effective treatments, but the costs of these treatments are very high and rapidly increasing.

## Supplementary Data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

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## Conflict of interest statement

Takahiro Osawa has received honoraria from Ono, MSD and Takeda. Hiroshi Kitamura has received honoraria from Astellas, AstraZeneca, Bristol-Myers Squibb, Janssen, MSD and Sanofi and has received research expenses from AstraZeneca, Bristol-Myers Squibb and MSD. Hiroyuki Nishiyama received honoraria from Astellas, AstraZeneca, Bristol-Myers Squibb, Ono, MSD and Merck, donations for education and research from Bayer and consultant fees from Janssen, MSD, One and AstraZeneca. The other authors have no conflicts of interest.

## Author contributions

T.O., K.S. and R.M. designed the research. T.O., K.S. and R.M. collected the data. T.O. analyzed the data. T.M., Y.M., H.K., and H.N supervised the project. T.O. wrote the paper. All authors read and approved the final manuscript.

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Original Article

# Current status of the cost burden of first-line systemic treatment for patients with advanced hepatocellular carcinoma in Japan, 2021–22

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## Abstract

**Background:** Although recent advances in systemic therapies for hepatocellular carcinoma (HCC) have led to prolonged patient survival, the high costs of the drugs place a heavy burden on both

patients and society. The objectives of this study were to examine the treatment regimens used as first-line systemic treatment for patients with advanced HCC in Japan and to estimate the treatment costs per regimen.

**Methods:** For this study, we aggregated the data of patients who had received first-line systemic treatment for advanced HCC between July 2021 and June 2022. The treatment cost per month of each regimen was estimated based on standard usage, assuming an average weight of 60 kg for male patients. The data were categorized by the treatment regimen, and the treatments were categorized based on the cost into very high-cost ( $\geq 1\,000\,000$  Japanese yen [JPY]/month), high-cost ( $\geq 500\,000$  JPY/month) and other ( $< 500\,000$  JPY/month) treatments.

**Results:** Of the total of 552 patients from 24 institutions whose data were analyzed in this study, 439 (79.5%) received atezolizumab plus bevacizumab, 98 (17.8%) received lenvatinib and 15 (2.7%) received sorafenib as the first-line treatment. The treatment cost per month for each of the above regimens was as follows: atezolizumab plus bevacizumab, 1 176 284 JPY; lenvatinib, 362 295 JPY and sorafenib, 571 644 JPY. In total, 82.2% of patients received high-cost regimens, and the majority of these patients received a very high-cost regimen of atezolizumab plus bevacizumab.

**Conclusions:** Advances in systemic therapies for HCC have led to prolonged patient survival. However, the treatment costs are also increasing, imposing a burden on both the patients and society.

**Key words:** hepatocellular carcinoma, treatment cost, immune checkpoint inhibitor, tyrosine kinase inhibitor, cost burden

## Introduction

Hepatocellular carcinoma (HCC) is one of the deadliest cancers known and the third leading cause of cancer death. In 2020, it is estimated that over 830 000 patients worldwide died from this disease (1). Although the incidence of HCC has declined globally, it remains one of the most commonly diagnosed cancers, with over 900 000 new patients diagnosed each year (2). One of the clinical problems associated with HCC is its resistance to systemic treatments. Patients with advanced disease (e.g. those with portal vein invasion and distant metastases) are candidates for systemic therapies, and ~50–60% of patients will receive systemic therapy at some point during the clinical course of the disease (3). However, advanced disease carries a dismal prognosis, with an overall survival (OS) of ~2 years (4).

There has been a rapid expansion of systemic treatment options approved by the Japan Pharmaceuticals and Medical Devices Agency (PMDA) for patients with advanced HCC, ranging from anti-vascular endothelial growth factor (VEGF) antibodies to multi-targeted tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors (ICIs) and combinations of the above. Consequently, sorafenib, lenvatinib, atezolizumab plus bevacizumab and durvalumab plus tremelimumab have come to be used as first-line treatments for HCC in Japan. While these therapeutic regimens are effective for treating advanced HCC, many patients with advanced HCC, not only in Japan but around the world, face substantial financial pressure due to medical expenses (5). Furthermore, the high costs of the treatments also place a heavy burden on the social health resources (6–8). Therefore, we performed a multicenter survey to clarify the current status of the cost burden of first-line systemic treatment of advanced HCC in Japan. The objectives of this study were to examine the treatment regimens used as first-line systemic treatment for advanced HCC and estimate the cost of treatment using each of these regimens in Japan. This study was carried out under the leadership of the Japan Clinical Oncology Group's (JCOG) Health Economic Committee.

## Methods

For this study, we distributed an online questionnaire via Google Forms to institutions affiliated with the JCOG Hepatobiliary and Pancreatic Oncology Group and aggregated the treatment data obtained in response to the questionnaire. The treatment data of patients who had received first-line systemic treatment for advanced HCC between July 2021 and June 2022 were aggregated, but no patient personal data were collected. Thus, this study did not require individual consent or Institutional Review Board approval. The data of patients in different age categories ( $\leq 74$  and  $\geq 75$  years) were collected separately. The treatments were categorized into very high-cost ( $\geq 1\,000\,000$  Japanese yen [JPY]/months), high-cost ( $\geq 500\,000$  JPY/months) and other ( $< 500\,000$  JPY/month) treatments based on the definition provided by the JCOG Health Economic Committee. The treatment cost per month of each regimen was estimated based on standard usage, that is, assuming an average weight of 60 kg for male patients treated without any skips, delays and/or dose reductions (Table 1). The standard usage protocol of each of the regimens was as follows: atezolizumab plus bevacizumab: atezolizumab 1200 mg plus bevacizumab at 15 mg/kg body weight administered intravenously every 3 weeks; lenvatinib: 12 mg/day (for patients with a body weight of  $\geq 60$  kg) or 8 mg/day (for patients with a body weight of  $< 60$  kg) administered orally and sorafenib: 400 mg administered orally twice-daily in 28-day cycles. Treatment costs were calculated based on the drug prices as of March 2024; the costs of supportive care (e.g. antiemetics and medications for adverse events) were not included.

## Results

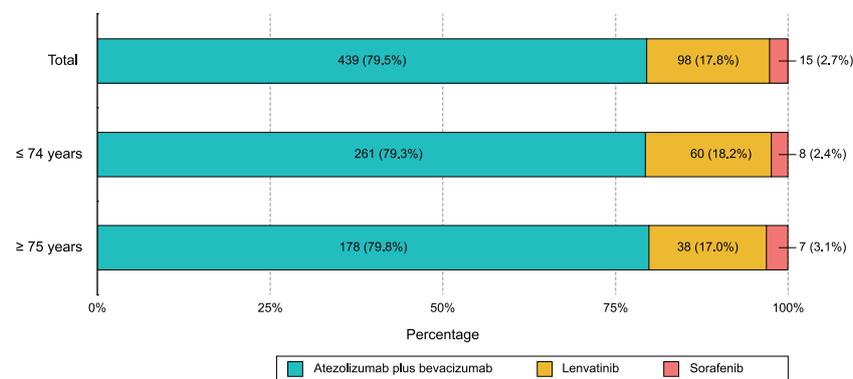
Data on a total of 552 patients who had received first-line systemic therapy for HCC between July 2021 and June 2022 were collected from 24 institutions. Of the 552 patients, 329 (59.6%) were  $\leq 74$  years old and 223 patients (40.4%) were  $\geq 75$  years old.

**Table 1.** Results of pivotal studies for advanced HCC and cost in Japan

Regimen	Publication year	median OS (months)	median PFS (months)	Mean dose intensity (%)	Cost <sup>a</sup> (JPY)
Atezolizumab plus bevacizumab (11)	2020	19.2 (9)	6.9	95 (Atezolizumab)	1 176 284
Durvalumab plus tremelimumab (13)	2022	16.43	3.78	93 (Bevacizumab) not reported	3 806 181 (first month) 1 329 232 (after the first month)
Durvalumab (13)	2022	16.56	3.65	not reported	1 329 232
Lenvatinib (10)	2018	13.6	7.4	88	362 295
Sorafenib (9)	2008	10.7	5.5 <sup>b</sup>	84 (12)	571 644

OS, overall survival; PFS, progression-free survival; JPY, Japanese yen. <sup>a</sup>The costs were calculated as the cost for body weight (60 kg) per month (30 days).

<sup>b</sup>Time to radiologic progression.



**Figure 1.** Bar chart presenting the percentages of patients receiving each of the major treatment regimens used as first-line systemic treatment for advanced hepatocellular carcinoma in Japan.

The details of the treatment regimens these patients received were as follows: atezolizumab plus bevacizumab, 439 patients (79.5%); lenvatinib, 98 patients (17.8%) and sorafenib, 15 patients (2.7%) (Fig. 1). Of the 329 patients who were ≤74 years old, 261 (79.3%) received atezolizumab plus bevacizumab, 60 (18.2%) received lenvatinib and 8 (2.4%) received sorafenib. Of the total 223 patients who were ≥75 years old, 178 (79.8%) received atezolizumab plus bevacizumab, 38 (17.0%) received lenvatinib and 7 (3.1%) received sorafenib.

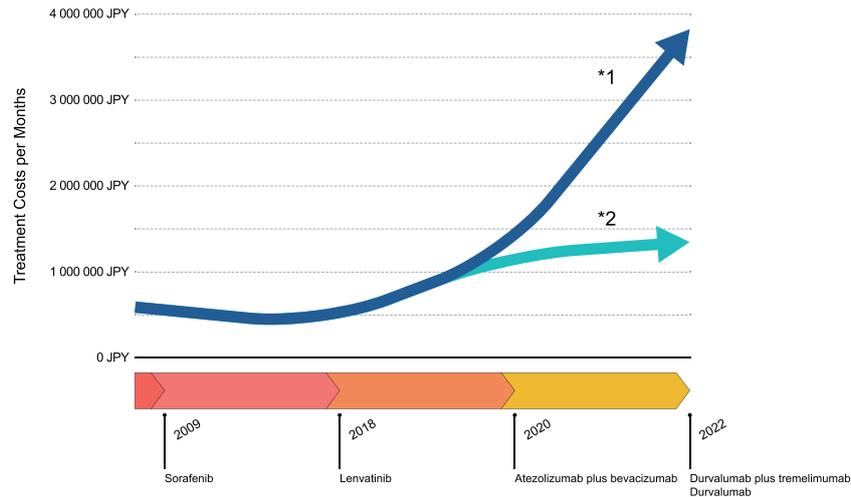
The details of the treatment costs per month for each regimen were as follows: atezolizumab plus bevacizumab, 1 176 284 JPY; lenvatinib, 362 295 JPY and sorafenib, 571 644 JPY (Table 1). In all, 82.2% of patients received high-cost treatments, and 79.5% received the very high-cost treatment of atezolizumab plus bevacizumab. Similarly, 83.0% of patients received high-cost treatments, and 79.8% received the very high-cost treatment in elderly patients.

## Discussion

In the present study, using data obtained from a multicenter survey, we clarified the current status of the cost burden of first-line systemic treatment for advanced HCC in Japan. Over 80% of patients received high-cost treatments (atezolizumab plus bevacizumab or sorafenib), of which the majority received very-high-cost treatment (atezolizumab plus bevacizumab). This finding was nearly identical among both the age groups (≤74 and ≥75 years) of HCC patients included in the analysis. Advances in systemic therapies for HCC

have led to prolonged patient survival. However, they are also leading to healthcare economic issues, including increased treatment costs.

In recent years, the landscape of advanced HCC treatment has changed dramatically (Table 1), primarily with the advent of targeted therapies and immunotherapy. The initial era of systemic therapy for advanced HCC was dominated by single-agent treatment with sorafenib, following its approval by the PMDA in 2009; this approval was granted on the basis of data from the phase III SHARP trial, which demonstrated an OS benefit in the treatment arm over the placebo arm (9). Around a decade later, the phase III REFLECT trial showed the non-inferiority of lenvatinib, a multikinase inhibitor with activities against both VEGFR and FGFR, as compared with sorafenib (10). Although lenvatinib failed to yield superior OS, it demonstrated activity and a statistically significantly improved progression-free survival (PFS) and objective response rate. Thus, lenvatinib is generally preferred over sorafenib for the systemic treatment of patients with HCC. Now, a new era of ICI therapy has begun. In the phase III IMbrave150 trial, atezolizumab plus bevacizumab (an anti-PD-L1 inhibitor and anti-VEGF antibody, respectively) were demonstrated to show substantial OS and PFS benefits as compared with sorafenib (11,12). The toxicity profile of the patients treated with atezolizumab plus bevacizumab was also manageable; based on this evidence, the PMDA approved this combination treatment in 2020. Subsequently, the phase III HIMALAYA trial demonstrated the superiority of durvalumab plus tremelimumab over sorafenib as a first-line systemic treatment for advanced HCC. Similarly, durvalumab monotherapy can also be considered in this setting, being



**Figure 2.** History of approved treatment regimens for advanced hepatocellular carcinoma and their costs in Japan. JPY, Japanese yen; \*1, Durvalumab plus tremelimumab; \*2, Durvalumab monotherapy.

non-inferior to sorafenib and having a more favorable toxicity profile (13). Consequently, a paradigm shift from the use of TKIs to the use of ICIs for the treatment of HCC has led to prolonged survival of the patients, but also a significant increase in treatment costs.

We did not examine the treatment costs of durvalumab and tremelimumab, which began to be reimbursed by national health insurance only in 2023; if this combination of ICIs were also to be included, the derived treatment costs could increase further (Fig. 2). There is a lack of robust head-to-head trial data to compare the efficacy and safety of atezolizumab plus bevacizumab and durvalumab plus tremelimumab. Thus, there is currently no consensus on the use of atezolizumab plus bevacizumab, durvalumab and tremelimumab for the treatment of advanced HCC. Additionally, many ongoing trials still use TKIs as controls since trials comparing TKIs and ICIs were initiated almost simultaneously, and several trials have not yet reported their results (Table 2). The growth of ICI-based regimens may confuse clinicians in making treatment decisions in the future (14). However, given the efficacy data (median OS, 19.2 months for atezolizumab plus bevacizumab versus 16.43 months for durvalumab and tremelimumab) and treatment costs per month (1 176 284 JPY for atezolizumab plus bevacizumab versus 3 806 181 JPY for durvalumab and tremelimumab) of the two combination treatments, durvalumab and tremelimumab are unlikely to be cost-effective due to similar survival benefits and much higher treatment costs. Such cost-effectiveness considerations may help clinicians in making optimal decisions regarding the treatment of advanced HCC. Therefore, further randomized trials and cost-effectiveness analyses of these regimens are warranted.

Another problem in relation to the treatment costs of advanced HCC is the advancing age of the patients. With the aging of the population in developed countries, patients with HCC are also aging. One epidemiological report based on the SEER registry data showed that although the incidence of HCC is decreasing among younger patients, it continues to increase among elderly patients, in both men and women of all races/ethnicities (15). This phenomenon could affect the health care system through two scenarios. First, as the proportion of the aging population increases, the proportion that pays taxes and premiums to finance the system decreases. The treatment cost is financed not only by governmental revenues but also by insurance premiums imposed on employers and employees. This means that

the younger generation will have to bear a greater cost burden in the future. Second, elderly patients face higher health risks, including adverse events caused by the systemic treatments themselves, and require a greater amount of care than younger patients. Japan's insurance system maintains a low patient copayment rate for medical expenses. However, in recent years, the rate has been raised to control the growing cost burden among elderly patients. Despite these efforts, the socioeconomic burden continues to increase since the high-cost medical care system sets an upper limit on the total amount of medical expenses per month, even for elderly patients. Several studies have reported that systemic treatments are equally effective in elderly patients. For example, Li et al. (16) reported from a *post hoc* analysis of the IMbrave150 trial that the atezolizumab plus bevacizumab arm, showed a prolonged OS and PFS as compared with the sorafenib arm even among elderly patients ( $\geq 75$  years old). However, the aforementioned risks could lead to reduced cost-effectiveness in elderly patients (17–19). When considering the cost burden of systemic therapy for HCC and making treatment decisions, it is necessary to evaluate not only the effectiveness but also the cost-effectiveness of the available therapeutic strategies.

Currently, many clinical trials are being conducted to explore effective treatment options (Table 2). The majority of these trials are of combination regimens with ICIs: anti-PD-1/PD-L1 antibody, anti-CTLA-4 antibody, anti-TIGIT antibody and anti-LAG-3 antibody. Furthermore, several late-phase trials are underway to evaluate the efficacy of triplet therapies, including ICIs and TKIs, with the expectation of higher anti-tumor efficacies. Another trend of the ongoing clinical trials is to examine the expansion of the indications of ICIs. Several trials of ICIs in combination with local and adjuvant treatments are underway (Table 2), and some have reported positive results. In the phase III EMERALD-1 trial assessing transarterial chemoembolization (TACE) in combination with durvalumab and/or bevacizumab versus TACE plus placebo, the TACE with durvalumab plus bevacizumab arm showed a statistically significantly better PFS as compared with the TACE plus placebo arm in patients with intermediate-stage HCC (20). The IMbrave050 trial evaluated the efficacy of atezolizumab plus bevacizumab in the adjuvant setting in patients with HCC with high-risk features after curative resection or ablation (21). The study was the first successful phase III trial to show improved recurrence-free survival after curative treatment in patients

**Table 2.** Ongoing major clinical trials for advanced hepatocellular carcinoma

Trial name and/or ID	Investigational treatment	Control	Phase	Primary end points	Treatment line
Advanced stage					
Checkmate 9DW NCT04039607	Nivolumab (anti-PD-1 antibody) plus ipilimumab (anti-CTLA-4 antibody)	Sorafenib (TKI) or lenvatinib (TKI)	III	OS	First-line
IMbrave152 NCT05904886	Tiragolumab (anti-TIGIT antibody) plus atezolizumab (anti-PD-L1 antibody) + bevacizumab (anti-VEGF antibody)	Atezolizumab plus bevacizumab	III	OS & PFS	First-line
NCT04183088	Tislelizumab (anti-PD-1 antibody) plus regorafenib (TKI)	–	II	ORR & PFS	First-line
NCT03680508	Cobolimab (TIM-3 binding antibody) plus dostarlimab (anti-PD-1 antibody)	–	II	ORR	First-line
TRIPLET NCT05665348	Atezolizumab plus bevacizumab plus ipilimumab	Atezolizumab plus bevacizumab	II/III	ORR & OS	First-line
RELATIVITY-106 NCT05337137	Relatlimab (anti-LAG-3 antibody) plus nivolumab plus bevacizumab	Nivolumab plus bevacizumab	I/II	ORR	First-line
NCT04194775	Nofazlimab (anti-PD-1 antibody) plus lenvatinib	Lenvatinib	III	OS	First-line
NCT04523493	Toripalimab (anti-PD-1 antibody) plus lenvatinib	Lenvatinib	III	OS	First-line
NCT03605706	SHR-1210 (anti-PD-1 antibody) plus FOLFOX4	SHR-1210	III	OS	First-line
NCT03764293	SHR-1210 (anti-PD-1 antibody) plus apatinib (TKI)	Sorafenib	III	OS & PFS	First-line
NCT04720716	IBI310 (anti-CTLA-4 antibody) plus sintilimab (anti-PD-1 antibody)	Sorafenib	III	ORR & OS	First-line
NCT04723004	Toripalimab (anti-PD-1 antibody) plus bevacizumab	Sorafenib	III	OS & PFS	First-line
NCT05408221	Rulonilimab (anti-PD-1 antibody) plus lenvatinib	Lenvatinib	II/III	ORR	First-line
IMbrave-251 NCT04770896	Atezolizumab plus sorafenib or lenvatinib	Sorafenib or lenvatinib	III	OS	Second-line
Intermediate stage					
EMERALD-3 NCT05301842	TACE plus durvalumab (anti-PD-L1 antibody) plus tremelimumab (anti-CTLA-4 antibody) and/or lenvatinib	TACE	III	PFS	
CheckMate 74 W NCT04340193	TACE plus nivolumab and/or ipilimumab	TACE	III	OS & Time to TACE progression	
IMPACT jRCTs051230037	TACE plus atezolizumab plus bevacizumab	Atezolizumab plus bevacizumab	III	OS	
ABC-HCC NCT04803994	Atezolizumab plus bevacizumab	TACE	III	Time to failure of treatment strategy	
Adjuvant setting					
CheckMate 9DX NCT03383458	Nivolumab	Placebo	III	RFS	
KEYNOTE-937 NCT03867084	Pembrolizumab (anti-PD-1 antibody)	Placebo	III	RFS	
EMERALD-2 NCT03847428	Durvalumab and/or bevacizumab	Durvalumab	III	RFS	

TKI, tyrosine kinase inhibitor; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; TACE, transarterial chemoembolization; RFS, recurrence-free survival.

with HCC. These combination therapies of ICIs in combination with local and adjuvant therapies may improve the prognosis of patients with HCC, but they can also be expected to further increase the treatment costs.

The expansion of the indications of expensive immunotherapy regimens raises significant concerns about the current and future treatment costs worldwide. Due to the rising treatment costs, new oncology products frequently fail to meet the willingness-to-pay

threshold, or in other words, the maximum price a cancer patient is willing to pay for his/her treatment (22). Zou et al. (5) reported that the treatment for HCC places a significant economic burden on the patients and their families. Su et al. (23) reported that atezolizumab plus bevacizumab treatment was unlikely to be a cost-effective option as compared with sorafenib in patients with advanced HCC. The PMDA does not take cost-effectiveness into consideration when making approval decisions, so that cost-effectiveness analyses often end up only as academic exercises (22). To effect a change in this scenario, the oncology community should consider the cost-effectiveness of treatments in their guidelines and daily practices. In addition, the pricing and payment systems should be reformed in order to reduce the cost burden on the patients and society.

Other potential measures to improve the situation include promoting the use of less expensive but equally effective drugs. The use of biosimilars can improve cost-effectiveness. Although the development of biosimilars with large molecular weights is difficult due to technical difficulties, bevacizumab biosimilars have also received approval in Japan for the treatment of metastatic colorectal cancer, non-small cell lung cancer and breast cancer. Although convincing evidence is often thought to be lacking for biosimilars, over the past few years, a number of reports have demonstrated their benefits. A network meta-analysis showed that atezolizumab plus bevacizumab and sintilimab plus IBI305, a bevacizumab biosimilar, showed comparable efficacy (24). The rapid approval of such biosimilars for HCC is expected to reduce the treatment costs. In recent years, ICIs have been manufactured at a lower cost in China. Liu (25) reported that tislelizumab, an anti-PD-1 antibody, is the most cost-effective first-line systemic treatment agent for advanced HCC. Considering their cost-effectiveness, such drugs could be useful treatment options.

The present study had some limitations. The first was that this survey covered only institutions affiliated with the JCOG. In Japan, HCC treatment is not exclusively confined to oncologists but is also performed by hepatologists who oversee antiviral and local therapies. Therefore, the study data may not reflect the overall systemic treatment trends for HCC in Japan. The second limitation was that this study was a hospital-based study based on estimates of the proportion of patients who received the major systemic treatment regimens at each of the participating institutions. Patient-level data (e.g. duration of treatment, drug discontinuations and dose reductions) were not collected in this study. Therefore, our survey data cannot be used to assess the individual cost-effectiveness of the treatment regimens.

## Conclusion

In ~80% of patients with advanced HCC in Japan, the first-line systemic treatment prescribed was atezolizumab plus bevacizumab, a treatment regimen categorized as a very high-cost ( $\geq 1\,000\,000$  JPY/month) treatment. Advances in systemic therapies for HCC have led to prolonged patient survival but are also expected to lead to increased treatment costs and a heavy cost burden on patients and society in the future.

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## Authors' contributions

Hiroshi Imaoka (Conceptualization, Collection and assembly of data, Data curation, Formal analysis, Methodology, Supervision, Writing—original draft, Writing—review & editing), Sohei Satoi (Collection and assembly of data, Supervision), Hiroaki Nagano (Collection and assembly of data, Supervision), Satoshi Kobayashi (Collection and assembly of data), Taro Yamashita (Collection and assembly of data), Takuji Okusaka (Collection and assembly of data), Akio Ido (Collection and assembly of data), Etsuro Hatano (Collection and assembly of data), Kazuhiko Shioji (Collection and assembly of data, Methodology), Haruo Miwa (Collection and assembly of data), Masaki Ueno (Collection and assembly of data), Kazuhiko Nakao (Collection and assembly of data), Satoshi Shimizu (Collection and assembly of data), Hidekazu Kuramochi (Collection and assembly of data), Ryotaro Sakamori (Collection and assembly of data), Hidetaka Tsumura (Collection and assembly of data), Naohiro Okano (Collection and assembly of data), Keita Sasaki (Methodology, Writing—review & editing), Hirofumi Shirakawa (Collection and assembly of data), Noriyuki Akutsu (Collection and assembly of data), Kunihiro Tsuji (Collection and assembly of data), Hiroshi Ishii (Collection and assembly of data), Kumiko Umemoto (Collection and assembly of data), Akinori Asagi (Collection and assembly of data), Ryunosuke Machida (Methodology, Writing—review & editing), Masafumi Ikeda (Supervision, Writing—review & editing), and Makoto Ueno (Supervision, Writing—review & editing)

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Original Article

# High cost of chemotherapy for gynecologic malignancies

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## Abstract

**Background:** The prognosis of gynecological malignancies has improved with the recent advent of molecularly targeted drugs and immune checkpoint inhibitors. However, these drugs are expensive and contribute to the increasing costs of medical care.

**Methods:** The Japanese Clinical Oncology Group (JCOG) Health Economics Committee conducted a questionnaire survey of JCOG-affiliated facilities from July 2021 to June 2022 to assess the prevalence of high-cost regimens.

**Results:** A total of 57 affiliated facilities were surveyed regarding standard regimens for advanced ovarian and cervical cancers for gynecological malignancies. Responses were obtained from 39 facilities (68.4%) regarding ovarian cancer and 37 (64.9%) concerning cervical cancer, with respective case counts of 854 and 163. For ovarian cancer, 505 of 854 patients (59.1%) were treated with regimens that included PARP inhibitors, costing >500 000 Japanese yen monthly, while 111 patients (13.0%) received treatments that included bevacizumab, with costs exceeding 200 000 Japanese yen monthly. These costs are ~20 and ~10 times higher than those of the conventional regimens, respectively. For cervical cancer, 79 patients (48.4%) were treated with bevacizumab regimens costing >200 000 Japanese yen per month, ~10 times the cost of conventional treatments.

**Conclusions:** In this survey, >70% of patients with ovarian cancer were treated with regimens that included poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors or bevacizumab; ~50% of patients with cervical cancer were treated with regimens containing bevacizumab. These treatments were ~10 and ~20 times more expensive than conventional regimens, respectively. These

findings can inform future health economics studies, particularly in assessing cost-effectiveness and related matters.

**Key words:** poly (adenosine diphosphate-ribose) polymerase inhibitors, molecular targeted therapy, carcinoma, gynecologic oncology, cost-effectiveness

## Introduction

Similar to other carcinomas, chemotherapy is the primary treatment strategy for advanced gynecologic malignancies. Despite treatment advancements, the median survival time for cervical cancer with distant metastasis remains <12 months with cytotoxic combination therapy alone [1]. Ovarian cancer is the fifth leading cause of cancer-related deaths among women [2]. Advanced gynecologic malignancies have been treated using platinum-based regimens such as cisplatin [3–5].

Paclitaxel plus carboplatin (TC) therapy has become the standard of care for advanced ovarian cancer since the advent of paclitaxel, remaining unchanged for a long time [6,7]. Following the introduction of bevacizumab (Bev), a molecularly targeted agent, TC plus Bev, and subsequent Bev maintenance therapy, emerged as the next standard of care for advanced ovarian cancer [8,9]. With the introduction of Bev, progression-free survival (PFS) has been extended, although it has not improved overall survival (OS). Furthermore, with the introduction of poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi), PFS has been extended, and TC plus PARPi maintenance therapy has become a new treatment option [10,11]. The advent of PARPi has significantly extended PFS and marginally extended OS (84% vs. 80% at 36 months [10], 84% vs. 77% at 24 months [11]) in the overall population. The current standard chemotherapy for advanced ovarian cancer is primarily TC plus Bev, followed by Bev maintenance therapy or TC plus PARPi maintenance therapy (Table 1).

For advanced cervical cancer, paclitaxel plus cisplatin (TP) therapy has been the standard of care in combination with cytotoxic anticancer agents [12]. Similar to ovarian cancer, TP or TC plus Bev have become the standard of care with the introduction of Bev with the extension of PFS and OS. [13,14] (Table 2). The programmed death receptor (PD)-1 inhibitor pembrolizumab (Pem), an immune checkpoint inhibitor, has been introduced as a new treatment option [15]. The PFS and OS benefit brought about by Bev was further extended by the advent of Pem. The current standard chemotherapy for advanced cervical cancer predominantly involves TP plus Bev and Pem or TC plus Bev and Pem. Notably, Pem was not included in this survey because it was not covered by insurance for cervical cancer until after September 2022.

One challenge posed by advances in the treatment of these cancers is economic toxicity. For example, Bev costs >200 000 Japanese yen (JPY) per month at a standard dosage, whereas PARPi costs >500 000 JPY per month at a standard dosage.

In Japan, the universal health insurance system typically permits the use of expensive drugs, if approved, without special restrictions. However, the pressure on medical costs from these drugs poses a concern, potentially leading to future financial strain on healthcare finances and even bankruptcy [16–18].

In the future, integrating health economic evaluations into clinical research will be crucial to increasing treatment value, managing costs

effectively, maintaining treatment quality, and ensuring treatment affordability and sustainability.

Therefore, we conducted a questionnaire survey in Japanese Clinical Oncology Group (JCOG)-affiliated facilities to assess the current status of high-cost medical care in Japan. This study was conducted under the supervision of the JCOG Health Economic Committee.

## Materials and methods

We conducted an online questionnaire survey (Google form) of patients with Stages 3 and 4 ovarian cancer and Stage 4b cervical cancer at 57 JCOG-affiliated facilities. Patients targeted for this survey were first diagnosed with advanced ovarian or cervical cancer at JCOG institutions between July 2021 and June 2022. We gathered information on first-line chemotherapy regimens used for each patient without collecting any personal patient data. The number of patients in different age categories ( $\leq 74$  and  $\geq 75$  years) was collected separately. Moreover, costs for supportive care, such as antiemetics or granulocyte-colony stimulating factor (G-CSF), were not included.

For this study, high-cost medical care was defined as >500 000 JPY per month, whereas very high-cost medical care was defined as >1 million JPY per month by the JCOG Health Economics Committee. The personal data of patients were not collected. Thus, this study did not require individual consent or Institutional Review Board approval [19].

## Regimens

### Ovarian cancer

The regimens studied for advanced ovarian cancer were predetermined as the standard of care before the study began. These regimens were selected by the attending physician based on the patient's background, including homologous recombination deficiency and breast cancer susceptibility (BRCA) status [10,20], and disease status (e.g. presence of tumor invasion into the intestinal tract).

- Paclitaxel + Carboplatin → Niraparib maintenance therapy
- Paclitaxel + Carboplatin → Olaparib maintenance therapy
- Paclitaxel + Carboplatin + Bevacizumab → Bevacizumab maintenance therapy
- Paclitaxel + Carboplatin + Bevacizumab → Olaparib + Bevacizumab maintenance therapy

The primary results of these regimens in the trials are shown in Table 1.

### Cervical cancer

The current standard of care for advanced or recurrent cervical cancer is TC plus Bev plus pembrolizumab; however, pembrolizumab was not covered by insurance until September 2022. As the regimen

**Table 1.** Primary outcomes of advanced ovarian cancer regimens

Regimen	Reference number (publication year)	Main results (median PFS; months)	Main results (OS)	Median cycles or dose completion proportion
TC → Niraparib maintenance	[11] (2019)	Niraparib 13.8 Placebo 8.2	Niraparib 84% Placebo 77% (at 24 months)	177/484 (36.5%) received at data cut off
TC → Olaparib maintenance	[10] (2018)	Olaparib 56.0 Placebo 13.8	Olaparib 84% Placebo 80% (at 36 months)	123/260 (47.3%) completed at the 2-year mark
TC + Bev → Bev maintenance	[8,9] (2011)	Bev 14.1 Placebo 10.3	Bev 39.7 Placebo 39.3 (months)	A median of 16–17 cycles
TC + Bev → Bev + Olaparib maintenance	[16] (2019)	Olaparib + Bev 37.2 Placebo 17.7	Data are immature	196/537 (36.4%) completed at the 2-year mark

TC, paclitaxel + carboplatin; Bev, Bevacizumab; PFS, progression-free survival; OS, overall survival.

**Table 2.** Main results of advanced cervical cancer regimen

Regimen	Reference number (publication year)	Main results (median PFS; months)	Main results (OS)	Median cycles or dose completion ration
TC + Bev → Bev maintenance <sup>a</sup>	[14] (2020)	Bev 10.9	Bev 25.0 (months, median)	a median of nine cycles
TP + Bev → Bev maintenance	[13] (2013)	Bev 8.2 Placebo 5.9	Bev 17.0 Placebo 13.3 (months)	a median of seven cycles
TC or TP + Pem + Bev → Pem + Bev maintenance	[15] (2021)	Pem 10.4 Placebo 8.2	Pem 50.4% Placebo 40.4% (at 24 months)	a median of 18 cycles

TC, paclitaxel + carboplatin; TP, paclitaxel + cisplatin; Bev, Bevacizumab; Pem, Pembrolizumab; PFS, progression-free survival; OS, overall survival.

<sup>a</sup>Single-arm Phase II study.

was not covered by insurance in 2021, the regimens listed below were included in this study.

·Paclitaxel + Cisplatin + Bevacizumab → Bevacizumab maintenance therapy

·Paclitaxel + Carboplatin + Bevacizumab → Bevacizumab maintenance therapy

The primary results of these regimens in the trials are shown in Table 2.

The cost of the regimen was calculated based on a height of 157 cm and weight of 55 kg, with a body surface area of 1.552 m<sup>2</sup> [21,22]. The carboplatin dose was calculated using Jelliffe formula at an area under the curve of 5 or 6. The cost of each drug is presented in Table S1.

#### Calculation of costs of each regimen of ovarian cancer\*

·Paclitaxel + Carboplatin → Niraparib maintenance therapy

\*Paclitaxel(175 mg/m<sup>2</sup>) + Carboplatin (AUC = 6) → Niraparib × 200 mg daily × 30 days

·Paclitaxel + Carboplatin → Olaparib maintenance therapy

\* Paclitaxel (175 mg/m<sup>2</sup>) + Carboplatin (AUC = 6) → Olaparib × 600 mg daily × 30 days

·Paclitaxel + Carboplatin + Bevacizumab → Bevacizumab maintenance therapy

\*Paclitaxel (175 mg/m<sup>2</sup>) + Carboplatin (AUC = 6) + Bevacizumab (15 mg/kg) every 3 weeks → Bevacizumab (15 mg/kg) every 3 weeks

·Paclitaxel + Carboplatin + Bevacizumab → Olaparib + Bevacizumab maintenance therapy

\*Paclitaxel (175 mg/m<sup>2</sup>) + Carboplatin (AUC = 6) + Bevacizumab (15 mg/kg) every 3 weeks → Olaparib × 600 mg daily × 30 days + Bevacizumab (15 mg/kg) every 3 weeks

#### Calculation of costs of each regimen of cervical cancer\*

·Paclitaxel + Carboplatin + Bevacizumab → Bevacizumab maintenance therapy

\*Paclitaxel (175 mg/m<sup>2</sup>) + Carboplatin (AUC = 5) + Bevacizumab (15 mg/kg) every 3 weeks → Bevacizumab (15 mg/kg) every 3 weeks

·Paclitaxel + Cisplatin + Bevacizumab → Bevacizumab maintenance therapy

\*Paclitaxel (135 mg/m<sup>2</sup>) + Cisplatin (50 mg/m<sup>2</sup>) + Bevacizumab (15 mg/kg) every 3 weeks → Bevacizumab (15 mg/kg) every 3 weeks

## Results

Questionnaires were distributed to 57 JCOG-affiliated facilities, and responses were received from 39 centers (68.4%) for ovarian cancer and 37 centers (64.9%) for cervical cancer.

The number of patients with ovarian cancer during the study period was 854 (Figure 1), of whom 616 (72.1%, 616/854) were eligible for the study regimen. The most common regimen for ovarian cancer was TC plus niraparib maintenance, involving a total of 267 patients (31%, 267/854). The second most common regimen was TC plus Bev, followed by Bev plus olaparib maintenance, with 170 patients (20%, 170/854). TC plus Bev after Bev maintenance was administered to 111 patients (13%, 111/854). TC plus olaparib maintenance therapy was administered to 68 patients (8%, 68/854). Chemotherapy-alone regimens, including TC and dose-dense TC, were administered to 238 patients (28%, 238/854). Of the 616 patients, 542 (87.9%, 542/616) were under 75 years old, while 74 (12.1%, 74/616) were 75 years or older. Therefore, according to the definition used in this study, 505 patients (59.1%, 505/854) received high-cost medical care as primary therapy. Among the 542

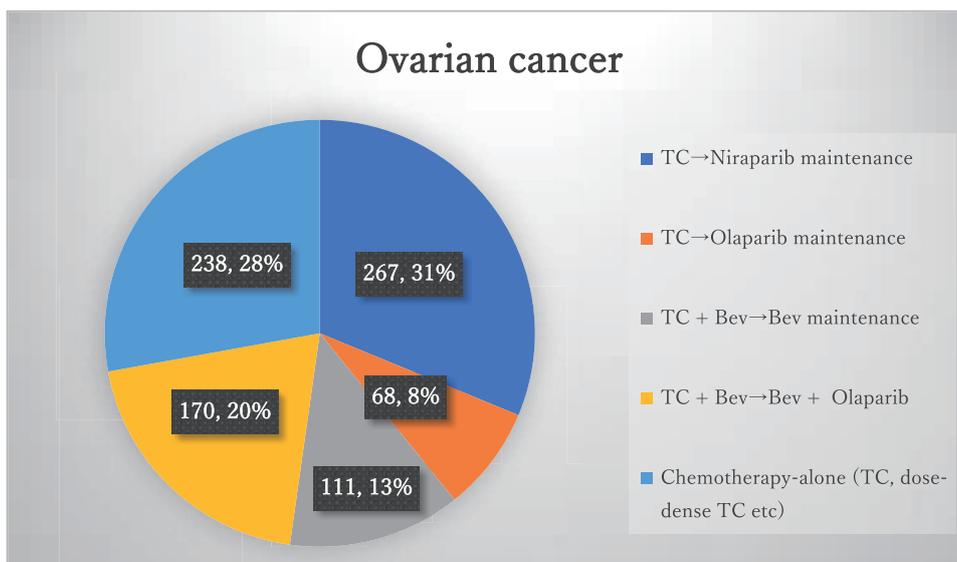


Figure 1. Results of the questionnaires for ovarian cancer TC, paclitaxel + carboplatin; Bev, bevacizumab.

Table 3. Cost of advanced ovarian cancer regimens

Treatment	Age, <75 yr	Age, >75 yr	Total	Cost per month, JPY
TC → Niraparib maintenance	231 (27%)	36 (4%)	267 (31%)	27 561 → 558 960
TC → Olaparib maintenance	64 (7.5%)	4 (0.5%)	68 (8%)	27 561 → 574 560
TC + Bev → Bev maintenance	89 (10.5%)	22 (2.5%)	111 (13%)	264 222 → 236 661
TC + Bev → Bev + Olaparib maintenance	158 (18.5%)	12 (1.5%)	170 (20%)	264 222 → 811 221
TC	n/s	n/s	n/s	27 561

TC, paclitaxel + carboplatin; Bev, Bevacizumab; n/s not surveyed.

younger patients, 453 (83.5%, 453/542) received high-cost medical care. Among the 72 older patients, 52 (72.2%, 52/72) received high-cost medical care. Regimens containing Bev were 10 times as costly as conventional TC, with no significant OS benefit. Similarly, regimens containing PARPi were 20 times as costly as conventional TC, with no significant OS benefit. The cost of each regimen and its classification as high cost are presented in Table 3.

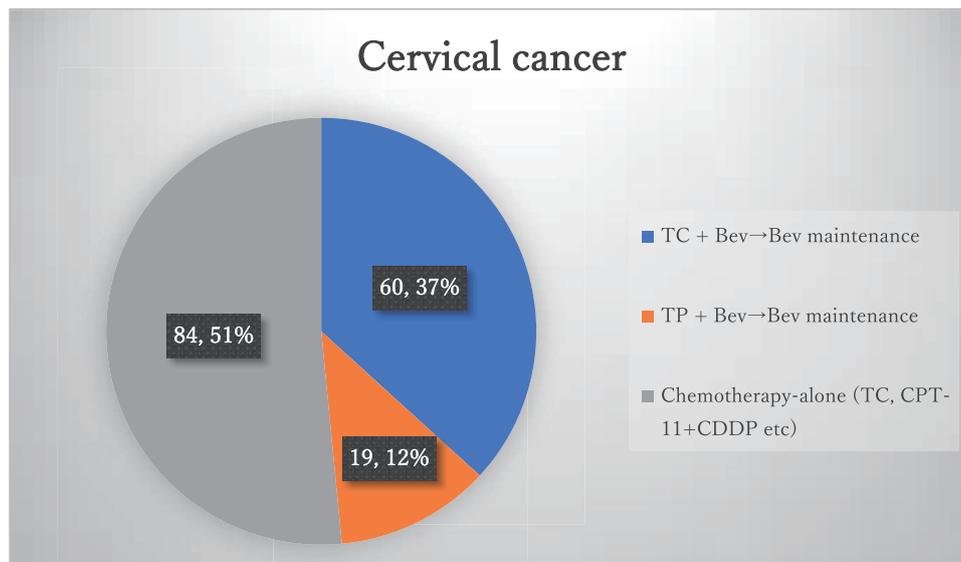
During the study period, 163 patients were diagnosed with cervical cancer (Figure 2), and 79 (49.0%) received the study regimen. The most common regimen for cervical cancer was TC plus Bev, followed by Bev maintenance, with 60 patients (36.8%). TC plus Bev, followed by Bev maintenance, was administered to 19 patients (11.6%). Among these 79 patients, 72 (91.1%, 72/79) were under the age of 75, while seven (8.9%) were over 75. Regimens containing Bev were 10 times as costly as conventional TP or TC, with an OS benefit of several months. The costs of each regimen and their classification as high costs are listed in Table 4.

### Discussion

Responses were received from 39 out of 57 centers (68.4%) for ovarian cancer and from 37 centers (64.9%) for cervical cancer. For ovarian cancer, high-cost medical care was applicable to 505 (82.1%) of the 615 patients. In addition, 52 (72.2%) received high-cost medical care among the 72 older patients. The trials of PARPi added to chemotherapy alone have shown only marginally prolonged OS

(84% vs. 80% at 36 months [10], 84% vs. 77% at 24 months [11]) in the overall population, suggesting that from a cost-effectiveness perspective, the indication of these regimens would be controversial, especially in older patients [10,11].

PARPi introduction has made maintenance therapy with PARPi a standard treatment for ovarian cancer. More cases of TC plus niraparib than TC plus olaparib in this study may be attributed to olaparib being restricted to BRCA-positive patients due to insurance coverage, while niraparib can be used regardless of BRCA status. Considering that the patient was previously monitored only following TC therapy, the introduction of a cytotoxic anticancer drug raised medical costs by ~600 000 JPY per month, potentially for up to 2 or 3 years of maintenance therapy. Prolonged PFS associated with maintenance therapy incurs significant costs [23]. Although the healthcare system differs from that of Japan, generous reimbursement by public insurance could lead to overtreatment and waste of medical resources. High-cost medical care was also provided to patients aged 75 years and older in this study. Considering their prognosis and adverse events, we should consider criteria when administering expensive drugs that allow only a marginal prolongation of OS. The cost of medical care in Japan continues to increase yearly, and measures are required to reduce those costs. The use of biosimilars can be one of those measures [18]. Biosimilars differ from the original drugs, although their clinical efficacy is almost equal to that of the original drugs. They are inexpensive, making them suitable drugs for reducing medical care costs. Biosimilars of Bev have already been used for several carcinomas [24,25].



**Figure 2.** Results of the questionnaires for cervical cancer, TC, paclitaxel + carboplatin; TP, paclitaxel + cisplatin; Bev, bevacizumab.

**Table 4.** Cost of advanced cervical cancer regimens

Treatment	Age, <75 yr	Age, >75 yr	Total	Cost per month, JPY
TC + Bev → Bev maintenance	54 (33%)	6 (4%)	60 (37%)	256 974 → 236 661
TP + Bev → Bev maintenance	18 (11.4%)	1 (0.6%)	19 (12%)	254 446 → 236 661
TC	n/s	n/s	n/s	24 115
TP	n/s	n/s	n/s	17 785

TC, paclitaxel + carboplatin; TP, paclitaxel + cisplatin; Bev, Bevacizumab; n/s not surveyed.

None of the patients with cervical cancer received high-cost treatments as defined by the JCOG committee, although the regimens were ~200 000 JPY more expensive per month than conventional chemotherapy alone. However, this study excluded patients who received pembrolizumab because it was not covered by insurance in Japan at the time of the study. PD-1 inhibitors, including pembrolizumab, are now indicated for gynecological malignancies, alongside their indications for other cancer types. Four-drug combination therapy consisting of TC plus Bev plus this agent is currently one of the standard treatments for advanced cervical cancer [15]. The estimated cost of this regimen exceeds 600 000 JPY, which corresponds to the high cost of this study (Table S3). Therefore, the proportion of patients receiving high-cost medical care may have increased if this agent was included in the survey.

In cervical cancer, the trial of pembrolizumab added to chemotherapy alone has shown prolonged OS (50.4% vs. 40.4% at 24 months), suggesting that from a cost-effectiveness perspective, these regimens' indication in all patients, including older patients, is controversial. The use of Bev biosimilar in ovarian cancer is also expected to reduce costs; therefore, the development of biosimilars for PD-1 inhibitors and PARPi is expected to advance.

The standard treatments of gynecological cancers are decided by PFS elongation, and thus include drugs without OS benefit (Bev for ovarian cancer) or with OS benefit with only marginal OS benefit (PARPi for ovarian cancer). These drugs, however, bring a 10- to 20-fold increase in treatment costs, questioning the sustainability of cancer care.

This study had several limitations. This survey was conducted over a limited period at JCOG-affiliated facilities. Individual patient data were not collected; therefore, the actual dosing periods, drug discontinuations, or dose reduction could not be considered. In addition, they were not evaluated using measures such as the incremental cost-effectiveness ratio of the most recent PAPRi and ICI treatment regimens.

## Conclusion

More than 70% of patients with ovarian cancer received regimens containing PARP inhibitors or Bev, and ~50% of patients with cervical cancer received regimens containing Bev, which were ~10 or ~20 times more expensive than conventional regimens, respectively. Japanese patients with gynecological cancers receive state-of-the-art therapies, but the associated costs have increased substantially. The results of this study may be used in future health economics studies examining cost-effectiveness and other issues.

## Acknowledgements

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## Supplementary data

Supplementary data is available at *Japanese Journal of Clinical Oncology* online.

## Conflict of interest

The authors declare no conflict of interest.

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Original Article

# High-cost treatments for advanced lung cancer in Japan (Lung Cancer Study Group of the Japan Clinical Oncology Group)

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## Abstract

**Background:** The treatment of lung cancer has made dramatic progress in the past decade, but due to the high cost of drugs, the total pharmaceutical cost has been rising explosively. There are currently no data available in Japan on which regimens are used, to what extent they are used, and what their total cost is.

**Methods:** Sixty Japanese centers belonging to the Lung Cancer Study Group of the Japan Clinical Oncology Group were surveyed for information about the first-line treatment for advanced lung cancer in practice from July 2021 to June 2022. Three types of cancer were included: driver gene mutation-negative NSCLC, EGFR mutation-positive NSCLC, and extensive-stage small cell lung cancer (ES-SCLC).

**Results:** Recent treatment costs for ICIs or ICI plus chemotherapy were about 20–55 times higher than those for conventional chemotherapy. Of the 3738 patients with driver gene aberration-negative NSCLC, 2573 (68.8%) received treatments with monthly cost of 500 000 Japanese yen (JPY) or more; 2555 (68.4%) received ICI therapy. Of the 1486 patients with EGFR mutation-positive NSCLC, 1290 (86.8%) received treatments with a monthly cost of 500 000 JPY or more; 1207 (81.2%) received osimertinib. ICI treatments with a monthly cost of 500 000 JPY or more were administered to 607 (56.3%) of 1079 patients with ES-SCLC. Elderly NSCLC patients received slightly more high-cost treatment than younger patients.

**Conclusion:** Recent treatments cost many times more than conventional chemotherapy. This study revealed that high-cost treatments were widely used in advanced lung cancer and some of high-cost treatments were used despite the lack of clear evidence. Physicians should pay attention to the cost of treatments they use.

**Key words:** high-cost treatment, immune checkpoint inhibitor, nonsmall cell lung cancer, epidermal growth factor receptor mutation-positive non-small cell lung cancer, extensive-stage small cell lung cancer

## Introduction

Cancer treatment has made great progress over the past decade with the advent of various, molecularly targeted drugs and immune checkpoint inhibitors (ICIs). However, these drugs are expensive, and the total pharmaceutical cost for cancer treatment continues to rise explosively. Owing to their high cost, these drugs are sometimes said to be ‘financially toxic’ and have become a social problem in both developing and developed countries, including Japan [1–4]. In Japan, this trend in the increasing cost of treatments is particularly pronounced due to the aging population. The Japan Clinical Oncology Group (JCOG) Health Economics Committee is currently grappling with these issues.

The cost problems could be divided to two aspects. First, recent treatments cost many times more than conventional chemotherapy. Second, some drugs cost far more than others of the same class without clear benefit in efficacy or toxicity, and physicians are indifferent to cost. This led to use of low-value (similar efficacy, similar toxicity, no head-to-head comparison data, only higher cost) treatments, which makes waste and burden to society. These low-value treatments for lung cancer include durvalumab (as opposed to atezolizumab) in small cell lung cancer (SCLC) and ramucirumab plus epidermal growth factor receptor—tyrosine kinase inhibitor (EGFR-TKI) (as opposed to bevacizumab plus EGFR-TKI) in epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC).

To understand the details of the use of expensive drugs in the treatment of lung cancer, the Lung Cancer Study Group of the JCOG conducted a survey to determine which drugs were currently being used in clinical practice.

Lung cancer yearly affects approximately 126 000 individuals, causing 75 000 deaths in Japan [5]. Lung cancer is also the leading cause of cancer-related deaths in men and the second leading cause of cancer-related deaths in women [5]. Lung cancer comprises NSCLC and SCLC. The former has many driver gene mutations, such as EGFR gene mutation and anaplastic lymphoma kinase (ALK) fusion gene translocation, and the cost of the molecularly targeted drugs, which are most commonly used in their treatment, is reimbursed under the Japanese National Health Insurance scheme [6]. For this reason, these drugs are widely used in clinical practice. In addition, six types of ICI, namely, the anti-programmed cell death-1 (PD-1) antibodies, pembrolizumab and nivolumab, the anti-programmed

cell death-ligand 1 (PD-L1) antibodies, atezolizumab and durvalumab, and the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies, ipilimumab, and tremelimumab, are widely used to treat driver gene mutation-negative NSCLC and extensive-stage SCLC (ES-SCLC). Their cost is likewise covered by National Health Insurance, leading to the wide use of these drugs in clinical practice.

While costly medications are extensively utilized in the treatment of lung cancer, comprehensive data regarding their utilization, extent of usage, and associated expenses are currently unavailable in Japan. Consequently, we conducted a retrospective study to ascertain the utilization patterns of high-cost treatments for advanced lung cancer treatment in Japan.

## Materials and methods

The present study surveyed 60 Japanese health centers belonging to the Lung Cancer Study Group of the JCOG to determine which regimens were being used as first-line treatment for advanced or recurrent lung cancer between July 2021 and June 2022. The survey covered the following, three disease categories: driver gene mutation and translocation-negative or indeterminate type NSCLC; EGFR mutation-positive NSCLC; and ES-SCLC; all of which are widely treated with high-cost regimens. In the survey, data on the total number of patients receiving one of these first-line treatment regimens and their age (74 years or younger, 75 years or older) were collected. Treatment regimens were tabulated for those listed in the Japanese Lung Cancer Society Guideline (2022 ed.) [7], and those not listed were classified as ‘other’. Individual patient data, including detailed histology, number of doses, treatment duration, efficacy (response, progression-free survival (PFS), overall survival (OS), adverse events, and quality of life were not investigated. Patients treated by investigational agents were excluded, but those who had participated in clinical trials such as the JCOG trials were included. Each center investigated these data categories retrospectively, entered their findings into a Google form format, and tabulated the results. Treatment costs were calculated on a monthly and total cost basis. Costs were calculated assuming a typical patient (70-year-old male, height 170 cm, weight 60 kg, body surface area 1.7 m<sup>2</sup>, Cr 0.8 mg/dl, Ccr 72.9 ml/min [Cockcroft-Gault]) receiving treatment. The total treatment cost was calculated by multiplying the cost of a single dose, the median number of

administrations, and the number of persons receiving the drug. The price of the medications as of 1 April 2024 was used to calculate the cost. Pembrolizumab, nivolumab, ipilimumab, and atezolizumab cost 214 498 JPY (Japanese Yen)/100 mg, 469 104 JPY/360 mg, 419 578 JPY/50 mg, and 563 917 JPY/1200 mg, respectively. If a generic version of a drug was available, the lowest price was used. The JCOG Health Economics Committee defined treatments that cost more than 500 000 JPY per month as high-cost treatments and treatments that cost more than 1 million JPY per month as very high-cost treatments.

## Results

Responses were received from all 60 centers belonging to the Lung Cancer Study Group of the JCOG. Table 1 shows a list of the high-cost treatments and very high-cost treatments. The cost of recent treatment with ICIs or ICI plus chemotherapy for NSCLC is approximately 19.3 to 38.7 times more expensive than conventional chemotherapy, carboplatin plus paclitaxel. The cost of recent treatment with osimertinib monotherapy or erlotinib plus ramucirumab for EGFR mutation-positive NSCLC is 6.8 times and 15.3 times more expensive than conventional drug, gefitinib. The cost of recent treatment with ICI plus chemotherapy for ES-SCLC is approximately 33.5 to 54.7 times more expensive than conventional chemotherapy, carboplatin plus etoposide (Table 1).

### Driver gene mutation and translocation-negative NSCLC

In total, 3738 patients were treated; of these, 2330 (62.3%) were aged 74 years or younger, 1057 (28.3%) were aged 75 years or older, and 351 (9.4%) were unknown; 2555 patients (68.4%) received an ICI, and 832 (22.3%) did not. Of the ICI used, pembrolizumab, nivolumab plus ipilimumab, and atezolizumab was administered to 1504 (40.2%), 718 (19.2%), and 333 (8.9%) patients, respectively. The regimens consisted of pembrolizumab monotherapy ( $n = 605$ , 16.2%), carboplatin + pemetrexed + pembrolizumab ( $n = 497$ , 13.3%), nivolumab + ipilimumab ( $n = 349$ , 9.3%), carboplatin + pemetrexed ( $n = 302$ , 8.1%), carboplatin + nab-paclitaxel ( $n = 238$ , 6.4%), and carboplatin + pemetrexed + nivolumab + ipilimumab ( $n = 221$ , 5.9%) (Table 2).

In terms of age, 1749 (75.1%) patients aged 74 years or younger received ICI treatment, 806 (76.3%) patients aged 75 years or older received ICI treatment, with the proportion of patients aged 75 years or older being slightly greater. About, 308 (29.1%) patients aged 75 years or older received pembrolizumab monotherapy and 173 (16.4%) patients received nivolumab plus ipilimumab. The proportion of patients receiving these regimens was significantly greater in those aged 75 years or older than in those aged 74 years or younger. In contrast, the percentage of chemotherapy + ICI was lower in those aged 75 or older.

At six-weeks of ICI treatment, the cost (based on 60 kg body weight) of pembrolizumab, nivolumab + ipilimumab, and atezolizumab was 857 992 JPY, 1 450 002 JPY, and 1 127 834 JPY, respectively. The monthly cost was 623 066 JPY, 1 052 978 JPY, and 819 022 JPY, respectively. Assuming that each patient received the median number of ICI doses given in a clinical trial [8–16], the total treatment cost of ICI therapy was estimated to be 6.34 billion JPY for a pembrolizumab-based regimen, 4.32 billion JPY for a nivolumab + ipilimumab-based regimen, and 2.18 billion JPY for an atezolizumab-based regimen. Furthermore, 2573 (68.8%) patients

received high-cost treatments, and 1013 (27.1%) patients received very high-cost treatments (Tables 1 and 2).

### EGFR mutation-positive NSCLC

In total, 1486 patients were treated; of these, 908 patients (61.1%) were aged 74 years or younger, 516 patients (34.7%) were aged 75 years or older, and 62 (4.2%) were of unknown age. By regimen, 1207 (81.2%) patients received osimertinib, 83 (5.6%) received erlotinib + ramucirumab, and 81 (5.5%) received afatinib. Osimertinib was administered to 758 patients (83.5%) aged 74 years or younger and 449 patients (87.0%) aged 75 years or older, with the proportion of patients aged 75 years or older being significantly greater. As of 1 April 2024, the price of an 80 mg tablet of osimertinib was 18 540.2 JPY; thus, the cost of this drug per month per patient was 565 476 JPY, making osimertinib a high-cost drug. Assuming that osimertinib was administered until the median PFS of 18.9 months [17], the total cost of treatment per patient was 10 687 000 JPY. In the present survey, the total cost of this regimen was estimated to be 12.8 billion JPY. In contrast, the price of a 250 mg tablet of gefitinib, a first-generation EGFR-TKI, was 2715.3 JPY. Thus, the cost of gefitinib per month per patient was 82 817 JPY. Assuming that gefitinib was administered until the median PFS of 10.2 months [17], total cost of this regimen per patient was 844 700 JPY. In summary, 1290 (86.8%) patients received high-cost treatments, and 83 (5.6%) patients received very high-cost treatments (Tables 1 and 3).

### ES-SCLC

In total, 1079 patients were treated, 686 (63.6%) patients were aged 74 years or younger, 377 (34.9%) patients were aged 75 years or older, and 16 (1.5%) were of unknown age. ICI was administered to 607 (56.3%) patients but not to 472 (43.7%) patients. The most commonly administered regimen was carboplatin + etoposide ( $n = 381$ , 35.3%), followed by carboplatin + etoposide + durvalumab ( $n = 290$ , 26.9%), carboplatin + etoposide + atezolizumab ( $n = 222$ , 20.6%), and cisplatin + etoposide + durvalumab ( $n = 95$  patients, 8.8%). By age, more patients aged 75 years or older received carboplatin + etoposide than patients aged 74 years or younger ( $n = 191$ , 50.7% and  $n = 190$ , 27.7%, respectively). Conversely, fewer of the former than of the latter age-group received cisplatin + etoposide + durvalumab ( $n = 1$ , 0.3% and  $n = 94$ , 13.7%). There was no difference in the proportion of patients receiving carboplatin + etoposide + ICI by age Table 4.

The number of ICI doses was assumed to be the median number of ICI doses given in a clinical trial [18,19]. The cost of carboplatin (area under the curve [AUC] = 5, day 1) + etoposide (80 mg/m<sup>2</sup>, days 1–3) was 17 338 JPY per cycle and 69 352 JPY per four cycles of chemotherapy for a total cost of about 26.4 million JPY. For carboplatin (AUC = 5, day 1) + etoposide (80 mg/m<sup>2</sup>, days 1–3) + durvalumab (1500 mg/body, day 1), the cost was 947 800 JPY per cycle and 6 582 586 JPY for seven ICI doses for a total cost of about 1.91 billion JPY. For cisplatin (80 mg/m<sup>2</sup>, day 1) + etoposide (100 mg/m<sup>2</sup>, days 1–3) + durvalumab (1500 mg/body, day 1), the cost was 949 666 JPY per cycle and 6 724 478 JPY for seven ICI doses for a total cost of 638.8 million JPY. One cycle of carboplatin (AUC = 5, day 1) + etoposide (100 mg/m<sup>2</sup>, days 1–3) + atezolizumab (1200 mg/body, day 1) cost 581 255 JPY, and seven ICI doses cost 4 016 771 JPY for a total cost of 891.7 million JPY. Cisplatin or carboplatin + etoposide + durvalumab were considered very

**Table 1.** List of high-cost treatments and very high-cost treatments in lung cancer

Regimen	Treatment cost per 3 weeks (JPY)	Treatment cost per month (JPY)	High-cost treatment	Very high-cost treatment
NIVO + IPI	725 001	1 052 978	○	○
CBDCA + PEM + NIVO + IPI	814 534	1 183 014	○	○
CDDP + PEM + NIVO + IPI	815 660	1 184 649	○	○
CBDCA + PTX + NIVO + IPI	747 252	1 085 295	○	○
Pembrolizumab	428 996	623 066	○	
CBDCA + PEM + Pembrolizumab	518 529	753 102	○	
CDDP + PEM + Pembrolizumab	519 655	754 737	○	
CBDCA + nab-PTX + Pembrolizumab	726 521	1 055 185	○	○
CBDCA + PTX + Pembrolizumab	451 247	655 383	○	
Atezolizumab	563 917	819 022	○	
CBDCA + nab-PTX + Atezolizumab	861 442	1 251 142	○	○
CBDCA + PEM + Atezolizumab	654 343	950 355	○	
CDDP + PEM + Atezolizumab	654 576	950 694	○	
CBDCA + PTX + BEV + Atezolizumab	681 876	990 344	○	
CBDCA + PTX + BEV	117 959	171 321		
CDDP + GEM + necitumumab	487 474	707 998	○	
CBDCA + PEM	89 533	130 036		
CDDP + PEM	90 659	131 671		
CBDCA + nab-PTX	297 525	432 120		
CBDCA + PTX	22 251	32 317		
Osimertinib	389 344	565 476	○	
Gefitinib	57 021	82 817		
Erlotinib	212 293	308 331		
Afatinib	181 213	263 191		
Dacomitinib	172 859	251 058		
Erlotinib + Bevacizumab	308 001	447 335		
Erlotinib + Ramucirumab	870 330	1 264 050	○	○
Gefitinib + CBDCA + PEM	146 554	212 853		
CBDCA + ETP + Atezolizumab	581 255	844 204	○	
CBDCA + ETP + Durvalumab	947 800	1 376 567	○	○
CDDP + ETP + Durvalumab	948 926	1 378 202	○	○
CDDP + irinotecan	17 593	25 552		
CDDP + ETP	19 204	27 892		
CBDCA + ETP	17 338	25 181		

Abbreviations: JPY, Japanese Yen; NIVO, nivolumab; IPI, ipilimumab; CBDCA, carboplatin; PEM, pemetrexed; CDDP, cisplatin; PTX, paclitaxel; nab-PTX, nab-paclitaxel; BEV, bevacizumab; GEM, gemcitabine; ETP, etoposide. “○” is placed in the appropriate treatment.

Costs were calculated assuming a typical patient (70-year-old male, height 170 cm, weight 60 kg, body surface area 1.7 m<sup>2</sup>, Cr 0.8 mg/dl, Ccr 72.9 ml/min [Cockcroft-Gault]). The price of the medications as of 1 April 2024 was used to calculate the treatment cost.

high-cost drugs and were used in 35.7% of patients with ES-SCLC. Carboplatin + etoposide + atezolizumab was considered a high-cost regimen and was used in 20.6% of patients with ES-SCLC. Six hundred seven (56.3%) patients were treated with high-cost treatments, and 385 (35.7%) patients were treated with very high-cost treatments (Tables 1 and 4).

## Discussion

No studies have to date have provided a real-world cost analysis of lung cancer treatments in Japan. The present study surveyed 60 centers belonging to the Lung Cancer Study Group of the JCOG, a leading lung cancer treatment group in Japan. The survey revealed which regimens were used in clinical practice and to what extent they were used at all 60 centers while also estimating the approximate cost of the treatments.

The large number of patients with lung cancer and the high cost of many drugs are contributing to increasing the total cost of treatments. The cost of treatments for driver gene mutation and translocation-negative NSCLC, EGFR mutation-positive NSCLC, and ES-SCLC was 12.84 billion JPY, 12.8 billion JPY, and 3.44 billion JPY, respectively.

The efficacy of each ICIs and ICI-containing treatments has been proven by comparison with chemotherapy, which has been the standard of care. However, comparative data between various ICIs and ICI-containing treatments are not fully available. As a result, physicians use ICIs and ICI-containing treatments for their patients lacking adequate selection criteria.

The cost of treatments for driver gene mutation and translocation-negative NSCLC was particularly high because ICI is the mainstay of treatment. Pembrolizumab, the cheapest of the three ICI, was the most used but is nonetheless expensive.

**Table 2.** List of treatments for driver gene mutation and translocation-negative NSCLC

Regimen (Treatment cost per month, JPY)	Number (%)	≤74 yrs (%)	≥75 yrs (%)	ICI total (%)
<b>NIVO + IPI regimen</b>				
NIVO + IPI (1 052 978)	349 (9.3)	176 (7.6)	173 (16.4)	718 (19.2)
NIVO + IPI + CBDCA + PEM (1 183 014)	221 (5.9)	189 (8.1)	32 (3.0)	
NIVO + IPI + CDDP + PEM (1 184 649)	25 (0.7)	24 (1.0)	1 (0.1)	
NIVO + IPI + CBDCA + PTX (1 085 295)	123 (3.3)	102 (4.4)	21 (2.0)	
<b>PEMBRO regimen</b>				
PEMBRO (623 066)	605 (16.2)	297 (12.7)	308 (29.1)	1504 (40.2)
PEMBRO + CBDCA + PEM (753 102)	497 (13.3)	388 (16.7)	109 (10.3)	
PEMBRO + CDDP + PEM (754 737)	81 (2.2)	79 (3.4)	2 (0.2)	
PEMBRO + CBDCA + nab-PTX (1 055 185)	167 (4.5)	116 (5.0)	51 (4.8)	
PEMBRO + CBDCA + PTX (655 383)	154 (4.1)	128 (5.5)	26 (2.5)	
<b>ATEZO regimen</b>				
ATEZO (819 022)	24 (0.6)	15 (0.6)	9 (0.9)	333 (8.9)
ATEZO + CBDCA + nab-PTX (1 251 142)	128 (3.4)	83 (3.6)	45 (4.3)	
ATEZO + CBDCA + PEM (950 355)	48 (1.3)	28 (1.2)	20 (1.9)	
ATEZO + CDDP + PEM (950 694)	6 (0.2)	4 (0.2)	2 (0.2)	
ATEZO + CBDCA + PTX + BEV (990 344)	127 (3.4)	120 (5.2)	7 (0.7)	
<b>Regimen without ICI</b>				
CBDCA + PTX + BEV (171 321)	50 (1.3)	37 (1.6)	13 (1.2)	832 (22.3)
CDDP + GEM + NECI (707 998)	18 (0.5)	18 (0.8)	0 (0)	
CBDCA + PEM (130 036)	302 (8.1)	212 (9.1)	90 (8.5)	
CDDP + PEM (131 671)	43 (1.2)	43 (1.8)	0 (0)	
CBDCA + nab-PTX (432 120)	238 (6.4)	144 (6.2)	94 (8.9)	
CBDCA + PTX (32 317)	181 (4.8)	127 (5.5)	54 (5.1)	
Other (9.4)	351 (9.4)	NE	NE	
<b>Total</b>	<b>3738</b>	<b>2330</b>	<b>1057</b>	

Abbreviations: NSCLC, non-small cell lung cancer; JPY, Japanese Yen; ICI, immune checkpoint inhibitor; NIVO, nivolumab; IPI, ipilimumab; CBDCA, carboplatin; PEM, pemetrexed; CDDP, cisplatin; PTX, paclitaxel; PEMBRO, pembrolizumab; nab-PTX, nab-paclitaxel; ATEZO, atezolizumab; BEV, bevacizumab; GEM, gemcitabine; NECI, necitumumab; NE, not evaluable.

For EGFR mutation-positive NSCLC, there is a problem that despite being in the same class and having the same efficacy and safety, the costs vary widely; EGFR-TKI plus angiogenesis inhibitors (bevacizumab or ramucirumab) is an example [20,21]. Treatment with ramucirumab plus erlotinib is 2.8 times more expensive than treatment with bevacizumab plus erlotinib, even though the efficacy and safety are almost identical. It would be difficult to justify the use

of high-cost treatment without documented superiority in efficacy and/or safety to a less costly alternative. There is no single reason why the more expensive treatment should be chosen.

EGFR mutation-positive NSCLC accounted for about 80% of all the cases treated with osimertinib, and the total cost was correspondingly high. It is obvious that protracted therapy with expensive, oral, anticancer drugs will result in correspondingly higher costs.

**Table 3.** List of treatments for EGFR mutation-positive NSCLC

Regimen (Treatment cost per month, JPY)	Number (%)	≤74 yrs (%)	≥75 yrs (%)
Osimertinib (565 476)	1207 (81.2)	758 (83.5)	449 (87.0)
Gefitinib (82 817)	31 (2.1)	14 (1.5)	17 (3.3)
Erlotinib (308 331)	16 (1.1)	12 (1.3)	4 (0.8)
Afatinib (263 191)	81 (5.5)	62 (6.8)	19 (3.7)
Dacomitinib (251 058)	1 (0.1)	1 (0.1)	0 (0)
Erlotinib + Bevacizumab (447 335)	3 (0.2)	3 (0.3)	0 (0)
Erlotinib + Ramucirumab (1 264 050)	83 (5.6)	56 (6.2)	27 (5.2)
Gefitinib + CBDCA + PEM (212 853)	2 (0.1)	2 (0.2)	0 (0)
Other	62 (4.2)	NE	NE
<b>Total</b>	<b>1486</b>	<b>908</b>	<b>516</b>

Abbreviations: EGFR, epidermal growth factor receptor; JPY, Japanese Yen; NSCLC, non-small cell lung cancer; CBDCA, carboplatin; PEM, pemetrexed; NE, not evaluable.

**Table 4.** List of treatments for ES-SCLC

Regimen (Treatment cost per month, JPY)	Number (%)	≤74 yrs (%)	≥75 yrs (%)
CBDCA + ETP + Atezolizumab (844 204)	222 (20.6)	149 (21.7)	73 (19.4)
CBDCA + ETP + Durvalumab (1 376 567)	290 (26.9)	185 (27.0)	105 (27.9)
CDDP + ETP + Durvalumab (1 378 202)	95 (8.8)	94 (13.7)	1 (0.3)
CDDP + irinotecan (25 552)	8 (0.7)	7 (1.0)	1 (0.3)
CDDP + ETP (27 892)	67 (6.2)	61 (8.9)	6 (1.6)
CBDCA + ETP (25 181)	381 (35.3)	190 (27.7)	191 (50.7)
Other	16 (1.5)	NE	NE
<b>Total</b>	<b>1079</b>	<b>686</b>	<b>377</b>

Abbreviations: ES-SCLC, extensive-stage small cell lung cancer; JPY, Japanese Yen; CBDCA, carboplatin; CDDP, cisplatin; ETP, etoposide; NE, not evaluable.

Comparison of the efficacy and cost of osimertinib and gefitinib, extending the median PFS of 8.7 months and median OS of 6.8 months in patients with EGFR mutation-positive NSCLC would cost 9 842 000 JPY per patient [17].

The percentage of patients with ES-SCLC receiving ICI therapy was 56.3%, which was lower than that of patients with NSCLC. In addition, about half the patients older than 75 years did not receive ICI therapy possibly because SCLC is a smoking-related cancer and therefore occurs more often in patients with poor pulmonary status, making the drug less effective for prolonging PFS and OS than in cases of NSCLC. Using atezolizumab to extend the median PFS by 0.9 months and the median OS by 2.0 months increased the cost of therapy to 3 950 000 JPY per patient [19]. Using durvalumab

to extend the median PFS by 0.8 months and the median OS by 2.6 months increased the cost of therapy to 6 510 000 JPY per patient [18].

Atezolizumab and durvalumab are the same PD-L1 inhibitor. The efficacy and safety of treatment with carboplatin plus etoposide plus atezolizumab in the Impower133 trial and platinum plus etoposide plus durvalumab in the CASPIAN trial are nearly identical [18,19]. Slight differences in trial design and slight differences in results between the two trials are not inadequate to select one over the other. The only major and clear difference is cost, with the cost of durvalumab combination therapy being approximately 1.6 times the cost of atezolizumab combination therapy. However, durvalumab combination therapy was used about 1.7 times more than

atezolizumab combination therapy in this study. This fact demonstrates how indifferent physicians are to the cost of treatment. It would be difficult to justify the use of high-cost treatment without documented superiority in efficacy and/or safety to a less costly alternative. There is no single reason why the more expensive treatment should be chosen.

The long-term response and long-term survival rate can be achieved in a small percentage of ES-SCLC patients using an ICI combination regimen. In the future, patient selection will hopefully be made more efficient using biomarkers and newly developed treatment strategies.

In addition, the actual total treatment cost may be higher than the results of this study have shown. One reason for this may be that in Japanese clinical practice, ICIs and target-based drugs continue to be used beyond progressive disease; i.e. the high frequency of their use cannot be justified by the current evidence. The appropriate duration of ICIs dosing is currently under investigation in the JCOG 1701 trial to evaluate the benefit of discontinuing ICI therapy after one year in NSCLC patients who have responded to ICI therapy [22]. There have also been several dose-optimization studies of target-based drugs, and the efficacy of low-dose EGFR-TKI therapy has been reported [23–26]. All of these trials are very appropriate strategies to control treatment costs.

This study has several limitations. First, the accurate cost of drugs for lung cancer treatment in Japan was not determined because lung cancer treatment is also conducted at other treatment centers besides the 60 centers belonging to the Lung Cancer Study Group of the JCOG. Second, the duration of drug administration, efficacy, and side effects of each regimen, which might impact the total treatment cost, were not investigated at all. Since ICI therapy aims to achieve a long-term response, it is incorrect to assume that the number of ICI doses used in a cost estimate is equivalent to the median number of ICI doses administered in a clinical trial. Third, the cost of cancer treatment involves not only the cost of the drugs mentioned above, but also that of ancillary drugs, such as antiemetics and granulocyte colony-stimulating factor (G-CSF), as well of countermeasures for adverse events. Since these treatment costs were not investigated, the actual, total treatment cost of lung cancer therapy is unknown. Fourth, cost-effectiveness analysis in medical care is generally done using quality adjusted life years (QALY) [27]. However, the present survey did not examine the patients' quality of life. A more thorough cost-effectiveness analysis for lung cancer awaits future research.

Lung cancer was a disease with an extremely poor prognosis until about ten years ago. Over the past decade, treatments and the prognosis have greatly improved [28]. At the same time, however, drug costs have drastically increased. The present survey revealed the scale of this increase. Currently, ICI and molecularly targeted drugs in lung cancer treatment are mainly administered in the advanced stage, but if they should come to be used widely at the perioperative stage, their treatment cost may be expected to increase even more.

Pharmaceutical company are also focusing their attention on the development of expensive drugs and are hesitant to produce inexpensive drugs. As a result, there is a new problem in the US: drug-shortage crisis for classical but essential anti-cancer agents such as platinum and etoposide [29–31].

Efforts to optimize drug use, including drug costs, in cancer treatment are already underway mainly in Europe [32]. The issues surrounding the cost of health care, including the cost of drugs, must be addressed by all parties involved in providing health care services, including the government, regulatory authorities, academia, the pharmaceutical industry, patients, and physicians. To develop

better treatments, the 'financial toxicity' of high medical costs must be seriously addressed.

## Conclusion

Recent treatments for advanced lung cancer cost about 20–55 times more than conventional chemotherapy. This study revealed that high-cost treatments were widely used in driver gene mutation and translocation-negative NSCLC, EGFR mutation-positive NSCLC, and ES-SCLC, and that some high-cost treatments were used despite the lack of clear evidence, because physicians are indifferent to the cost. Inappropriate high-cost treatments make waste and burden to society. Physicians should pay attention to the cost of treatments they use. The results of this study will serve as a benchmark for future cost-effectiveness analyses of lung cancer treatments.

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### Supplementary data

Supplementary data is available at *Japanese Journal of Clinical Oncology* online.

### Conflict of interest

Kageaki Watanabe received honoraria from AstraZeneca, Chugai Pharmaceutical, Merck Biopharma, Amgen, Novartis Pharma, Bristol-Myers Squibb, MSD, Nippon Boehringer Ingelheim, Ono Pharmaceutical, RIKEN GENESIS, Sysmex Corporation, Pfizer, Taiho Pharmaceutical, Takeda Pharmaceutical, and Guardant Health outside the submitted work. Junichi Shimizu received honoraria from Taiho Pharmaceutical, Takeda Pharmaceutical, Chugai Pharmaceutical, MSD, AstraZeneca, Novartis, Pfizer, Amgen, Merck outside the submitted work. Motohiro Tamiya received Consulting fees from Pfizer and honoraria from Pfizer, Ono Pharmaceutical, Takeda Pharmaceutical, AstraZeneca, Chugai Pharmaceutical, MSD, Eli Lilly, Bristol-Mayers, Amgen outside the submitted work. Kiyotaka Yoh received grants or contracts from Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Lilly, MSD, Pfizer, Taiho, Takeda and consulting fees from Boehringer Ingelheim and honoraria for lectures from Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Janssen, Kyowa kirin, Lilly, Merck Serono, Novartis, Ono, Otsuka, Taiho, Takeda outside the submitted work. Hiroshige Yoshioka received research funding from Daichi Sanko, AstraZeneca, Janssen Pharmaceutical, MSD, Novartis Pharma, Delta Fly Pharma, Boehringer Ingelheim, and consulting fees from Delta Fly Pharma and honoraria for lectures from Eli Lilly, Chugai Pharmaceutical, MSD, AstraZeneca, Boehringer Ingelheim, Taiho Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Novartis Pharma, Kyowa Kirin, Nippon Kayaku, Otsuka Pharmaceutical, Amgen, Pfizer, Nipro Pharma, Daiichi Sankyo, Merck Biopharma outside the submitted work. Haruyasu Murakami received research grant and funding from Chugai pharma, AstraZeneca, AbbVie, Daiichi Sankyo, IQvia, Taiho Pharmaceutical, Bayer and honoraria from Chugai pharma, Daiichi Sankyo, AstraZeneca, Takeda, Amgen, Ono Pharmaceutical, Bristol-Myers Squibb Japan, MSD, Pfizer, Novartis, Lilly Japan, Taiho Pharmaceutical, Eisai, Nihonkayaku and participated on a Data Safety Monitoring Board or Advisory Board of Chugai pharma, GAIA BioMedicine, Daiichi Sankyo, Takeda, Kyowa Kirin outside the submitted work. Satoru Kitazono received honoraria for lectures from Chugai Pharmaceutical, Ono Pharmaceuticals, Janssen Pharmaceutical, Eli Lilly Japan outside the submitted work. Yasuhiro Goto received grants or contracts from Teijin Pharma Limited, and honoraria from Taiho Pharmaceutical, Nippon Boehringer Ingelheim, Chugai Pharmaceutical, MSD, AstraZeneca, GlaxoSmithKline, Pfizer, Takeda Pharmaceutical outside the submitted work. Hidehito Horinouchi received grants or contracts from AstraZeneca, Roche/Chugai Pharmaceutical, MSD, Abbvie, Bristol-Myers Squibb, Ono Pharmaceutical, and Daiichi Sankyo and honoraria from AstraZeneca, Roche/Chugai Pharmaceutical, MSD, Abbvie, Bristol-Myers Squibb, and Ono Pharmaceutical outside the submitted work. Yuichiro Ohe received grants or contracts from AstraZeneca, Chugai, Eli Lilly, LOXO Kirin, Sumitomo, Pfizer, Taiho, Novartis, Takeda, kissey, Daiichi-Sankyo, Janssen, LOXO, and honoraria from AstraZeneca, Chugai, Eli Lilly, ONO, BMS, Boehringer Ingelheim, Bayer, Pfizer, MSD, Taiho, Nippon Kayaku, Kyowa Hakkō Kirin, Eisai, Daiichi-Sankyo, and payment for expert testimony from AstraZeneca, Chugai, ONO, BMS, Kyorin, Celltrion, Amgen, Nippon Kayaku, Boehringer Ingelheim, AnHeart Therapeutics Inc. PharmaMar outside the submitted work. Keita Sasaki, Ryunosuke Machida, Yuki Yamane, Shin Saito, Yuji Takada declare that they have no conflicts of interest to disclose.

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Original Article

# Status of incremental costs of first-line treatment recommended in Japanese clinical guidelines for metastatic breast cancer patients

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## Abstract

**Background:** The increasing incidence and prevalence of breast cancer alongside diagnostic and treatment technology advances have produced a debate about the financial burden cancer places on the healthcare system and concerns about access.

**Methods:** This study was conducted at 51 hospitals belonging to the Breast Cancer Study Group of the Japan Clinical Oncology Group using a web-based survey. The survey period conducted from July 2021 to June 2022. The study population included patients with metastatic breast cancer who received the related treatment as their first-line therapy. The proportion of patients who selected that regimen as their first-line treatment was tabulated. The total cost increase for each current standard therapy in comparison to conventional treatments was calculated.

**Results:** A total of 702 patients (pts) were surveyed. Of those enrolled, 342 (48.7%) received high-cost treatment [estimated monthly drug costs exceeding ~500 000 Japanese Yen (JPY)]. Of these, 16 pts (4.7%) were receiving very high-cost treatment, amounting to more than 1 000 000 JPY per month. Fifty three (15.5%) of the patients who received high-cost treatment were 75 years of age or older. Of these, 1 pt (0.3%) were receiving very high-cost treatment. Analyses of incremental costs by current drugs showed that abemaciclib was costly with total additional cost of 6 365 670 JPY per patient. The total additional cost of the regimen per patient that included palbociclib was the second highest at 4011248 JPY, followed by atezolizumab at 3209033 JPY.

**Conclusions:** The findings indicate that evaluating the financial implications of high-cost treatments requires considering not only drug prices but also analysis of total cost increase.

**Key words:** breast cancer, cost, incremental cost, guideline

## Background

Breast cancer is the second most commonly diagnosed cancer worldwide and one of the leading causes of cancer-related mortality. In 2022, more than 2.2 million individuals worldwide were diagnosed with breast cancer, and more than 666 000 patients died (1). In Japan, more than 90 000 patients were diagnosed with cancer in 2022, with more than 17 000 deaths (2). Cancer's increasing incidence and prevalence, as well as diagnostic and treatment technology advances, have prompted a public debate about the financial burden cancer places on the healthcare system and concerns about access. New cancer drugs are expensive, and their prices are rising rapidly. For instance, in the USA in 2012, the average cost of treating a patient with a new cancer drug was ~US\$89 000 per year (3). By 2016–17, this amount had nearly doubled to US\$174 000 (4). One factor may be the 'individualization' of treatments, which refers to the use of a treatment only for a subpopulation of patients with characteristics that potentially predict that the treatment will be effective. If only a small proportion of the total number of patients has characteristics known to be necessary for therapeutic efficacy, the market size will necessarily be limited because only a small number of patients will receive treatment. Consequently, a higher cost per patient may be required to recoup the costs of drug development.

The cost of cancer care is a significant concern and challenge in countries with well-developed healthcare systems (5–11). For example, an analysis of healthcare spending in 27 European Union (EU) countries revealed that higher healthcare spending in Western than in Eastern European countries was associated with both higher cancer incidence and lower cancer mortality, particularly for breast cancer (12).

Similar to the EU countries, breast cancer statistics in Japan are characterized by high prevalence and low mortality rates (13). National healthcare expenditure in fiscal year (FY) 2019 was 44389.5 billion Japanese Yen (JPY), an increase of 994.6 billion JPY from the previous year. Regarding healthcare expenditures for medical treatment by injury and disease category, neoplasms (tumors) accounted for 4745.9 billion JPY (14.9%), following the cost of cardiovascular diseases. The healthcare cost for breast cancer amounted to 390.9 billion JPY, which was the third largest after lung and colorectal cancers. The healthcare cost for breast cancer was 254.6 billion JPY in 2009, and this figure increased by about 140 billion JPY during the 10 years to 2019 (14).

The Japanese healthcare system offers universal health coverage and a multi-payer system. The reimbursement prices for medicines were constant across Japan, although they changed over time. Because the public insurer pays the majority of medical costs, an increase in breast cancer medical costs will affect the Japanese healthcare system.

We therefore conducted a multicenter survey to ascertain the incremental cost of the first-line treatment recommended in the Japanese clinical guidelines for patients with metastatic breast cancer (MBC). The Japan Clinical Oncology Group (JCOG) Health Economics Committee oversaw this study.

## Objectives

This study's objective was to examine the regimens used in Japan as first-line systemic treatment for MBC and to estimate the incremental treatment cost using each of these novel, high-cost regimens in comparison with traditional regimens, and to ascertain the current financial burden on public health expenditures associated with advances in breast cancer care.

## Materials and methods

### Data collection

This survey was conducted at 51 hospitals belonging to the Breast Cancer Study Group of the JCOG using a web-based survey. One representative from each hospital was asked to respond to the survey. The survey period spanned 1 year, from July 2021 to June 2022. The number of patients who received high-cost treatments during this period was also examined. The study population included patients with MBC who had received treatment as their first-line therapy. The regimens were recommended in the Guidelines for Breast Cancer Treatment (edited by the Japanese Breast Cancer Society) (15). Regimens were established for each breast cancer subtype, including hormone receptor (HR) positive human epidermal growth factor receptor 2 negative (HR + HER2-), HER2-positive (HER2+), and triple-negative (TN). The study also included drugs for patients with pathogenic mutations in the BRCA1/2 gene.

In accordance with the aforementioned criteria, the following treatments were included in the analysis: nonsteroidal aromatase inhibitors (NSAI) in combination with cyclin-dependent kinase 4/6 inhibitors (CDKIs) (palbociclib and abemaciclib) for HR + HER2-breast cancer (16–22); and trastuzumab in combination with trastuzumab and docetaxel (Tmab+Pmab+DTX) for HER2+ breast cancer (23). The TN subtype adopted regimens that incorporate immune checkpoint inhibitors (ICIs) with four established regimens: nab-paclitaxel (nab-PTX) + atezolizumab, nab-PTX + pembrolizumab, PTX + pembrolizumab, and carboplatin (CBDCA) + gemcitabine (GEM) + pembrolizumab (24,25). Olaparib, a poly ADP-ribose polymerase inhibitor, was included as a regimen for patients with BRCA1/2 gene pathogenic variants (26).

### Analytical methods

Medical expenditures were tabulated as monthly drug costs, excluding supportive medications, such as antiemetics and antiallergic medications. The proportion of patients who selected that regimen as their first-line treatment was tabulated, and differences in the proportion of patients who selected the high-cost regimen were examined using an age of 75 years as the cutoff.

Medical expenditures were based on the official drug prices in Japan as of 2023. The monthly drug costs were tabulated excluding supportive medications, such as antiemetics and antiallergic drugs. The regimens were categorized into very high-cost ( $\geq 1\,000\,000$  JPY/month), high-cost ( $\geq 500\,000$  JPY/month), and other ( $< 500\,000$  JPY/month) treatments defined by the JCOG Health Economics Committee in this survey.

The proportion of patients who selected that regimen as their primary treatment was tabulated, and differences in the proportion of patients who selected the high-cost regimen were examined using an age of 75 years as the cutoff. We then tabulated the median course of administration from the literature on pivotal trials that provided the basis for regimen reimbursement (16–26). Subsequently, the total cost increase for each high-cost regimen as compared with the control arm of the pivotal trial (the conventional standard of care) was calculated, based on drug prices and incremental median progression-free interval (see below). For drugs administered on a per-body surface area basis, the dose was calculated based on the average physique of Japanese women, assuming a height of 160 cm and a weight of 60 kg (1.622 m<sup>2</sup>).

### Cost calculation

All costs associated with this survey are presented in terms of drug costs per month. First, for a treatment cycle of 28 days, the drug cost for this one cycle was calculated as the cost of the drug. For a treatment cycle of 21 days, the annual cost was calculated assuming 18 cycles of treatment per year, and this was divided by 12 to obtain the cost per month.

To ascertain the current financial burden on public health expenditures, incremental cost analysis was conducted. The incremental cost analysis was based on the drug cost per month calculated in this manner. The incremental cost per month was defined as the difference between the cost of the novel treatment regimen and the cost of the comparator. Finally, the clinical benefit [progression free survival (PFS) gained in months] of the novel treatment regimens derived from the clinical trial results was multiplied by the incremental cost per month to calculate total cost increase, assuming that the novel treatment was administered for the period of the median PFS.

### Results

Responses were received from 30 of the 51 institutions (59%). A total of 702 patients (pts) were surveyed: HR + HER2- type, 405 patients; HER2+, 145 patients; TN type, 127 patients; and BRCA1/2+ type, 25 patients. Of all enrolled patients, 342 (48.7%) received high-cost treatment and 16 (4.7%) received very high-cost treatment. In this survey, nab-PTX+ atezolizumab was classified as very high-cost treatment. The most prevalent breast cancer subtype was the HR + HER2- type, accounting for 27.8% of all cases. The next most prevalent subtype was HER2+, which accounted for 12.3% of all cases. The TN type was the third most common, accounting for 7.1% of all cases, whereas the BRCA1/2+ type was the least prevalent, accounting for 1.6% of all cases. In a survey per breast cancer subtypes, the largest percentage of patients treated with high-cost treatment regimens were of the HER2+ type (59.3%), followed by the HR + HER2- type (48.1%), BRCA1/2+ type (44.0%), and TN type (39.3%) (Fig. 1 and Table 1).

An analysis of the implementation of high-cost treatment regimens by age revealed that 53 (15.5%) of the 342 patients who received high-cost treatment were 75 years of age or older (Table 2). Of 53 elderly patients who received high-cost therapy, 40 were treated with NSAI+CDKIs. Only two patients received regimens that included ICIs. Of these, 1 patient (0.3%) were receiving very high-cost treatment ( $\geq 1\,000\,000$  JPY/month).

Table 3 presents the median extended PFS and associated incremental costs from the pivotal study for each treatment. The

treatments with the highest incremental cost per month were regimens that ICIs: nab-PTX + atezolizumab, 1 180 586 JPY, nab-PTX + pembrolizumab, 932 682 JPY, CBDCA+GEM+pembrolizumab, 681 792, and JPY and PTX + pembrolizumab, 669 126 JPY. Conversely, the lowest incremental cost per month was observed for CDKIs, at 481 581 JPY for abemaciclib and 437 848 JPY for palbociclib.

A study on the incremental cost of the drug was conducted, assuming that treatment could be continued for the median duration of PFS based on clinical trial results. The results indicate that abemaciclib was the most costly with total additional cost of 6365670JPY per patient. Then, the incremental cost of palbociclib was 4 011 248 JPY. The incremental cost of the regimen that included atezolizumab was the third highest, at 3209033 JPY. Conversely, the lowest incremental cost administered for median PFS was olaparib, which was compared to eribulin mesylate, at 766368 JPY.

### Discussion

The results of this survey provide a comprehensive overview of the status of first-line treatment regimens and associated costs for MBC based on the Japanese healthcare system. One regimen was identified as being matched to very high-cost regimens among recent first-line treatments. High-cost treatments, such as CDKIs, were used for a substantial number of patients, particularly those under 74 years of age.

The first discussion concerns the status of high-cost treatments for MBC patients in Japan. The lack of a clear definition of what constitutes high-cost treatment has led to defining it as a regimen with drug costs exceeding an average of 500 000 JPY per month (equivalent to 6 million JPY per year). Given that the average annual income per salaried employee working throughout the year was 4.58 million JPY according to the National Tax Agency's "Statistical Survey of Private Salaries for 2021," our definition is  $\sim 1.31$  times that amount (27). Accordingly, our survey revealed that 48.7% of patients selected the high-cost treatment recommended as the first-line treatment for MBC in the practice guidelines (Fig. 1 and Table 1). This outcome may be attributed to physicians selecting treatment options without being fully aware of the associated drug costs. This discrepancy in the perception of medical cost explanations was observed by Saeki et al. (28) in their study of financial toxicity in Japanese patients with breast cancer. It examined the extent to which physicians and patients explained the medical costs. Specifically, the study reported that physicians "explained medical costs to their patients," while a higher percentage of patients reported that "physicians did not explain medical costs to them." Consequently, we suggest that the cost of drugs be incorporated into practice guidelines to facilitate communication between healthcare providers and patients regarding the financial implications of drug therapies. Then, from the standpoint of regulating pharmaceutical expenditures, it would be advantageous to incorporate data regarding the accessibility and costs of generic drugs and biosimilars.

The second issue concerns the proportion of older patients receiving high-cost treatment. Elderly individuals frequently present with comorbidities, suggesting considerable interindividual variability in organ function, cognitive function, and social living environments. It is also crucial to evaluate life expectancy. Jolly et al. reported that 21% of elderly breast cancer patients died of causes other than breast cancer within 5 years (29). The proportion of elderly participants in clinical trials is relatively low. When treating elderly patients,

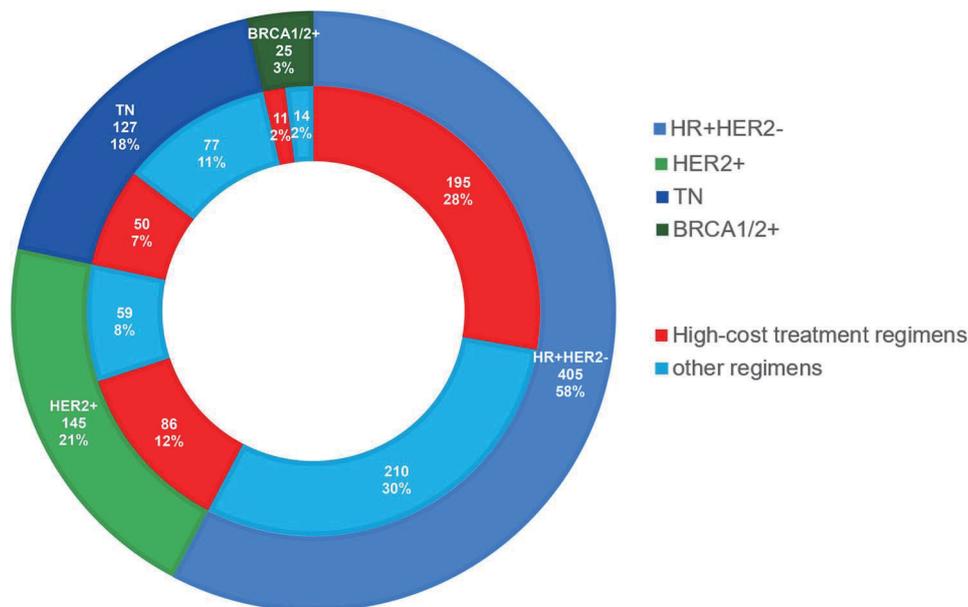


Figure 1. Proportion of high-cost regimens per subtype hormone receptor-positive HER2-negative (HR+HER2-), HER2-positive (HER2+), TN, and a pathogenic variant of the BRCA1/2 gene (BRCA1/2+).

Table 1. Status of application of regimens by breast cancer subtype

Subtype	First line treatment regimen	Number of patients by high-cost treatment
HR + HER2-	<sup>a</sup> NSAI+CDKIs	195 (27.8%)
	others	210 (29.9%)
HER2+	<sup>a</sup> Tmab+Pmab+DTX	86 (12.3%)
	others	59 (8.4%)
TN	<sup>a</sup> nab-PTX+ atezolizumab	16 (2.3%)
	<sup>a</sup> nab-PTX+ pembrolizumab	1 (0.1%)
	<sup>a</sup> PTX+ pembrolizumab	4 (0.6%)
	<sup>a</sup> CBDCA+ GEM+ pembrolizumab	29 (4.1%)
	others	77 (11.0%)
	others	11 (1.6%)
BRCA1/2+	<sup>a</sup> olaparib	14 (2.0%)
Total	others	702

Hormone receptor-positive HER2-negative (HR + HER2-), HER2-positive (HER2+), and TN, non-steroidal aromatase inhibitor (NSAI), CDKIs, trastuzumab + pertuzumab + docetaxel (Tmab+Pmab+DTX), nab-paclitaxel (nab-PTX), paclitaxel (PTX), carboplatin (CBDCA), gemcitabine (GEM), a pathogenic variant of the BRCA1/2 gene (BRCA1/2+).

<sup>a</sup>High-cost regimens.

physicians must meticulously ascertain the treatment indications and proactively manage adverse events at the outset based on a comprehensive geriatric assessment and effective comorbidity management, despite the limited evidence available.

In fact, we found that only 15.5% of the high-cost patients were older than 75 years. The most common high-cost treatment was for HR + HER2- type MBC, which accounted for 40 cases (11.7%). A report examining the age and frequency of adverse events for CDKIs for HR + HER2- type (30), Tmab+Pmab+DTX for HER2+ type (31), and ICIs for TN type (32) revealed an increased frequency of adverse events in the elderly for all regimens. The reasons why clinicians avoid high-cost treatment for the elder patients are thought to be complex, but the high incidence of adverse events in this demographic may be a contributing factor.

The final issues for consideration are the drug price and the incremental cost of obtaining the clinical benefit identified in the clinical study. Our study revealed that the drug with the highest incremental cost per month was atezolizumab. This was followed by regimens containing pembrolizumab. The rationale for this might attributed to the high drug price, despite the transient efficacy of ICIs, which ranged from 2.5 to 4.1 months. Then, as demonstrated in Table 3, in examining drug price and clinical efficacy, the greatest incremental cost in achieving clinical efficacy was not for atezolizumab, which has the highest drug cost, but for abemaciclib, a CDKIs. The next most significant incremental cost was pembrolizumab, followed by palbociclib and atezolizumab. These results show that when a high-cost treatment is introduced, the healthcare provider focuses on the drug price; however, we need to consider the incremental cost, including

**Table 2.** Status of high-cost treatment indications for elderly patients

Subtype	First line treatment regimen	Number of <75 years old patients using high-cost treatment	Number of ≥75 years old patients using high-cost treatment	Number of patients by high-cost treatment
HR + HER2-	NSAI+CDKIs	155 (45.3%)	40 (11.7%)	195 (57.0%)
HER2+	Tmab+Pmab+DTX	75 (21.9%)	11 (3.2%)	86 (25.1%)
TN	nab-PTX+ atezolizumab	15 (4.4%)	1 (0.3%)	16 (4.7%)
	nab-PTX+ pembrolizumab	1 (0.3%)	0	1 (0.3%)
	PTX+ pembrolizumab	4 (1.2%)	0	4 (1.2%)
	CBDCA+ GEM+ pembrolizumab	28 (8.2%)	1 (0.3%)	29 (8.5%)
	BRCA1/2+	olaparib	11 (3.2%)	0
Total		289 (84.5%)	53 (15.5%)	342

hormone receptor-positive HER2-negative (HR + HER2-), HER2-positive (HER2+), and TN, NSAI, CDKIs, trastuzumab + pertuzumab + docetaxel (Tmab+Pmab+DTX), nab-paclitaxel (nab-PTX), paclitaxel (PTX), carboplatin (CBDCA), gemcitabine (GEM), a pathogenic variant of the BRCA1/2 gene (BRCA1/2+).

**Table 3.** Analysis of the incremental costs required to obtain the benefits of pivotal trials

Subtype	Comparator	Cost of comparator/-month	Novel treatment regimen	Cost of novel treatment regimen/-month	Clinical benefit Median PFS	Incremental cost/month	Incremental cost administered for median PFS
HR+ HER2-	NSAI	6531JPY	NSAI+CDKIs (palbociclib)	437848JPY	9.3 months gained	431317JPY	4011248JPY
	NSAI	6531JPY	NSAI+CDKIs (Abemaciclib)	481581JPY	13.4 months gained	475050JPY	6365670JPY
HER2+	Tmab+DTX	159179JPY	Tmab+Pmab+DTX	486093JPY	6.3 months gained	326914JPY	2059558JPY
TN	nab-PTX	361485JPY	nab-PTX+ atezolizumab	1180586JPY	2.5 months gained	819101JPY	3209033JPY
	nab-PTX	361485JPY	nab-PTX+ pembrolizumab	932682JPY	4.1 months gained	571197JPY	2341908JPY
	PTX	25635JPY	PTX+ pembrolizumab,	669126JPY		643491JPY	2638313JPY
	CBDCA+GEM	38298JPY	CBDCA+ GEM+ pembrolizumab	681792JPY		643494JPY	2638325JPY
BRCA 1/2+	capecitabine	39720JPY	olaparib	574560JPY	2.8 months gained	534840JPY	1497552JPY
	eribulin mesylate	300857JPY				273703JPY	766368JPY
	vinorelbine	24042JPY				550518JPY	1541450JPY

HR, human epidermal growth factor receptor 2 (HER2), TN, a pathogenic variant of the BRCA1/2 gene (BRCA1/2+), NSAI, CDKIs, trastuzumab + pertuzumab + docetaxel (Tmab+Pmab+DTX), nab-paclitaxel (nab-PTX), paclitaxel (PTX), carboplatin (CBDCA), gemcitabine (GEM).

the length of the clinical benefit. Additionally, when evaluating the budget impact of high-cost drugs, it is crucial to consider the number of patients for whom the drugs are indicated. As shown in Tables 1 and 2, the regimens with the greatest number of patients treated at a high cost were those combining NSAI and CDKIs in patients with HR + HER2-type MBC. This indicates that CDKIs have the greatest financial burden impact on public health expenditures among breast cancer drugs because of their high incremental costs and the large number of patients for whom they are indicated. In addition, from a clinical standpoint, as Griggs et al. have asserted (33), the dearth of data directly comparing the efficacy and safety of multiple CDKI options renders it challenging for clinicians to select between them with any degree of certainty.

This study has several limitations. The first is the study's comprehensiveness. It was conducted exclusively at centers participating in the JCOG Breast Cancer Group. Consequently, this study does not represent all the breast cancer treatment centers in Japan. Given that individual data were not collected, the cost calculation was based on the assumption of a standard Japanese female patient with breast cancer. The survey period was short. Drug costs in Japan are subject to regular reviews, which may result in future fluctuations in estimated costs. Furthermore, the guidelines in the 2022 edition are subject to future updates, given the evolving nature of first-line treatment. It should be noted that, as the present study is not a cost-effectiveness analysis of treatment regimens, but rather a survey of the current situation, the results cannot be used as a basis for clinicians to

make decisions about which treatment regimen to choose in clinical practice.

Our study is the first to report on the current status of high-cost medical care recommended by practice guidelines for the first-line treatment of patients with MBC in Japan. It is imperative to continue our research efforts, because we anticipate the emergence of more innovative and costly pharmaceuticals for the treatment of breast cancer in the near future. For instance, with respect to the treatment strategy for CDKIs, which our research has demonstrated to be costly, it is advisable to encourage clinical research such as the SONIA trial (34), which seeks to optimize the treatment strategy for CDKIs.

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## Conflict of interest

Tsuguo Iwatani received honoraria from Eisai outside of the submitted work. Tadahiko Shien received honoraria from Daiichi-Sankyo, Chugai, Eli Lilly, MSD, Eisai, Kyowa-Kirin, AstraZeneca, Gilliad, and Pfizer outside of the submitted work. Fumikata Hara received honoraria from Daiichi-Sankyo, Chugai, Eli Lilly, MSD, Kyowa-Kirin, and Pfizer outside of the submitted work. Kei Koizumi received honoraria from Chugai and Pfizer outside of the submitted work. Kanako Saito received honoraria from Daiichi-Sankyo, Chugai, Eli Lilly, MSD, Eisai, Kyowa-Kirin, AstraZeneca, and Pfizer outside of the submitted work. Hiroji Iwata received grants from Chugai, Daiichi Sankyo, AstraZeneca; consulting fees from Daiichi Sankyo, Chugai, AstraZeneca, Eli Lilly, MSD, Pfizer, Giliead; and honoraria from Daiichi Sankyo, Chugai, AstraZeneca, Eli Lilly, MSD, Pfizer, Taiho, Kyowa Kirin outside of the submitted work.

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Original Article

# A real-world survey on expensive drugs used as first-line chemotherapy in patients with HER2-negative unresectable advanced/recurrent gastric cancer in the stomach cancer study group of the Japan clinical oncology group

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## Abstract

**Background:** Molecular-targeted drugs and immune checkpoint inhibitors have been developed for various malignant diseases, thereby improving clinical outcomes. However, these drugs are expensive, and few studies have assessed their actual use and costs in Japan. This study aimed to survey the use and costs of first-line chemotherapy for advanced/recurrent gastric cancer (AGC) in real-world settings.

**Methods:** The survey included patients with human epidermal growth factor receptor type2 (HER2)-negative AGC who initiated first-line chemotherapy from January 2022 to December 2022 at the participating 92 institutions in the Japan Clinical Oncology Group. Data on the regimens were collected using Google Forms. A regimen that costs >500 000 Japanese yen (JPY) per month was defined as expensive.

**Results:** Data on chemotherapy regimens were collected from 2173 patients at all 92 institutions between March 2023 and May 2023. We analyzed 2113 patients who underwent the chemotherapy with recommended regimens and conditionally recommended regimens according to the Japanese Gastric Cancer Treatment Guidelines sixth edition. The expensive regimens were triplet chemotherapy with fluoropyrimidine (S-1 or capecitabine or 5-fluorouracil/levofolinate), oxaliplatin, and nivolumab. Their monthly costs ranged from 767 648 to 771 046 JPY. Nivolumab-containing regimens cost more than 20 times the price of conventional chemotherapy with fluoropyrimidine and oxaliplatin. These regimens were used in 1416 (67%) of 2113 patients: in 71% of patients aged ≤74 years and in 59% of patients aged ≥75 years.

**Conclusion:** The regimens with >20-fold cost of conventional chemotherapy were used as first-line chemotherapy in two-thirds of patients and more than half even in the elderly population with

HER2-negative AGC. This finding is important for future health economic studies on drug cost-efficacy.

**Key words:** gastric cancer, real-world survey, chemotherapy, nivolumab, cost

## Introduction

Gastric cancer is a relevant global health issue, with a high burden in Eastern Asia, Eastern Europe, and South America. It is the fifth most common cancer worldwide and the third leading cause of cancer-related mortality (1).

The prognosis of unresectable advanced/recurrent gastric cancer (AGC) is generally poor. The median survival time of patients who did not receive chemotherapy was reported as 3–5 months (2,3). Since a couple of randomized, controlled trials confirmed survival benefits of systemic chemotherapy compared with the best supportive care (2,3), systemic chemotherapy should be primarily considered for patients with AGC.

In the Japanese Gastric Cancer Treatment Guidelines sixth edition (4), first-line chemotherapy is categorized into the recommended regimens that are the standard of care, and the conditionally recommended regimens that are the options for patients unfit for the standard treatment due to various reasons in routine clinical practice.

In terms of first-line chemotherapy for human epidermal growth factor receptor type2 (HER2)-negative AGC (~80% of AGC cases), various combinations of fluoropyrimidine and platinum are recognized as recommended regimens based on the results of phase III studies (5–8). Several trials evaluated the addition of molecular-targeted agents, such as vascular endothelial growth factor inhibitors, epidermal growth factor receptor inhibitors, and mesenchymal–epithelial transition inhibitors to the combination of fluoropyrimidine and platinum-based agents. However, these combinations, except for vascular endothelial growth factor inhibitor, could not show survival benefits (9–11). Recently, the CheckMate 649 and ATTRACTION-4 trials have shown that the addition of nivolumab can prolong patient survival (12,13). Consequently, combinations of fluoropyrimidine and oxaliplatin plus nivolumab have become one of the recommended regimens by the Japanese Gastric Cancer Treatment Guidelines sixth edition (4).

Although nivolumab is effective against various types of cancers, it is expensive. The increased use of nivolumab in gastric cancer treatment may have a substantial impact not only on personal costs but also on healthcare budgets both at the national and institutional levels. However, in Japan, due to the universal health insurance system, medical professionals seldom pay attention to a high-medical cost. The issue of high-cost healthcare is widely recognized as a significant problem in high-income countries (14–16).

To ensure the sustainability of the health insurance system and from the perspective of improving the quality of medical care and enhancing patient quality of life, the appropriate use of expensive drugs in cancer treatment should be considered. However, a real-world survey on the actual usage of expensive treatments has not been sufficiently conducted. To collect and analyze the important fundamental data, the Japan Clinical Oncology Group (JCOG) Health Economics Committee conducted a survey on the use of expensive medical treatments for unresectable recurrent cancers, focusing on

first-line chemotherapy. The current study aimed to discuss about the utilization of expensive drugs as first-line chemotherapy for AGC based on the results of the real-world survey.

## Materials and methods

### Target patients of the survey

The survey included patients who initially received first-line chemotherapy for HER2 negative AGC from January 2022 to December 2022 at the participating institutions in the JCOG Stomach Cancer Study Group. Patients who recurred at least 6 months after last administration of preoperative/postoperative adjuvant chemotherapy were eligible.

### Targeted chemotherapy regimens in the survey

The chemotherapy regimens targeted by this survey were first-line chemotherapy for HER2-negative cancer categorized as recommended regimens and conditionally recommended regimens according to the Japanese Gastric Cancer Treatment Guidelines sixth edition (4). The recommended regimens were S-1 and cisplatin, S-1 and oxaliplatin (SOX), capecitabine and cisplatin (XP), capecitabine and oxaliplatin (CapeOX), and 5-FU/levofolinate calcium (LV) with oxaliplatin (FOLFOX), SOX plus nivolumab, CapeOX plus nivolumab, and FOLFOX plus nivolumab. The conditionally recommended regimens were 5-FU and cisplatin, 5-FU/LV, 5-FU/LV and paclitaxel, and S-1 and docetaxel. In addition to the specified regimens, the other regimens used in clinical practice were categorized as others. For the recommended and conditionally recommended chemotherapy, excluding the others, the patients were divided according to age ( $\leq 74$  vs.  $\geq 75$  years) at treatment initiation.

### Survey methods

Data on first-line regimens used for each patient were collected from each institution using Google Forms. No personal patient data were collected. Thus, this study did not require individual consent or Institutional Review Board approval.

### Calculation method for the regimen costs

The regimen costs were calculated assuming as a standard body type with height of 165 cm, weight of 60 kg, and body surface area of 1.66 m<sup>2</sup>. For medications with generic alternatives, the drug with a lower price was used. The regimen costs were calculated based on the prices as of 1 February 2024. The monthly regimen costs were calculated as the cost for 4 weeks. For example, in a regimen where one cycle is given every 3 weeks, the cost for one cycle was multiplied by 4/3 to calculate it as the cost for 4 weeks.

### Definition of expensive chemotherapy

The definitions of expensive chemotherapy were proposed by the JCOG Health Economics Committee. High-cost chemotherapy was

**Table 1.** Treatment regimens and costs

Regimen	One cycle	Drugs and dosage	Monthly cost
SOX + Nivolumab	3 wks	S-1: 120 mg/day, Days 1–14 Oxaliplatin: 130 mg/m <sup>2</sup> , Day 1 Nivolumab: 240 mg, Day 1	771 046 JPY
CapeOX + Nivolumab	3 wks	Capecitabine: 2000 mg/m <sup>2</sup> /day, Days 1–14 Oxaliplatin: 130 mg/m <sup>2</sup> , Day 1 Nivolumab: 240 mg, Day 1	767 648 JPY
FOLFOX + Nivolumab	2 wks	5-Fluorouracil: 400 mg/m <sup>2</sup> , Day 1 and 1200 mg/m <sup>2</sup> , Days 1–2 Levofolinate: 200 mg/m <sup>2</sup> , Day 1 Oxaliplatin: 85 mg/m <sup>2</sup> , Day 1 Nivolumab: 240 mg, Day 1	770 392 JPY
SOX	3 wks	S-1: 120 mg/d, Days 1–14 Oxaliplatin: 130 mg/m <sup>2</sup> , Day 1	35 199 JPY
CapeOX	3 wks	Capecitabine: 2000 mg/m <sup>2</sup> /day, Days 1–14 Oxaliplatin: 130 mg/m <sup>2</sup> , Day 1	31 799 JPY
FOLFOX	2 wks	5-Fluorouracil: 400 mg/m <sup>2</sup> , Day 1 and 1200 mg/m <sup>2</sup> , Days 1–2 Levofolinate: 200 mg/m <sup>2</sup> , Day 1 Oxaliplatin: 85 mg/m <sup>2</sup> , Day 1	37 582 JPY
S-1 + Cisplatin	5 wks	S-1: 120 mg/day, Days 1–21 Cisplatin: 60 mg/m <sup>2</sup> , Day 8	19 766 JPY
Capecitabine + Cisplatin	3 wks	Capecitabine: 2000 mg/m <sup>2</sup> /day, Days 1–14 Cisplatin: 80 mg/m <sup>2</sup> , Day 1	25 353 JPY
5-FU + Cisplatin	4 wks	5-Fluorouracil: 800 mg/m <sup>2</sup> , Days 1–5 Cisplatin: 80 mg/m <sup>2</sup> , Day 1	14 472 JPY
5-FU/l-LV	6 wks	5-Fluorouracil: 600 mg/m <sup>2</sup> , Days 1, 8, 15, and 22 Levofolinate: 250 mg/m <sup>2</sup> , Days 1, 8, 15, and 22	21 758 JPY
5-FU/l-LV + Paclitaxel	4 wks	5-Fluorouracil: 600 mg/m <sup>2</sup> , Days 1, 8, 15, and 22 Levofolinate: 250 mg/m <sup>2</sup> , Days 1, 8, 15, and 22 Paclitaxel: 80 mg/m <sup>2</sup> , Days 1, 8, 15, and 22	49 806 JPY
S-1	6 wks	S-1: 120 mg/day, Days 1–28	16 319 JPY
S-1 + Docetaxel	3 wks	S-1: 120 mg/day, Days 1–14 Docetaxel: 140 mg/m <sup>2</sup> , Day 1	23 014 JPY

SOX, S-1 + oxaliplatin; CapeOX, capecitabine + oxaliplatin; FOLFOX, 5-FU/Levofolinate with oxaliplatin; 5-FU, 5-Fluorouracil; l-LV, Levofolinate; JPY, Japanese yen; wks, weeks.

defined as expensive if costing >500 000 Japanese yen (JPY) per month and ultra-expensive if costing >1 000 000 JPY per month.

## Results

### Status of the real-world survey

The survey was conducted between March 2023 and May 2023, and responses were obtained from all 92 institutions participating in the Stomach Cancer Study Group of the JCOG.

### Regimen costs

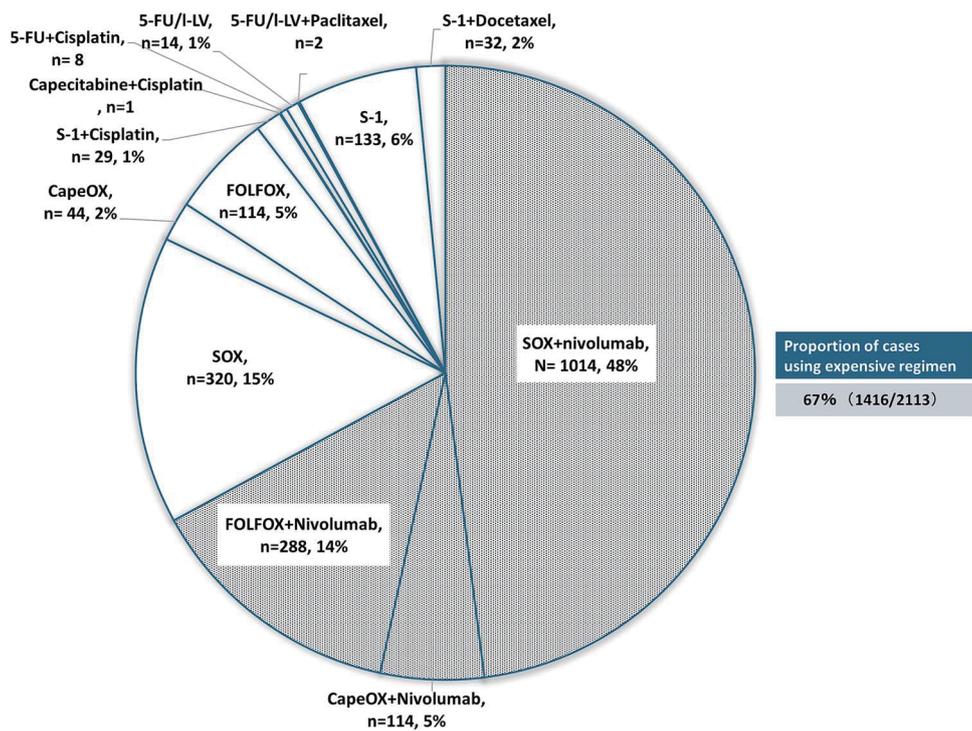
Table 1 shows the list of medication costs for each regimen per month. None of the regimens were classified as ultra-expensive. The regimens considered expensive were the combinations of fluorouracil and oxaliplatin (SOX, CapeOX, or FOLFOX) plus nivolumab. Their cost ranged from 767 648 to 771 046 JPY per month. On the other hand, the cost of the conventional chemotherapy regimens (S-1 or capecitabine or 5-FU/LV and oxaliplatin) ranged from 31 799 to 37 182 JPY per month. Nivolumab-containing regimens cost more than 20 times the higher price of conventional chemotherapy.

### Real-world survey results

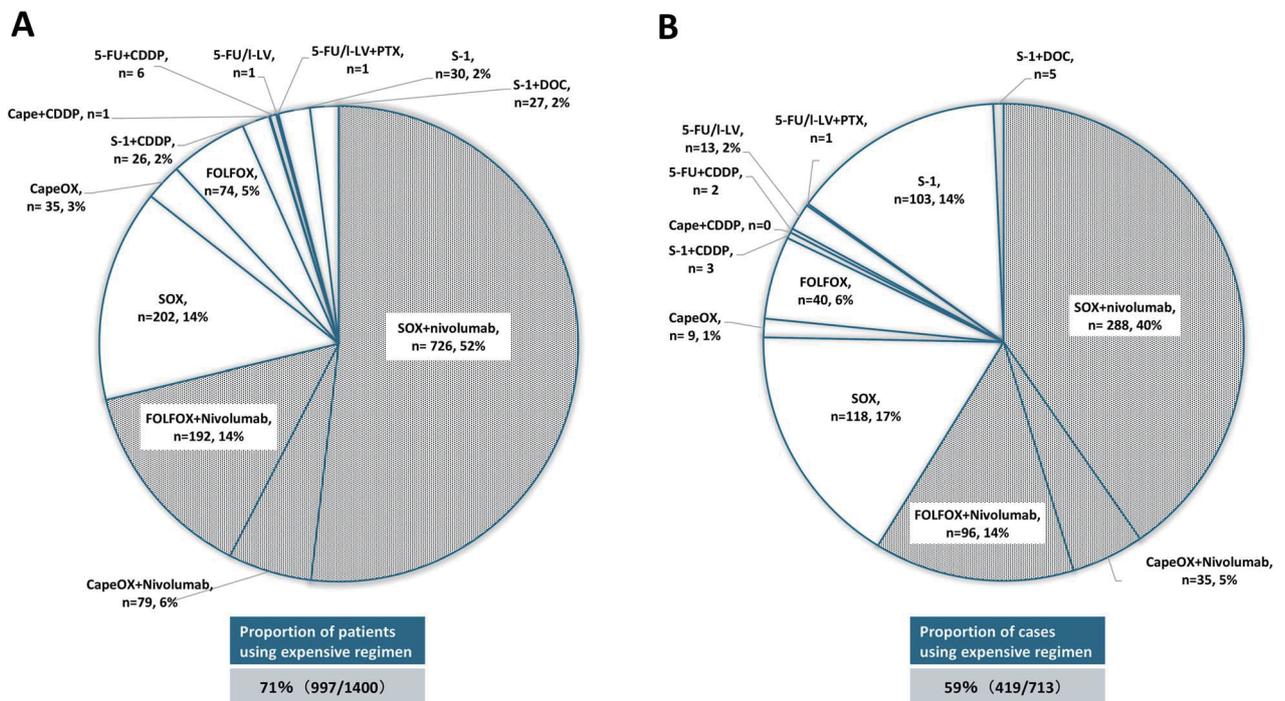
The total number of patients surveyed was 2173. Sixty patients treated with the regimen other than those described in the treatment guideline were excluded from the analysis because the details of the regimen costs and patient's age were not obtained. We analyzed 2113 patients who underwent the chemotherapy with recommended regimens and conditionally recommended regimens according to the Japanese Gastric Cancer Treatment Guidelines sixth edition (4).

Figure 1 shows the details of the chemotherapy regimens of all patients and the proportion of patients receiving expensive regimens. Further, 1894 (90%) patients received fluoropyrimidine and oxaliplatin (SOX or CapeOX or FOLFOX)-based treatments. The nivolumab combination regimens were as follows: SOX plus nivolumab ( $n = 1014$ , 48%), CapeOX plus nivolumab ( $n = 114$ , 5%), and FOLFOX plus nivolumab ( $n = 288$ , 14%). Totally, 1416(67%) of 2113 patients received expensive regimens.

Figure 2 shows the details of the regimens according to age; 713(34%) of 2113 patients were aged  $\geq 75$  years. The proportions of patients receiving fluoropyrimidine and oxaliplatin (SOX or CapeOX or FOLFOX)-based chemotherapy were 93% in patients aged  $\leq 74$  years and 82% in those aged  $\geq 75$  years. The proportion of patients receiving expensive regimens in the  $\leq 74$ -year-old age group



**Figure 1.** Chemotherapeutic regimens of all patients and the proportion of patients receiving expensive regimens. The gray shaded area of the graph represents expensive regimens. SOX, S-1 + oxaliplatin; CapeOX, capecitabine + oxaliplatin; FOLFOX, 5-fluorouracil/levofolinate with oxaliplatin; 5-FU, 5-fluorouracil; L-LV, levofolinate.



**Figure 2.** Subgroup data of the chemotherapeutic regimens of all patients and the proportion of patients receiving expensive regimens according to age: (A)  $\leq 74$  years old and (B)  $\geq 75$  years old. The gray shaded area of the graph represents expensive regimens. SOX, S-1 + oxaliplatin; CapeOX, capecitabine + oxaliplatin; FOLFOX, 5-fluorouracil/levofolinate with oxaliplatin; 5-FU, 5-fluorouracil; L-LV, levofolinate; cape, capecitabine; CDDP, cisplatin; DOC, docetaxel; PTX, paclitaxel.

was higher than that in the  $\geq 75$ -year-old age group (71% vs. 59%; Fig. 2A and B).

## Discussion

This real-world survey conducted by the Stomach Cancer Study Group of the JCOG evaluated the use of first-line chemotherapy for HER2-negative AGC. It was shown that 67% of patients received regimens with nivolumab, which were qualified as expensive treatments with monthly drug expenses exceeding 500 000 JPY. To the best of our knowledge, no real-world survey has assessed the use of expensive treatments as first-line chemotherapy for AGC.

Nivolumab has been clinically used in Japan since it was proven to prolong survival in patients with AGC receiving third- or later-line treatment compared with placebo based on the ATTRACTION-2 trial (17). In the CheckMate 649 trial, as first-line chemotherapy for HER2-negative AGC, the median overall survival was 13.8 months in the nivolumab plus chemotherapy group and 11.6 months in the chemotherapy alone group (hazard ratio 0.80;  $P < .0002$ ). Based on these findings, a combination of nivolumab with the doublet chemotherapy is recommended as the first-line treatment for HER2 negative AGC patients in the treatment guidelines in December 2021 (4).

In subgroup analyses of programmed death ligand 1 (PD-L1) expression in the CheckMate 649 trial, the relationship of the combined positive scores with progression-free survival and OS was examined. Results showed that the hazard ratios for OS in patients with a combined positive score (CPS) of  $< 5$  and  $\geq 5$  were 0.94 and 0.70, respectively, indicating a limited additional survival benefit in patients with a CPS of  $< 5$ . The ATTRACTION-4 trial showed a significant improvement in PFS, but not in OS (13). Thus, one of the reasons for no significant difference in the ATTRACTION-4 trial was considered to be that immune checkpoint inhibitors were used as the posttreatment in 27% of the placebo group, resulting in substantially longer OS of the placebo group compared with other trials. Based on these findings, the following comment has been made in the gastric cancer treatment guidelines (4), 'The survival benefit of adding nivolumab to chemotherapy in patients with a PD-L1 CPS of  $< 5$  has not been clearly elucidated. However, the risk-benefit balance of chemotherapy alone versus in combination with nivolumab should be considered based on the patient's condition. Consequently, either treatment can be selected according to the patient's informed consent'. The Japanese Gastric Cancer Treatment Guidelines state that there are no reviewed reports on the cost increase associated with the use of immune checkpoint inhibitors in first-line treatment for AGC, making it difficult to evaluate (4).

From the perspective of physicians, the combination proportion of nivolumab (67%) in the real-world setting is reasonable. This is because in first-line chemotherapy plus nivolumab for patients with PD-L1 CPS of  $\geq 5$ , the 3-year survival proportions of those receiving nivolumab plus chemotherapy versus chemotherapy alone were 21% versus 10% reported in a 3-year follow-up in the CheckMate 649 trial (18). Although recent advances in chemotherapy for AGC prolonged survival, it is difficult to obtain a cure by chemotherapy alone. The current goals of palliative chemotherapy are not only to prolong survival but also to delay the manifestation of the disease-related symptoms. From this perspective, a regimen containing nivolumab, which provides an additive effect of  $\sim 10\%$  in response rate regardless of CPS status, is considered beneficial for patients, and there are no other effective combination therapies available for HER2-negative patients at the time of this survey.

At present, the official price of nivolumab (over ¥700 000/month) is at least 20 times higher than that of SOX ( $\sim ¥35 000$ /month). If SOX plus nivolumab were continued without dose reduction and interruption for 6.3 months, which is the median duration of nivolumab treatment in the ATTRACTION-4 trial, the median total costs would reach  $\sim ¥4.85$  million, and most of them (95%) are occupied with nivolumab costs. From the individual patient's point of view, the actual payment per month would be approximately from ¥8000 to ¥260 000 according to the personal income, when patients use the Japanese medical insurance system and the High-Cost Medical Expense Benefit system. Thus, thanks to these national medical insurance systems, most patients and physicians select the best first-line chemotherapy regimen recommended without a concern of medical cost pressure.

According to the payer's perspective in Japan, the cost-efficacy of nivolumab for AGC has been evaluated. Previous studies using data from ATTRACTION-4 and ATTRACTION-2 reported that the use of nivolumab as third- or later-line treatment is considered to be cost-effective, but its application in combination with chemotherapy as a first-line treatment is not cost-effective (19). Previous studies analyzing the CheckMate 649 data found that even in patients with a CPS of  $\geq 5$ , the cost exceeded the cost-effectiveness threshold of USD 75 000–150 000/quality-adjusted life year in Japan. Therefore, it is not cost-effective (20). In patients with a CPS of  $< 5$ , it is important to contemplate the cost-benefit and to select the use of nivolumab in patients that can have more effective results based on biomarkers.

According to the NCCN Guidelines for Older Adult Oncology, elderly patients are classified into fit, vulnerable, and unfit categories based on their life expectancy, decision-making ability, treatment goals, and risk of side effects (21). For fit patients who satisfy the eligibility criteria of clinical trials, a chemotherapy regimen similar to that for younger patients is recommended in the Japanese Gastric Cancer Treatment Guidelines (4). However, for vulnerable or unfit patients, high-level evidence is scarce. The diverse conditions of these patients make it challenging to establish clear recommendations (4). In this survey, the use of nivolumab in adults aged  $\geq 75$  years was lower than that in younger adults aged  $\leq 74$  years. This result is reasonable because some elderly patients may not be qualified for platinum-based agents. In the post-marketing survey of nivolumab monotherapy, the risk of treatment-related adverse events was higher in elderly patients, while the possibility of response was also higher (22). The incidence of immune-related adverse events increases with the use of nivolumab combination regimen as first-line treatment for AGC (12,13). However, there are no established biomarkers for efficacy and immune-related adverse events. Recently, a randomized phase II trial (WJOG8315G) targeting first-line treatment for patients aged 70 and older compared S-1 monotherapy with SOX. This study suggested that the comprehensive Geriatric Assessment (G8), which evaluates the overall health status of elderly patients, may be useful in selecting appropriate chemotherapy regimens (23). In the future, the utility of these assessment tools in treatment selection needs to be validated. Japan, with its rapidly aging population, faces several critical issues in providing healthcare for the elderly. The cost-efficacy perspective in determining the appropriateness of nivolumab combination regimens for elderly patients is still lacking. When assessing the financial impact of systemic treatments for AGC and deciding on a treatment plan, it is important to consider not just the efficacy and safety, but also the cost-effectiveness of the therapeutic options.

As for the cost reduction, there are two ongoing phase III trials that aim to confirm the non-inferiority comparing continuation versus cessation of immune-checkpoint inhibitors for patients with non-small cell lung cancer (24) and renal cell carcinoma (25). If treatment can be paused without compromising efficacy, this can potentially reduce treatment-related adverse events, improve patients' quality of life, and result in significant healthcare savings.

The current study had several limitations. First, the survey was conducted over a limited period (1 year) at JCOG-affiliated institutions. Second, individual patient data were not collected. Thus, the actual treatment duration and therapy discontinuation or dose reduction could not be considered. Third, the lack of PD-L1 (CPS) data did not confirm whether nivolumab was used in the appropriate population.

## Conclusion

Sixty-seven percent of patients and more than half of the elderly population in Japan received expensive regimens as first-line chemotherapy for HER2-negative AGC. This information can be utilized in the planning of health economic studies that examine future cost-effectiveness from the perspective of physicians.

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**Conflict of interest:** T.N. received personal fees from Taiho, Chugai, Ono Pharmaceutical, Bristol Myers Squibb, Daiichi-Sankyo, Eli Lilly, Astellas and MSD, outside the submitted work.

N.B. reports personal fees Bristol Myers Squibb, Ono Pharmaceutical, Taiho Pharmaceutical, Eli Lilly, Daiichi-Sankyo, outside the submitted work. Y.K., R.M., and K.S. have no conflict of interest. T.Y. reports personal fees from Ono Pharmaceutical, Bristol Myers Squibb, MSD, Daiichi-Sankyo, Astellas, Taiho, and Chugai, outside the submitted work.

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Original Article

# Real-world treatment costs of first-line treatment for metastatic colorectal cancer: a survey of the JCOG colorectal cancer study group

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## Abstract

**Background:** Although treatment outcomes for metastatic colorectal cancer (mCRC) have dramatically improved over the past few decades, drug costs have also significantly increased. This study aimed to investigate which first-line treatment regimens for mCRC are actually used (frequency) in Japanese practice and at what cost.

**Methods:** We collected data on patients with mCRC who received first-line treatment at 37 institutions of the Japan Clinical Oncology Group Colorectal Cancer Study Group from July 2021 to June 2022, and calculated the cost of regimens. The cost per month of each regimen was estimated based on standard usage, assuming a patient with a weight of 70 kg and a body surface area of 1.8 m<sup>2</sup>. We categorized the regimens into very high-cost ( $\geq 1\,000\,000$  Japanese yen [JPY]/month), high-cost ( $\geq 500\,000$  JPY/month), and others ( $< 500\,000$  JPY/month).

**Results:** The study included 1880 participants, 24% of whom were  $\geq 75$  years. Molecular targeted containing regimens were received by 78% of the patients. The most frequently used regimen was the doublet regimen (fluoropyrimidine with either oxaliplatin or irinotecan) plus bevacizumab (43%), followed by doublet plus cetuximab or panitumumab (21%). The cost of molecular targeted drugs-containing regimens (ranging from 85 406 to 843 602 JPY/month) is much higher than that of only cytotoxic drug regimens (ranging from 17 672 to 51 004 JPY/month). About 16% received high-cost treatments that included panitumumab-containing regimens and pembrolizumab (17% of patients aged  $\leq 74$  years and 11% of patients aged  $\geq 75$  years).

**Conclusion:** About 16% of mCRC patients received first-line treatment with regimens costing  $> 500\,000$  JPY/month, and molecular targeted drugs being the main drivers of cost.

**Key words:** chemotherapy, colorectal cancer, treatment cost, cost of illness, financial toxicity

## Introduction

Colorectal cancer (CRC) is a common cancer that affects both men and women worldwide (1). Its incidence increases with age (2). According to the GLOBOCAN database 2022 (3), CRC is the third most frequently diagnosed cancer and the second leading cause of cancer deaths, responsible for almost 1.92 million new diagnoses and 0.93 million deaths globally (3). In 2022, CRC was the second leading cause of cancer deaths and the most frequent cancer site in Japan, with an estimated 5400 deaths and 158 200 incidences (4).

For patients with unresectable metastatic CRC (mCRC), systemic therapy, including cytotoxic drugs, molecular targeted agents, and immunotherapy, is the global standard treatment (5–7). In the 1990s, fluorouracil (FU) was the only key drug available for systemic therapy for mCRC, which had a median survival time (MST) of almost 1 year (8–10). As of 2024, over 20 key drugs are available in Japan, and they are used as part of both first-line and later line treatments. In the global guidelines, four or more lines is described as the standard treatment (5–7).

For first-line treatment, the standard regimens of cytotoxic drugs are doublet or triplet chemotherapy with fluoropyrimidine (FU), oxaliplatin (OX), and/or irinotecan (IRI). Based on the *RAS/BRAF* status and tumor sidelines, the molecular targeted drugs of bevacizumab (BEV), cetuximab (CET), or panitumumab (PANI) were combined with cytotoxic regimens. Pembrolizumab was used as the first-line treatment for patients with microsatellite instability-high (MSI-high) and/or mismatch repair deficient (dMMR) mCRC. Recently, it was reported that the MST was  $> 30$  months for patients receiving first-line treatment. Although more aggressive surgical resection of the metastatic sites has also contributed to longer

survival, it is clear that the prognosis is improving over time with the availability of more effective anticancer drugs (11–13).

At the same time, these dramatic advances are causing a marked increase in healthcare costs (14). In addition to the increased number of available regimens, the high price of newly introduced drugs is impacting healthcare costs (14,15). Patients with mCRC, not only in Japan but worldwide, face significant financial problems due to increasing medical costs (16–18). Additionally, the high costs of treatments place an enormous burden on social health resources. Dr. Schrag D. highlighted the cost problem for CRC in 2004 and suggested cost-effectiveness analysis parallel to clinical trials as one solution (19). While drug prices continue to rise, such analyses have been implemented in Western countries. However, in Japan, physicians have limited interest in healthcare costs and few reports on mCRC healthcare costs.

The Japan Clinical Oncology Group (JCOG) established a Health Economics Committee to address healthcare costs in March 2022. The first task of this committee was to conduct a multicenter survey to clarify the cost of first-line treatment of metastatic cancer in Japan. The objectives of this study were to examine the real-world treatment regimens used as first-line treatment for mCRC and estimate the cost of treatment using each of these regimens in the JCOG Colorectal Cancer Study Group.

## Methods

### Patients and data collection

We retrospectively collected data on mCRC patients from the JCOG Colorectal Cancer Study Group. Patients who received first-line

**Table 1.** Chemotherapy regimens.

Regimens	Molecularly targeted drug	Total n = 1880	%	Age ≤ 74 years n = 1436	%	Age ≥ 75 years n = 444	%
FU monotherapy	none	52	2.7	22	1.5	30	6.8
	BEV	141	7.5	57	4	84	18.9
	Anti-EGFR antibody	8	0.4	7	0.5	1	0.2
	CET	5		0		0	
	PANI	3		2		1	
Doublet	none	333	17.7	249	17.3	84	18.9
	BEV	813	43.2	647	45.1	166	37.4
	Anti-EGFR antibody	395	21	333	23.2	62	14
	CET	119		99		20	
	PANI	276		234		42	
Triplet	none	15	0.8	14	1	1	0.3
	BEV	99	5.3	91	6.3	8	1.8
	Anti-EGFR antibody	4	0.2	4	0.3	0	
	CET	3		3		0	
	PANI	1		1		0	
Pembrolizumab		20	1.1	12	0.8	8	1.8

FU, fluoropyrimidine; Doublet, fluoropyrimidine with either oxaliplatin or irinotecan; Triplet, fluoropyrimidine with oxaliplatin and irinotecan, BEV, bevacizumab; CET, cetuximab; EGFR, epidermal growth factor receptor; PANI, panitumumab.

palliative treatment for unresectable colorectal cancer diagnosed between July 2021 and June 2022 were included in this study. We distributed an online questionnaire via Google Forms to institutions affiliated with the JCOG Colorectal Cancer Study Group and aggregated the treatment data of first-line regimens obtained in response to the questionnaire. This study did not involve the use of personal data and therefore did not require individual consent or institutional review board approval.

#### Treatment regimens and calculation of costs

The collected cytotoxic regimens consisted of FU-monotherapy (fluorouracil plus calcium levofolinate [5-FU/l-LV], capecitabine [CAPE], tegafur gimeracil oteracil potassium[S1]), doublet regimens (FOLOFX [5-FU/l-LV+ OX], CAPOX [CAPE+OX], SOX [S1 + OX], FOLFIRI [5-FU/l-LV + IRI], CAPIRI [CAPE+IRI], SIR [S1 + IRI]), and triplet regimens (FOLFOXIRI [5-FU/l-LV + OX+IRI]). Molecular targeted drugs including BEV, CET, and PANI, with or without cytotoxic regimens, were also collected. Pembrolizumab monotherapy, which was approved in JAPAN in Aug 2021 for first-line treatment of mCRC, was included in the collection of immunotherapies. The data of patients in different age categories (≤74 years and ≥75 years) were collected separately for each regimen.

The cost of treatment for each regimen per month (4 weeks) was estimated based on standard usage and drug prices as of April 2024. In cases where generic or biosimilar drugs were available, the costs of the generic or biosimilar agents were also calculated, and the cost calculation was based on the lower price. This assumes a male patient with an average weight of 70 kg and a body surface area of 1.8 m<sup>2</sup>, receiving treatment without any skips, delays, or dose reductions. In this study, only the cost of chemotherapy drugs was calculated, and costs for supportive care (i.e. antiemetic drugs) were not considered.

The regimens were categorized into very high-cost (≥1 000 000 Japanese yen [JPY]/month), high-cost (≥500 000 JPY/month), and others (<500 000 JPY/month) treatments based on the definition provided by the JCOG Health Economic Committee.

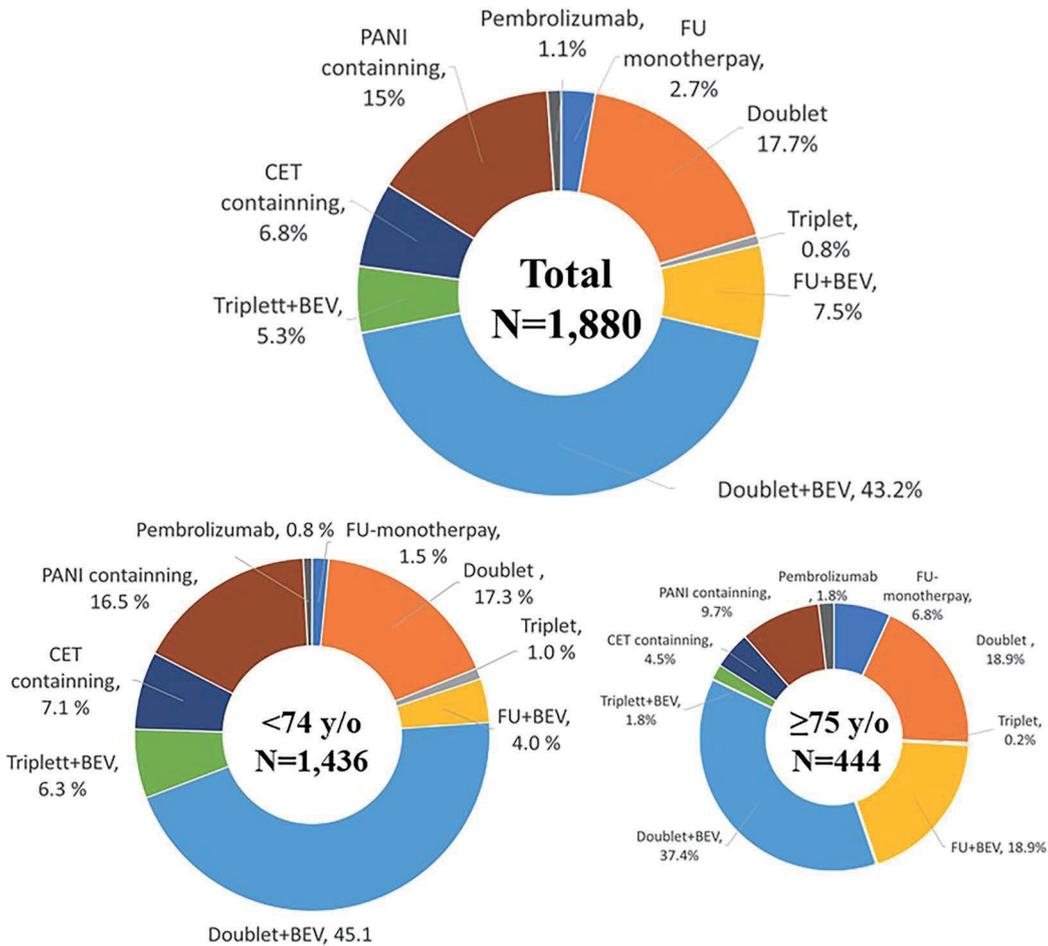
#### Results

A total of 37 institutions among 60 institutions of the JCOG Colorectal Cancer Study Group provided information. The 37 participating institutions are shown at the end of this article. The total number of eligible patients was 1880, of whom 1436 (76%) were <74 years old and 444 (24%) were ≥75 years old.

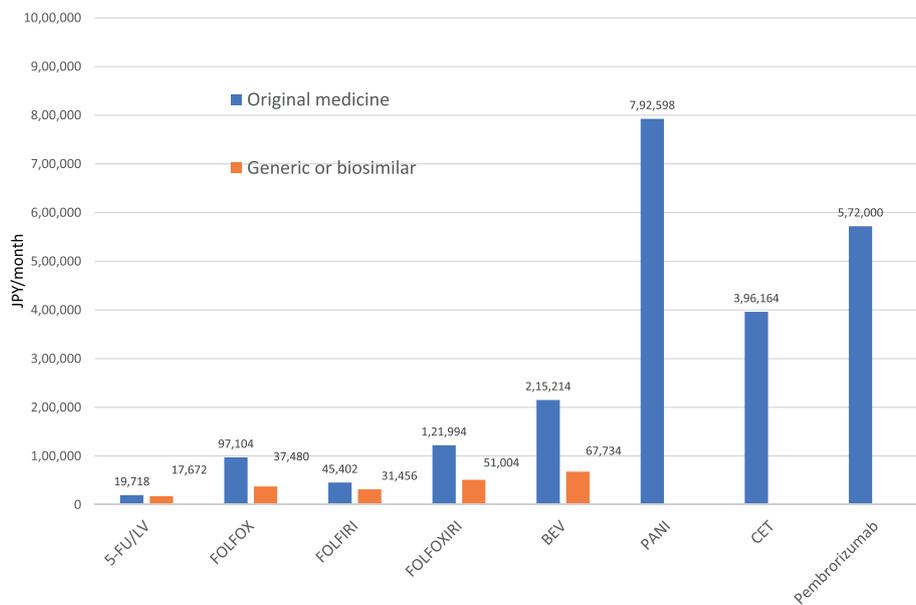
Table 1 and Figure 1 show the frequency of regimen. Regarding cytotoxic regimens, 11% (201/1880) of the patients received FU monotherapy, while 82% (1541/1880) received doublet regimens and 6% (118/1880) received triplet regimens. Molecular targeted containing regimens were received by 78% (1460/1880) of the patients. The most frequently used regimen was doublet plus BEV (43%), followed by doublet plus anti-epidermal growth factor receptor (EGFR) of CET or PANI (21%) and doublet without molecular targeted drugs (18%). Doublet plus BEV and doublet plus anti-EGFR antibody of CET or PANI were more common in patients aged ≤74 years (64%, 1146/1436) than in patients aged ≥75 years (51%, 228/444). On the other hand, FU monotherapy plus BEV was commonly administered to patients aged ≥75 years (19%, 84/444).

Table 2 describes the cost of each regimen per month and the number of patients who received it. Table 3 lists the details of the treatment regimens and the cost per month for each regimen. Figure 2 displays the costs of representative cytotoxic regimens, molecular targeted drugs, and pembrolizumab for both original medicine and generic or biosimilar. The cost of molecular targeted drugs-containing regimens (ranging from 85 406 to 843 602 JPY/month) is much higher than that of only cytotoxic drug regimens (ranging from 17 672 to 51 004 JPY/month). The most expensive molecularly targeted drug regimen of FOLFOXIRI+PANI is ~50 times more expensive than the cheapest cytotoxic regimen of 5-FU/l-LV. An anti-EGFR antibody of PANI was 2 times more expensive than CET (792 598 JPY/month vs. 396 164 JPY/month).

PANI-containing regimens and pembrolizumab were classified as high-cost regimens. Three hundred patients (16%) received high-cost regimens (PANI-containing regimens, n = 280 patients [15%]; pembrolizumab, n = 20 [1%]). High-cost regimens were administered to



**Figure 1.** Frequency of regimens. FU, fluoropyrimidine; doublet, fluoropyrimidine with either oxaliplatin or irinotecan; triplet, fluoropyrimidine with oxaliplatin and irinotecan, BEV, bevacizumab; CET, cetuximab; EGFR, epidermal growth factor receptor; PANI, panitumumab.



**Figure 2.** Cost of each regimen per month. 5-FU/l-LV, 5-fluorouracil plus calcium levofolinate; FOLFOX, fluorouracil plus calcium levofolinate plus oxaliplatin; FOLFIRI, fluorouracil plus calcium levofolinate plus irinotecan; FOLFOXIRI, fluorouracil plus calcium levofolinate plus oxaliplatin plus irinotecan; BEV, bevacizumab; CET, cetuximab; PANI, panitumumab; JPY, Japanese yen.

**Table 2.** Number of patients and cost of each regimen.

Regimens	Molecular targeted drug	Total n = 1880	%	Age ≤ 74 years n = 1436	%	Age ≥ 75 years n = 444	%	Cost per month (JPY)
5-FU/I-LV	none	12	0.6	5	0.3	7	1.6	17 672
	BEV	20	1.1	10	0.7	10	2.3	85 406
	CET	2	0.1	2	0.1	0	0.0	413 836
	PANI	2	0.1	1	0.1	1	0.2	810 270
CAPE	none	36	1.9	16	1.1	20	4.5	15 888
	BEV	115	6.1	44	3.1	71	16.0	85 406
S1	none	4	0.2	1	0.1	3	0.7	14 649
	BEV	6	0.3	3	0.2	3	0.7	82 383
	CET	3	0.2	3	0.2	0	0.0	410 813
	PANI	1	0.1	1	0.1	0	0.0	807 247
FOLFOX	none	138	7.3	101	7.0	37	8.3	37 480
	BEV	318	16.9	243	16.9	75	16.9	105 214
	CET	90	4.8	73	5.1	17	3.8	433 644
	PANI	240	12.8	199	13.9	41	9.2	830 078
CAPOX	none	161	8.6	122	8.5	39	8.8	30 499
	BEV	364	19.4	293	20.4	71	16.0	98 233
SOX	none	12	0.6	9	0.6	3	0.7	31 529
	BEV	27	1.4	23	1.6	4	0.9	99 263
FOLFIRI	none	15	0.8	13	0.9	2	0.5	31 456
	BEV	50	2.7	42	2.9	8	1.8	99 190
	CET	29	1.5	26	1.8	3	0.7	427 620
	PANI	36	1.9	35	2.4	1	0.2	824 054
CAPIRI	none	1	0.1	1	0.1	0	0.0	22 853
	BEV	9	0.5	8	0.6	1	0.2	90 587
S1 + IRI	none	6	0.3	3	0.2	3	0.7	22 853
	BEV	45	2.4	38	2.6	7	1.6	90 587
FOLFOXIRI	none	15	0.8	14	1.0	1	0.2	51 004
	BEV	99	5.3	91	6.3	8	1.8	118 738
	CET	3	0.2	3	0.2	0	0.0	447 168
	PANI	1	0.1	1	0.1	0	0.0	843 602
Pembrolizumab	none	20	1.1	12	0.8	8	1.8	572 000

BEV, bevacizumab; CAPE, capecitabine; CET, cetuximab; CAPIRI, capecitabine plus irinotecan; CAPOX, capecitabine plus oxaliplatin; FOLFIRI, fluorouracil plus calcium levofolinate plus irinotecan; FOLFOX, fluorouracil plus calcium levofolinate plus oxaliplatin; FOLFOXIRI, fluorouracil plus calcium levofolinate plus oxaliplatin plus irinotecan; 5-FU/I-LV, 5-fluorouracil plus calcium levofolinate; IRI, irinotecan; JPY, Japanese yen; PANI, panitumumab; SOX, S1 plus oxaliplatin.

17% (249/1436) of patients aged ≤74 years and 11% (51/444) of patients aged ≥75 years.

## Discussion

The results of this study provide a comprehensive overview of the current landscape of first-line treatment regimens and associated costs for mCRC based on the Japanese healthcare system. Although no patients received very high-cost regimens as first-line treatment, sixteen percent of patients, particularly those aged ≤74 years, received high-cost treatments, and molecular targeted drugs being the main drivers of cost.

The regimens that were classified as high-cost treatments were PANI-containing regimens and pembrolizumab. The PARADIGM (20) and KEYNOTE-177 (21) trials were pivotal phase III trials evaluating the efficacy of high-cost regimens. The PARADIGM trial showed that in patients with left-sided RAS wild-type mCRC, the addition of PANI to FOLFOX significantly improved OS relative to BEV. The MST was 37.9 months with PANI versus 34.3 months with BEV (hazard ratio [HR], 0.82; 95.798% CI,

0.68–0.99;  $P = 0.03$ ). The estimated median total costs based on mPFS were 10 874 022 JPY (830 078 JPY/month × 13.1 months) for FOLFOX+PANI and 1 252 047 JPY (105 214 JPY/month × 11.9 months) for FOLFOX+BEV. The difference in MST between the PANI and BEV regimens was ~3.6 months, with the cost being ~8.7 times higher (a difference of 10 million JPY). The KEYNOTE-177 trial (20) showed the survival benefit of pembrolizumab compared with standard regimens, including FOLFOX or FOLFIRI with or without BEV/CET, for MSI-high or dMMR mCRC. At the final analysis of the KEYNOTE-177 trial, the HR of OS was 0.74 (95% CI 0.53–1.03;  $P = 0.036$ , MST, not reached vs. 36.7 months). The estimated median total costs were 6 349 200 JPY (572 000 JPY/month × 11.1 months) for pembrolizumab and 2 471 771 JPY (433 644 JPY/month × 5.7 months) for FOLFOX+CET which had the highest cost among the standard regimens. The hazard ratio for OS was 0.74 in patients treated with pembrolizumab in comparison to those treated with standard regimens, but the cost was ~2.6 times higher, resulting in a difference of 3.9 million JPY. Both PANI and pembrolizumab are the key drugs for treating mCRC. However, addressing the financial burden of these treatments is essential for the benefit of all patients.

**Table 3.** Calculation of cost of chemotherapy regimens.

	Regimen	Drugs	Dose	Duration	Cost per cycle (JPY)		Cost per month (JPY)		
					Original	Generic or biosimilar	Original	Generic or biosimilar	
Cytotoxic regimens									
FU monotherapy	5-FU/l-LV	5-FU (bolus)	400 mg/m <sup>2</sup>	q2	9859	8836	19 718	17 672	
		5-FU (civ)	2400 mg/m <sup>2</sup>						
Doublet	CAPE	CAPE	4200 mg/day	day 1-14	q3	26 479	11 916	35 305	15 888
		S1	120 mg/day	day 1-14	q3	27 468	10 987	36 624	14 649
	FOLFOX	5-FU (bolus)	400 mg/m <sup>2</sup>	q2	48 552	18 740	97 104	37 480	
		5-FU (civ)	2400 mg/m <sup>2</sup>						
	CAPOX	l-LV	200 mg/m <sup>2</sup>	q3	73 809	22 874	98 412	30 499	
		oxaliplatin	85 mg/m <sup>2</sup>						
	SOX	CAPE	3600 mg/day	day 1-14	q3	78 580	23 647	104 773	31 529
		S-1	120 mg/day	day 1-14	q3	78 580	23 647	104 773	31 529
	FOLFIRI	oxaliplatin	130 mg/m <sup>2</sup>	q2	22 701	15 728	45 402	31 456	
		5-FU (bolus)	400 mg/m <sup>2</sup>						
CAPIRI	5-FU (civ)	2400 mg/m <sup>2</sup>	q3	54 453	17 140	72 604	22 853		
	l-LV	200 mg/m <sup>2</sup>							
S1 + IRI	irinotecan	150 mg/m <sup>2</sup>	q3	40 310	17 879	53 747	23 838		
	CAPE	3600 mg/day							
Triplet	FOLFOXIRI	irinotecan	150 mg/m <sup>2</sup>	q2	60 997	25 502	121 994	51 004	
		5-FU (bolus)	400 mg/m <sup>2</sup>						
		5-FU (civ)	2400 mg/m <sup>2</sup>						
		l-LV	200 mg/m <sup>2</sup>						
Molecular targeted drugs	BEV	oxaliplatin	85 mg/m <sup>2</sup>	q2	107 607	33 867	215 214	67 734	
		irinotecan	150 mg/m <sup>2</sup>						
	PANI	irinotecan	150 mg/m <sup>2</sup>	q2	396 299	-	792 598	-	
		5-FU (bolus)	400 mg/m <sup>2</sup>						
CET	5-FU (civ)	2400 mg/m <sup>2</sup>	q1	99 041	-	396 164	-		
	l-LV	200 mg/m <sup>2</sup>							
Immunotherapy	Pembrolizumab	oxaliplatin	85 mg/m <sup>2</sup>	q3	429 000	-	572 000	-	
		irinotecan	150 mg/m <sup>2</sup>						

FU, fluoropyrimidine; Doublet, fluoropyrimidine with either oxaliplatin or irinotecan; Triplet, fluoropyrimidine with oxaliplatin and irinotecan, l-LV, calcium levofolinate; 5-FU, 5-fluorouracil; BEV, bevacizumab; CAPE, capecitabine; CET, cetuximab; CAPIRI, capecitabine plus irinotecan; CAPOX, capecitabine plus oxaliplatin; FOLFIRI, fluorouracil plus calcium levofolinate plus irinotecan; FOLFOX, fluorouracil plus calcium levofolinate plus oxaliplatin; FOLFOXIRI, fluorouracil plus calcium levofolinate plus oxaliplatin plus irinotecan; 5-FU/l-LV, fluorouracil plus calcium levofolinate; IRI, irinotecan; JPY, Japanese yen; PANI, panitumumab; SOX, S1 plus oxaliplatin.

The cost of cytotoxic regimens for first-line treatment, including FU-monotherapy, doublet, and triplet, is similar, ranging from 17 672 JPY/month to 51 004 JPY/month. On the other hand, the cost of molecularly targeted drugs is quite different and much more expensive than cytotoxic regimens, ranging from 67 734 JPY/month to 792 598 JPY/month. While adding these molecularly targeted drugs to cytotoxic regimens has undoubtedly improved survival for patients with mCRC, the cost implications are substantial. Moreover, the cost of PANI and CET, which belong to the same class of anti-EGFR antibodies, is twice as high for PANI compared with CET (792 598 JPY/month vs. 396 164 JPY/month). There is currently no clear evidence comparing the efficacy and toxicities between these two drugs. This raises questions about the sustainability of healthcare

systems and whether all eligible patients will have access to these therapies.

Japan faces unique challenges due to its 'high-cost medical expense benefit system' (22), which may inadvertently discourage cost-conscious medical practice. Under this system, when the amount of the copayment at a hospital or clinic in one month exceeds the maximum copayment amount, the excess amount is paid by the public medical insurance. As a result, the patient pays the same amount regardless of which drug is used, as long as a certain amount is spent. In addition, there is a system in place to ensure that scientifically effective treatments are covered by insurance and reimbursed without cost-effectiveness analyses. These factors could potentially lead to a preference for more expensive treatment

options without a thorough consideration of cost-effectiveness. The healthcare cost burden is already close to bankruptcy, and there is an urgent need for serious discussion and concrete action by healthcare providers, patients, payers, and other stakeholders toward a realistic solution to this problem.

We propose several practical solutions. Firstly, promote the use of generic drugs and biosimilars. Switching from the expensive drug bevacizumab to a biosimilar can reduce costs by 150 000 JPY per month. This difference is even greater than the cost of the most expensive cytotoxic drug regimens like FOLFOXIRI. Secondly, it's important to include health economic evaluations in future clinical trials and discuss appropriate endpoints. Lastly, we believe that it's crucial for prescribing physicians to take healthcare costs into account. Currently, physicians rarely consider costs when deciding on treatment. Including cost information in treatment guidelines and displaying drug costs in electronic medical records can raise cost awareness among physicians.

Despite the insights gained from this study, several limitations should be acknowledged. Firstly, the retrospective nature of data collection may introduce inherent biases and limit the generalizability of findings. Furthermore, the frequency of pembrolizumab usage might be underestimated as it was approved during the survey period. Secondly, the study focused on first-line treatment regimens and did not explore subsequent lines of therapy or long-term cost implications. Recent standard treatment of mCRC typically involves using four or more lines of treatment. In addition, many of the later regimens involve very expensive molecular targeted drugs. Compared with front-line treatment, later treatment has shorter OS, making it easier to achieve statistically significant differences even if the absolute difference is minimal. It would be particularly important to include cost-effectiveness evaluations in later regimens. Additionally, the cost calculations were based on standard usage assumptions only for anti-cancer drugs and the prices within a specific time-frame, which may not reflect real-world variability in treatment patterns and costs. Moreover, the lack of patient-level outcome data linked to cost limits the ability to conduct a detailed cost-effectiveness analysis, which is crucial to inform policy and clinical practice.

## Conclusion

This study illuminates the utilization and cost of first-line treatment options for mCRC in Japan. It emphasizes the need for sustainable strategies to ensure fair access to innovative therapies amid the global increase in healthcare costs. Future research, including cost-effectiveness analysis, should continue to explore the evolving landscape of mCRC treatment to optimize patient care and healthcare resource allocation.

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## Conflict of interest

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Original Article

# Frequency of use and cost in Japan of first-line palliative chemotherapies for recurrent or metastatic squamous cell carcinoma of the head and neck

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## Abstract

**Background:** Over the last decade, novel anticancer drugs have improved the prognosis for recurrent or metastatic squamous cell carcinoma of the head and neck (RM-SCCHN). However, this has increased healthcare expenditures and placed a heavy burden on patients and society. This study investigated the frequency of use and costs of select palliative chemotherapy regimens in Japan.

**Methods:** From July 2021 to June 2022 in 54 healthcare facilities, we gathered data of patients diagnosed with RM-SCCHN and who had started first-line palliative chemotherapy with one of eight commonly used regimens. Patients with nasopharyngeal carcinomas were excluded. The number of patients receiving each regimen and the costs of each regimen for the first month and per year were tallied.

**Results:** The sample comprised 907 patients (674 were < 75 years old, 233 were  $\geq$  75 years old). 330 (36.4%) received Pembrolizumab monotherapy, and 202 (22.3%) received Nivolumab monotherapy. Over 90% of patients were treated with immune checkpoint inhibitors as monotherapy or in combination with chemotherapy. Treatment regimens' first-month costs were 612 851–849 241 Japanese yen (JPY). The cost of standard palliative chemotherapy until 2012 was about 20 000 JPY per month. The incremental cost over the past decade is approximately 600 000–800 000 JPY per month, a 30- to 40-fold increase in the cost of palliative chemotherapy for RM-SCCHN.

**Conclusion:** First-line palliative chemotherapy for RM-SCCHN exceeds 600 000 JPY monthly. Over the last decade, the prognosis for RM-SCCHN has improved, but the costs of palliative chemotherapy have surged, placing a heavy burden on patients and society.

**Key words:** palliative chemotherapy, head and neck cancer, immune checkpoint inhibitor, cost, health expenditures

## Introduction

Head and neck cancer (HNC) was the seventh most common cancer worldwide in 2020, comprising 870 000 diagnosed cases and contributing to 440 000 deaths per year, accounting for 4.5% of all cancer deaths (1). Squamous cell carcinoma (SCC) accounts for more than 90% of HNC (2). Approximately 10% of the patients with SCC of the head and neck (SCCHN) present with distant metastases at initial diagnosis (3). Most SCCHN patients are diagnosed with localized disease and undergo surgery or radiation therapy with or without platinum-based chemotherapy. Despite improvements in diagnosis and treatment, at least 50% of patients with locally advanced SCCHN develop recurrent and/or metastatic disease within 3 years of treatment (4,5). In patients with recurrent or metastatic SCCHN (RM-SCCHN), palliative chemotherapy is the treatment of choice when salvage surgery or radiation therapy is not indicated. Combination therapy comprising platinum (cisplatin or carboplatin) + 5-fluorouracil (5-FU) has been used as the standard of care for a long time. The EXTREME trial showed that adding cetuximab to the platinum +5-FU regimen improved overall survival (OS) (Table 1) (6). Since the approval of cetuximab for RM-SCCHN in 2012, this combined cetuximab/platinum +5-FU regimen has been the standard of first-line palliative chemotherapy until recently.

In ovarian cancer, a shorter interval between prior platinum-based chemotherapy and recurrence (platinum-free interval; PFI) is associated with poor prognosis (7,8). Recurrence at PFI  $\geq$  6 months is defined as 'platinum-sensitive' disease, while recurrence at PFI < 6 months is defined as 'platinum-refractory' or 'platinum-resistant' disease (9,10). The terms 'platinum-sensitive' and 'platinum-refractory' have been used for RM-SCCHN also (11,12).

Platinum-refractory RM-SCCHN has a poor prognosis, having a median survival time of 5–6 months (13–15). In the phase III trial, CheckMate 141 (16), Nivolumab significantly improved OS, showing a median OS of 7.7 months compared to 5.1 months for the treatment of physician's choice (TPC) group after 2 years of long-term follow-up (Table 1) (17,18). Based on these findings, in 2017, nivolumab was approved by the Japanese National Health Insurance system and was regarded as the standard of care for platinum-refractory RM-SCCHN.

KEYNOTE-040 was a randomized phase III trial that compared pembrolizumab against TPC in patients with platinum-refractory RM-SCCHN (19). The results of the KEYNOTE-040 trial reported a significant improvement with pembrolizumab (HR, 0.80; 95% CI, 0.65–0.98) (Table 1).

Another randomized phase III trial that compared pembrolizumab to platinum +5-FU + cetuximab (EXTREME regimen) and pembrolizumab + chemotherapy (platinum +5-FU) was conducted in platinum-sensitive RM-SCCHN patients (20). In this trial, called the KEYNOTE-048, pembrolizumab monotherapy was superior in OS in the CPS  $\geq$  20 group and CPS  $\geq$  1 group. Pembrolizumab was also superior in the pembrolizumab + chemotherapy group in OS in the CPS  $\geq$  1 group. In the ITT group, pembrolizumab was non-inferior to the EXTREME regimen group in OS, and the pembrolizumab + chemotherapy group was non-inferior and superior to the EXTREME regimen group (Table 1). In 2019, the Japanese National Insurance system approved pembrolizumab/platinum +5-FU combination therapy and pembrolizumab monotherapy for platinum-sensitive RM-SCCHN patients. In the Japanese Clinical Practice Guidelines for Head and Neck Cancer (2022), pembrolizumab + platinum +5-FU is recommended for all patients, and pembrolizumab monotherapy is recommended for patients with CPS  $\geq$  1 (21).

Since the approval of cetuximab in 2012, followed by nivolumab in 2017 and pembrolizumab in 2019, the prognosis for patients with RM-SCCHN has improved. Likewise, numerous molecularly targeted therapies and ICIs have been approved for other types of cancers (22,23). These approvals have come at a significant cost. Expenditures in Japan's healthcare system increased from 30 trillion Japanese yen (JPY) in 2000 to 46 trillion JPY in 2022. In general, novel anticancer drugs are expensive and increase healthcare costs (24–26). This trend is expected to continue with continued progress in anticancer drug development. However, little attention has been paid to rising medical costs in this area. Although a few cost-effectiveness studies have been conducted for some cancers recently in Japan (27–30), we know of no comprehensive studies on the costs of palliative chemotherapy for many other cancers, including RM-SCCHN in Japan. Moreover, to the best of our knowledge, no previous focused reports have appeared on this issue.

**Table 1. Results of pivotal studies for RM-SCCHN**

	EXTREME	Checkmate 141	KEYNOTE-040	KEYNOTE-048
Author	Vermorken (2008)	Ferris (2016, 2018)	Cohen (2019)	Burtress (2019, 2022) Harrington (2022)
New treatment	Cetuximab +CDDP/CBDCA +5-FU	Nivolumab	Pembrolizumab	Pembrolizumab ± CDDP/CBDCA +5-FU
Control	CDDP/CBDCA +5-FU	MTX or DTX or cetuximab	MTX or DTX or cetuximab	Cetuximab +CDDP/CBDCA +5-FU
Inclusion criteria	Platinum-sensitive RM-SCCHN	Platinum-refractory RM-SCCHN	Platinum-refractory RM-SCCHN	Platinum-sensitive RM-SCCHN
Age, years (new treatment)	56 (37–80)	59 (29–83)	60 (55–66)	Pembrolizumab alone: 62 (56–68)
Elderly patients, years (new treatment) No.(%)	≥65: 39 (18)	≥75: 12 (5)	≥75: 19 (8)	Pembrolizumab + chemo: 61 (55–68)
OS, months, median (95%CI) (new treatment)	10.1 (8.6–11.2)	7.7 (5.7–8.8)	8.4 (6.4–9.4)	not available
				ITT
				Pembrolizumab alone: 11.5 (10.3–13.5)
				Pembrolizumab + chemo: 13.0 (10.9–14.7)
				CPS < 1
				Pembrolizumab alone: 7.9 (4.7–13.6)
				Pembrolizumab + chemo: 11.3 (9.5–14.0)
				CPS 1–19
				Pembrolizumab alone: 10.8 (9.0–12.6)
				Pembrolizumab + chemo: 12.7 (9.4–15.3)
				CPS ≥ 20
				Pembrolizumab alone: 14.9 (11.5–20.6)
				Pembrolizumab + chemo: 14.7 (10.3–19.3)
OS, months, median (95%CI) (control)	7.4 (6.4–8.3)	5.1 (4.0–6.2)	6.9 (5.9–8.0)	ITT vs. Pembrolizumab alone: 10.7 (9.3–12.1)
				vs. Pembrolizumab + chemo: 10.7 (9.3–11.7)
				CPS < 1
				vs. Pembrolizumab alone: 11.3 (9.1–15.9)
				vs. Pembrolizumab + chemo: 10.7 (8.5–15.9)
				CPS 1–19
				vs. Pembrolizumab alone: 10.1 (8.7–12.1)
				vs. Pembrolizumab + chemo: 9.9 (8.6–11.5)
				CPS ≥ 20
				vs. Pembrolizumab alone: 10.8 (8.8–12.8)
				vs. Pembrolizumab + chemo: 11.1 (9.2–13.0)
				ITT
New treatment/control HR (95%CI:)	0.80 (0.64–0.99)	0.68 (0.54–0.86)	0.80 (0.62–0.98)	Pembrolizumab alone: 0.81 (0.68–0.97)
				Pembrolizumab + chemo: 0.71 (0.59–0.85)
				CPS < 1
				Pembrolizumab alone: 1.51 (0.96–2.37)
				Pembrolizumab + chemo: 1.21 (0.76–1.94)
				CPS 1–19
				Pembrolizumab alone: 0.86 (0.66–1.12)
				Pembrolizumab + chemo: 0.71 (0.54–0.94)
				CPS ≥ 20
				Pembrolizumab alone: 0.58 (0.44–0.78)
				Pembrolizumab + chemo: 0.60 (0.45–0.82)

RM-SCCHN, recurrent or metastatic squamous cell carcinoma of the head and neck; CDDP, cisplatin; CBDCA, carboplatin; 5-FU, 5-fluorouracil; MTX, methotrexate; DTX, docetaxel; ITT, intention to treat; CPS, combined positive score; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio.

On March 5, 2022, therefore, the Japan Clinical Oncology Group (JCOG) established the Health Economics Committee (HEC) to address these issues. The first mandate of this committee was to determine which palliative chemotherapy regimens are used most frequently in the Japanese healthcare system and how much they cost. This study was conducted in JCOG Head and Neck Cancer Study Group (JCOG-HNCSG) member or affiliated institutions.

## Methods

### Patients

We retrospectively collected data from 39 member institutions and 15 affiliated institutions of the JCOG-HNCSG. Participating institutions are listed in the Supplementary Material. The inclusion criteria were as follows: (1) a diagnosis of recurrent or metastatic SCCHN, (2) SCCHN with a clinical stage of IVc, and (3) SCCHN treated with first-line palliative chemotherapy according to one of eight regimens (see below) during the period from July 2021 to June 2022. Patients diagnosed with nasopharyngeal carcinoma were excluded from this study. Clinical staging was classified according to the 8th edition of the Union for International Cancer Control-TNM classification.

### Treatment regimens

Included patients received one of the following eight chemotherapy regimens: (1) pembrolizumab alone; (2) nivolumab alone; (3) pembrolizumab + cisplatin (CDDP) + 5-fluorouracil (5-FU); (4) pembrolizumab + carboplatin (CBDCA) + 5-FU; (5) cetuximab + CDDP + 5-FU (EXTREME regimen); (6) cetuximab + CBDCA + 5-FU (EXTREME regimen); (7) CBDCA + paclitaxel (PTX) + cetuximab (PCE regimen); or (8) any other clinical trial regimen not listed here.

### Scope of data collection

Responsible person(s) at each participating institution received an online questionnaire survey, which was used to tally the study information. The following data were collected: type of regimen each patient received as first-line palliative chemotherapy and each patient's demographic information (i.e. gender, age, etc.). Next, the patients' data were grouped into two age categories (<75 and ≥ 75 years), and the number of patients in each group was recorded. The patients' personal data were not collected or stored.

### Treatment costs

The first month and annual costs of treatment were calculated separately using the standard and regulated market prices for the drugs in each regimen in Japan as of March 1, 2024 (Table 2). Doses of treatment regimens were calculated according to a patient height of 165 cm, weight of 60 kg, and body surface area of 1.615 m<sup>2</sup>. The dose of carboplatin was calculated as follows:

$$\text{Dose (mg)} = \text{target AUC} \times (\text{GFR} + 25),$$

where AUC is the calculated 'area under the blood concentration-time curve,' and GRF is the glomerular filtration rate. GFR was calculated using the Cockcroft-Gault formula (31) for a male having a serum creatinine level of 0.7 and an age of 60 years.

For the pembrolizumab + platinum +5-FU and the EXTREME regimens, costs were calculated assuming that pembrolizumab and

cetuximab were administered as single agents for 6 cycles within 1 year. For the PCE regimen, after 6 cycles, CBDCA was discontinued, and PTX and cetuximab were continued at a dose of 80 mg/m<sup>2</sup> of PTX and 250 mg/m<sup>2</sup> of cetuximab in a 28-day cycle. PTX and cetuximab were administered on days 1, 8, and 15 for 1 year.

The first-month cost of all regimens was calculated separately by dividing the cost of the first cycle by the number of days in that cycle and multiplying the result by 30. Assuming pembrolizumab was administered for 17.3 cycles per year, the cost per year of pembrolizumab was calculated by multiplying the cost of one cycle by 17.3. Likewise, assuming nivolumab was administered for 26 cycles per year, the cost per year of nivolumab was calculated by multiplying the cost of one cycle by 26. The cost per year of pembrolizumab + platinum +5-FU was calculated by summing the total cost of the first six cycles of the combination therapy and the remaining 11.3 cycles of pembrolizumab monotherapy. The cost per year of the EXTREME regimen was also calculated by summing the total cost of the first 6 cycles of combination therapy and the remaining 11.3 cycles of cetuximab monotherapy. The cost per year of the PCE regimen was also calculated by summing the total cost of the first 6 cycles of CBDCA + PTX + cetuximab therapy and the remaining 8.5 cycles of PTX + cetuximab therapy.

It should be noted that our cost analysis included only the cost of the chemotherapy agents themselves. The cost of treatment administration and supportive care, such as antiemetic medications, were not included. The HEC of Japan defines high-cost medical care as care costing 500 000 JPY or more per month, and very-high-cost medical care as care costing 1 000 000 JPY or more per month.

## Results

All 54 institutions provided data for the analysis to meet the mandate of the HEC, which was to survey which palliative chemotherapy regimens are used most frequently in the Japanese healthcare system to treat RM-SCCHN and how much these regimens cost. The total number of eligible patients was 907; 673 were < 75 years old and 233 were ≥ 75 years old. Of the 906 patients, 29 participated in the clinical trial but their treatment details were not included in the survey questionnaire.

Overall, the most used regimen was pembrolizumab monotherapy, accounting for 36.4% of the cases (Table 3); for patients ≥75 years, pembrolizumab monotherapy accounted for 56.7% of the cases. The second most used regimen was nivolumab monotherapy, accounting for 22.3% of the cases. Of the 906 patients, more than 90% received ICI as a monotherapy or in combination with another therapy. ICI monotherapy was used more frequently in patients ≥75 years than in patients <75 years. In contrast, combination chemotherapy with ICI was used more frequently in patients <75 years. The least frequently used regimens were those that did not use ICI as a first-line therapy, accounting for 7.6% of the cases, and those used in the EXTREME trial, accounting for only 1.7% of the cases.

The monthly costs of all regimens were between 612 851 JPY and 849 241 JPY. Per our definition and that of the HEC of Japan, this is considered to be high-cost medical care. The annual costs of all regimens were between 7 and 10 million JPY.

The standard treatment for RM-SCCHN until 2012, the platinum +5-FU regimen, costs about 20 000 JPY per month. Now, the incremental cost over the last decade is approximately 600 000 to 800 000 JPY per month, a 30- to 40-fold increase in the cost of palliative chemotherapy for RM-SCCHN.

**Table 2.** Surveyed chemotherapy regimens and their calculated costs

Regimen	Agent	Vial size(s) (mg)	Price (JPY)	Dosing schedules	Median OS in pivotal trials (months)	First-month costs (JPY)	Annual costs (JPY)
Pembrolizumab	Pembrolizumab	100	214 498	200 mg/body, Q3W 400 mg/body, Q6W	CPS < 1: 7.9 CPS1-19: 10.8 CPS ≥20: 14.8	612 851	7 421 630
Nivolumab	Nivolumab	240	366 405	240 mg/body, Q2W 480 mg/body, Q4W	7.7	785 153	9 526 530
CDDP + 5-FU + Pembrolizumab	CDDP	50 10	3175 740	100 mg/m <sup>2</sup> , Q3W, up to 6 cycles	CPS < 1: 11.3 <sup>a</sup> CPS1-19: 12.7 CPS ≥ 20: 14.7	634 504	7 512 572
CBDCA + 5-FU + Pembrolizumab	5-FU	1000 250	519 255	4000 mg/m <sup>2</sup> , Q3W, up to 6 cycles			
	Pembrolizumab CBDCA	100 450 150	214 498 5846 2491	200 mg/body, Q3W AUC 5, Q3W, up to 6 cycles	CPS < 1: 11.3 <sup>a</sup> CPS1-19: 12.7 CPS ≥ 20: 14.7	630 692	7 496 564
CDDP + 5-FU + Cetuximab	5-FU	1000 250	519 255	4000 mg/m <sup>2</sup> , Q3W, up to 6 cycles			
	Pembrolizumab CDDP	100 50 10	214 498 3175 740	200 mg/body, Q3W 100 mg/m <sup>2</sup> , Q3W, up to 6 cycles	10.7 <sup>b</sup>	836 807	8 819 519
CBDCA + 5-FU + Cetuximab	5-FU	1000 250	519 255	4000 mg/m <sup>2</sup> , Q3W, up to 6 cycles			
	Cetuximab CBDCA	500 450 150	166 678 5846 2491	400 mg/m <sup>2</sup> , first week 250 mg/m <sup>2</sup> , Q1W thereafter AUC 5, Q3W, up to 6 cycles	10.7 <sup>b</sup>	832 995	8 796 096
PTX + CBDCA + Cetuximab	5-FU	1000 255	519 255	4000 mg/m <sup>2</sup> , Q3W, up to 6 cycles			
	Cetuximab PTX	500 100 150	166 678 35 287 5105	400 mg/m <sup>2</sup> , first week 250 mg/m <sup>2</sup> , Q1W thereafter 100 mg/m <sup>2</sup> , day 1, 8, Q3W, up to 6 cycles	14.7	849 241	7 594 495
Reference CDDP + 5-FU	CBDCA	30 450 150	1852 5846 2491	AUC 2.5, days land 8, Q3W, up to 6 cycles			
	Cetuximab	500 500 100	166 678 166 678 35 287	400 mg/m <sup>2</sup> , first week 250 mg/m <sup>2</sup> , Q1W thereafter 250 mg/m <sup>2</sup> , Q1W thereafter			
CBDCA + 5-FU	CDDP	50 10	3175 740	100 mg/m <sup>2</sup> , Q3W, up to 6 cycles	7.3	21 652	129 912
	5-FU	1000 250	519 255	4000 mg/m <sup>2</sup> , Q3W, up to 6 cycles			
CBDCA + 5-FU	CBDCA	450 150	5846 2491	AUC 5, Q3W, up to 6 cycles	8.3	17 841	107 046
	5-FU	1000 250	519 255	4000 mg/m <sup>2</sup> , Q3W, up to 6 cycles			

JPY, Japanese Yen; OS, overall survival; CDDP, cisplatin; CBDCA, carboplatin; 5-FU, 5-fluorouracil; PTX, paclitaxel; Q3W, once every 3 weeks; Q1W, once every week.  
<sup>a</sup>OS data for both CDDP and CBDCA were not available. <sup>b</sup>OS data for both CDDP and CBDCA were not available.

**Table 3.** Number of head and neck cancer patients receiving each regimen

Regimen	First-month costs (JPY)	Total (n = 907) No. (%)	<75 years (n = 674) No. (%)	≥75 years (n = 233) No. (%)
Pembrolizumab	612 851	330 (36.4)	198 (29.4)	132 (56.7)
Nivolumab	785 153	202 (22.3)	158 (2.4)	44 (18.9)
CDDP +5-FU + Pembrolizumab	634 504	153 (16.9)	139 (20.6)	14 (6.0)
CBDCA +5-FU + Pembrolizumab	630 692	125 (13.8)	95 (14.1)	30 (12.9)
PTX + CBDCA + Cetuximab	849 241	53 (5.8)	48 (7.1)	5 (2.1)
Clinical trial	–	29 (3.2)	24 (3.6)	5 (2.1)
CDDP +5-FU + Cetuximab <sup>a</sup>	836 807	8 (0.9)	6 (0.9)	2 (0.9)
CBDCA +5-FU + Cetuximab <sup>a</sup>	832 995	7 (0.8)	6 (0.9)	1 (0.4)

CDDP, cisplatin; CBDCA, carboplatin; 5-FU, 5-fluorouracil; ICI, immune checkpoint inhibitor; PTX, paclitaxel.

<sup>a</sup>EXTREME trial.

## Discussion

To the best of our knowledge, this is the first study to conduct a broad survey of the frequency of different palliative chemotherapy regimens for the treatment of RM-SCCHN and their costs in the Japanese healthcare system. Our survey of patients being treated at 39 member JCOG-HNCSG healthcare facilities and 15 affiliated facilities revealed that over 90% of the first-line palliative chemotherapy regimens included ICI and that all of these met the criteria for high-cost medical care having a monthly cost of more than 500 000 JPY. However, we found differences in these results when the data were analyzed according to patient age.

Our findings that ICIs were used widely as the first-line treatment for RM-SCCHN are consistent with recommendations of the 2022 Japanese Clinical Practice Guidelines for Head and Neck Cancer (21). Prior to 2022, the previous standard treatment for RM-SCCHN was a selection of one of the regimens of the EXTREME trial (6). As our current survey showed, the EXTREME regimens are rarely used as first-line palliative chemotherapy. Only about 30% of patients in our survey younger than 75 years old received ICI monotherapy, while patients 75 years and older accounted for nearly 80% of the cases receiving ICI monotherapy. One reason for this disparity may be that elderly patients are expected to be less tolerant of cytotoxic anticancer agents. Thus, they may be more likely to choose ICI monotherapy rather than ICI combination therapy. In general, regimens composed of ICI or molecular targeting agents are more expensive than regimens lacking these agents. Our survey also revealed that the regimens composed of cetuximab plus platinum-based chemotherapy were more expensive than regimens containing ICI. This is partly because cetuximab is typically administered more often, i.e. on a weekly basis.

There was no available data in Japan on the cost-effectiveness of the various treatments for RM-SCCHN. However, such studies have been conducted in the US, UK, China, Switzerland, and Argentina, among others (32–39). These studies evaluated the cost-effectiveness of different ICI monotherapies, and some concluded they were cost-effective, but others concluded they were not. In general, cost-effectiveness is evaluated by comparing an incremental cost-effectiveness ratio (ICER) to the willingness-to-pay (WTP) (40). ICER represents the incremental cost between two treatment approaches divided by the incremental effectiveness (measured with quality-adjusted life year [QALY]). QALY is a product of a patient's health utility over survival time (41). Health utility measures quality of life and ranges from 0 (death) to 1 (perfect health). If the ICER is less than the WTP, the treatment is considered 'cost-effective' (40).

It is difficult to compare the cost-effectiveness of the same regimens across countries, because extrapolating foreign cost-effectiveness studies into the Japanese healthcare system is fraught with problems. These include fundamental differences in healthcare systems and implementation of care, variations in drug prices among countries, fluctuations in the drug prices over time, and differences between WTP and ICER thresholds (42). These metrics are significantly influenced by each country's social and economic situations (41). To assess the future cost-effectiveness of palliative chemotherapy for RM-SCCHN, it is crucial to discuss the WTP and ICER thresholds for anticancer drugs in Japan, which typically range from 5 to 15 million JPY/QALY (43). Ongoing WTP surveys need to be conducted because gross domestic product fluctuations affect ICER thresholds (43). Therefore, since the present study was merely a survey of the number of RM-SCCHN patients who received palliative chemotherapy and estimates of the drug costs of their treatment regimens, it is impossible to draw conclusions about cost-effectiveness without knowing the ICER thresholds and WTP.

To address the cost issue, it is important to have not only cost-effectiveness studies but also cost-control studies, such as those investigating less expensive treatments or shorter treatment durations. However, there are no such reports currently.

Regardless of several useful findings in our study, our survey had several limitations. First, because our survey did not collect data on the actual dosage of the drugs and whether the drugs were discontinued or reduced, the calculated costs do not reflect the actual costs of the chemotherapeutic drugs administered to the patients. Furthermore, the cost of therapy administration and imaging, treatment for adverse events, supportive care, and end-of-life care were not included in our survey and were thus not computed. Hence, the treatment regimen costs we computed might be underestimated. Third, we did not collect CPS data in this study, and since CPS will be essential for the choice of ICI alone or in combination with chemotherapy, the analysis including CPS could have provided a more profound discussion. Fourth, only eight pre-selected regimens were assessed in the present study, and the survey did not include patients who started treatment with S-1 or PTX + cetuximab. Thus, our findings do not fully reflect all the possible palliative chemotherapy regimens used in Japan for RM-SCCHN.

## Conclusion

In Japan, the first-line palliative chemotherapy for RM-SCCHN is costly at more than 600 000 JPY per month, which is 30–40 times

higher than it was until 2012. The incremental cost is approximately 600 000–800 000 JPY per month. Over the last decade, the prognosis for RM-SCCHN has improved, but the costs of palliative chemotherapy have surged, placing a heavy burden on patients and society.

## Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

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## Author contributions

KY, KW, KS, and RM (conception and design); JT, KS, AO, AN, HY, SS, MN, NT, KY, AS, FI, MS, RO, YM, AS, KK, DS, KE, YO, DN, AW, IT, HN, HS, CS, TT, KT, MS, KK, TS, YI, HM, TK, NA, TH, NM, ST, TN, MM, NM, SM, KY, MN, FM, YK, YT, MF, YT, SF, AH, TK, KK, SM, and SS (study materials and/patients); KY and KW (data collection); KY and KW (data analysis and interpretation). All authors contributed to the writing of this manuscript, approved the final version of this manuscript, and are accountable for this study.

## Conflict of interest

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## Data availability statement

The de-identified data reported in this study will be made available upon reasonable request made to the corresponding author.

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Original Article

# Cost of medical care for malignant brain tumors at hospitals in the Japan Clinical Oncology Group brain-tumor study group

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## Abstract

**Background:** This study aimed to investigate what treatment are selected for malignant brain tumors, particularly glioblastoma (GBM) and primary central nervous system lymphoma (PCNSL), in real-world Japan and the costs involved.

**Methods:** We conducted a questionnaire survey regarding treatment selections for newly diagnosed GBM and PCNSL treated between July 2021 and June 2022 among 47 institutions in the Japan Clinical Oncology Group-Brain Tumor Study Group. We calculated the total cost and cost per month of the initial therapy for newly diagnosed GBM or PCNSL.

**Results:** The most used regimen (46.8%) for GBM in patients aged  $\leq 74$  years was 'Surgery + radiotherapy concomitant with temozolomide'. This regimen's total cost was 7.50 million JPY (Japanese yen). Adding carmustine wafer implantation (used in 15.0%), TTFIELDS (used in 14.1%), and bevacizumab (BEV) (used in 14.5%) to the standard treatment of GBM increased the cost by 1.24 million JPY for initial treatment, and 1.44 and 0.22 million JPY per month, respectively. Regarding PCNSL, 'Surgery (biopsy) + rituximab, methotrexate, procarbazine, and vincristine (R-MPV) therapy' was the most used regimen (42.5%) for patients of all ages. This regimen incurred 1.07 million JPY per month. The three PCNSL regimens based on R-MPV therapy were in ultra-high-cost medical care (exceeding 1 million JPY per month).

**Conclusions:** Treatment of malignant brain tumors is generally expensive, and cost-ineffective treatments such as BEV are frequently used. We believe that the results of this study can be used to design future economic health studies examining the cost-effectiveness of malignant brain tumors.

**Key words:** glioblastoma, primary central nervous system lymphoma, treatment regimen, high-cost medical care, cost

## Introduction

Glioblastoma (GBM) is one of the most malignant primary brain tumors and diffusely infiltrates the central nervous system (1,2). In Japan, GBM is a rare cancer, accounting for 1.68 cases of 100 000 people per year (3). Postoperative concomitant chemoradiotherapy with temozolomide (TMZ) and adjuvant TMZ are the standard treatments for GBM worldwide (4), with a median overall survival (OS) period of 14.6 months (5).

As GBM has the poor prognosis, treatment development is currently underway to determine what to add to TMZ to prolong survival for GBM. Firstly, carmustine wafer implantation (Gliadel) is an intracavity sustained-release formulation containing carmustine, a nitrosourea alkylating antineoplastic agent, implanted on the resection surface during the resection of malignant gliomas (6). Secondly, bevacizumab (BEV) is another drug approved for GBM treatment. Although there are two randomized controlled trials (AVAglio and RTOG0805) on BEV in combination with TMZ plus chemoradiotherapy for newly diagnosed GBM, it is not considered the standard of care for newly diagnosed GBM, mainly because two large placebo-controlled phase III trials showed no significant differences in OS, and this has not been approved for use in newly diagnosed GBM in any country other than Japan. Thirdly, the NovoTTF-100A system is a portable device that generates a low-intensity, intermediate-frequency alternating electric field called a tumor-treating field (TTF), which is believed to kill cancer cells by inhibiting their replication (7). However, the actual treatment selections for GBM in the real world as well as their associated costs have not been fully investigated.

According to the Report of the Brain Tumor Registry of Japan (2005–2008) (5), primary central nervous system lymphoma (PCNSL) accounts for 4.9% (814 per 4 years) of all primary brain tumors, and the incidence of PCNSL has been increasing in recent years. Currently, the standard treatment for PCNSL is HD-MTX-based remission induction therapy and consolidation therapy with high-dose cytarabine (AraC) or WBRT. The 2-year survival rate of patients treated with rituximab + MTX + procarbazine + vincristine (R-MPV), which is a combination of HD-MTX-based multiple agent remission induction therapy and HD-AraC, consolidation pharmacotherapy, and 23.4 Gy of reduced dose whole brain radiation, was 90% (8).

In addition to the standard treatment for these malignant brain tumors, further therapeutic development should be conducted to enable prolonged survival and may achieve a cure in the future. However, the high development costs of these new drugs render them costly. Japan has a universal health insurance system that significantly reduces patients' out-of-pocket expenses, even when medical costs are high (9). The reduced costs come from insurance premiums and taxes paid by Japanese citizens. As the cost of medical care continues to increase, the burden on the public is approaching its limit. In the future, it will be necessary to consider drug costs and the effects of treatment choices on patient outcomes and the effects on healthcare costs and the use of limited healthcare resources from a broad perspective. Particularly, the burden of cancer continues to grow, and the disease is becoming a major economic burden for all industrialized countries (10,11). Therefore, the Japan Clinical Oncology Group (JCOG) Health Economic Committee considered that it was necessary to discuss sustainable medical care for the next generation of patients.

In the present study, we conducted a survey at a hospital in the JCOG-BTSG to reveal the treatment options available for GBM and PCNSL among malignant brain tumors and the medical costs for

each regimen. This study aimed to investigate what treatment are available for malignant brain tumors, particularly GBM and PCNSL, in real-world Japan and the costs involved. It was led by the JCOG Health Economic Committee.

## Materials and methods

### A questionnaire survey

A questionnaire survey was conducted at 47 JCOG-BTSG-registered centers to determine the initial treatment regimens used for malignant brain tumors that are not curable: (1) newly diagnosed GBM and (2) PCNSL. The survey was conducted using Google Form, which included the name of the facility and the name of the researchers. The lists of initial treatment regimens established in the questionnaire survey items are shown in Tables 1 (newly diagnosed GBM) and Table 2 (PCNSL). There were 11 treatment regimens for GBM and eight treatment regimens for PCNSL (Tables 1 and 2). The content of each treatment regimen was extracted from regimens used mainly in Japan. In the survey, the total number of patients receiving each treatment was collected, but individual patient data were not collected. The number of patients who were treated with each regimen was divided by 'age  $\leq$  74 years/ $\geq$  75 years (at the start of treatment)' in the survey. The study period covered cases of newly diagnosed GBM or PCNSL from July 2021 to June 2022 at each institution.

### Calculation of the cost of each treatment for malignant brain tumors

This study calculated the total cost of the initial therapy for newly diagnosed GBM and PCNSL (not including the cost of maintenance therapy). Medical costs were calculated based on Japanese receipt scores. Monthly cost was calculated based on the treatment duration for each treatment regimen. Among the treatments, we defined 'high-cost medical care' as treatments of  $\geq$ 0.5 million JPY per month and 'ultra-high-cost medical care' as treatments of  $\geq$ 1 million JPY per month, as defined by the JCOG Health Economics Committee.

## Results

### General information

Questionnaires were collected from patients with newly diagnosed GBM or PCNSL treated between April 2022 and March 2023 from 47 JCOG-BTSG registries. The questionnaires collected from patients with newly diagnosed GBM received responses from 42 of all 47 JCOG-BTSG-registered centers (89.4%). In contrast, the survey for PCNSL received responses from 39 of the 47 JCOG-BTSG-registered centers (83.0%). Among these centers, the total numbers of patients surveyed for GBM and PCNSL were 733 and 258, respectively. In Japan, the Center for Cancer Genomics and Advanced Therapeutics offers a next-generation sequencing-based comprehensive genomic profiling test for patients with malignant brain tumors. This test targets patients with GBM or PCNSL. The cost is 0.56 million JPY (12).

### Results of a survey of treatment regimens used for newly diagnosed GBM

Overall, 733 GBM cases were reported, of which 530 GBM cases were reported for those aged  $\leq$ 74 years and 203 GBM cases were reported for those aged  $\geq$ 75 years. The proportions of elderly and non-elderly patients receiving each treatment regimen for newly diagnosed GBM are shown in Fig. 1 and Table 1. The most used regimen for GBM in patients aged  $\leq$ 74 years was 'Surgery + radiotherapy

**Table 1.** Initial treatment regimens for newly diagnosed GBM surveyed in the questionnaire.

Treatment regimens	74 years old or younger		75 years old or older	
	No. of patients ( <i>n</i> = 530)	(%)	No. of patients ( <i>n</i> = 203)	(%)
Surgery + RT (60Gy/30fr)	5	1.0	14	6.9
Surgery + RT (60Gy/30fr) + TMZ	248	46.8	16	7.9
Surgery + RT (60Gy/30fr) + TMZ + Carmustine wafer implantation	57	10.8	6	3.0
Surgery + RT (60Gy/30fr) + TMZ + TTFields	56	10.6	3	1.5
Surgery + RT (60Gy/30fr) + TMZ + Carmustine wafer implantation + TTFields	29	5.5	0	0
Surgery + RT (40Gy/15fr) + TMZ	40	7.6	117	57.7
Surgery + RT (25Gy/5fr) + TMZ	14	2.7	22	10.9
Surgery + RT (60Gy/30fr) + TMZ + BEV	54	10.2	24	11.9
Surgery + RT (60Gy/30fr) + TMZ + BEV + Carmustine wafer implantation	12	2.3	1	0.5
Surgery + RT (60Gy/30fr) + TMZ + BEV + TTFields	10	1.9	0	0
Surgery + RT (60Gy/30fr) + TMZ + BEV + Carmustine wafer implantation + TTFields	5	1.0	0	0

Number of facilities that responded to the survey: 42 of the 47 JCOG-BTSG-registered centers (89.4%)

Abbreviation: RT, radiation therapy; TMZ, temozolomide, TTFields, tumor-treating fields; BEV, bevacizumab.

**Table 2.** Initial treatment regimens for newly diagnosed PCNSL surveyed in the questionnaire.

Treatment regimens	74 years old or younger		75 years old or older	
	No. of patients ( <i>n</i> = 172)	(%)	No. of patients ( <i>n</i> = 86)	(%)
Surgery (biopsy) + HD-MTX therapy	11	6.4	12	14.0
Surgery (biopsy) + HD-MTX therapy + Tirabrutinib	2	1.2	3	3.5
Surgery (biopsy) + HD-MTX therapy + ASCT/HDC	3	1.8	0	0
Surgery (biopsy) + HD-MTX therapy + WBRT	7	4.1	5	5.9
Surgery (biopsy) + R-MPV therapy	73	42.5	46	53.5
Surgery (biopsy) + R-MPV therapy + Tirabrutinib	12	7.0	8	9.4
Surgery (biopsy) + R-MPV therapy + ASCT/HDC	19	11.1	0	0
Surgery (biopsy) + R-MPV therapy + WBRT	45	26.2	12	14.0

Number of facilities that responded to the survey: 39 of the 47 JCOG-BTSG-registered centers (83.0%)

Abbreviation: HD-MTX, high-dose methotrexate; WBRT, whole brain radiotherapy; R-MPV, rituximab, methotrexate, procarbazine, and vincristine; ASCT/HDC, autologous stem cell transplantation/high-dose chemotherapy.

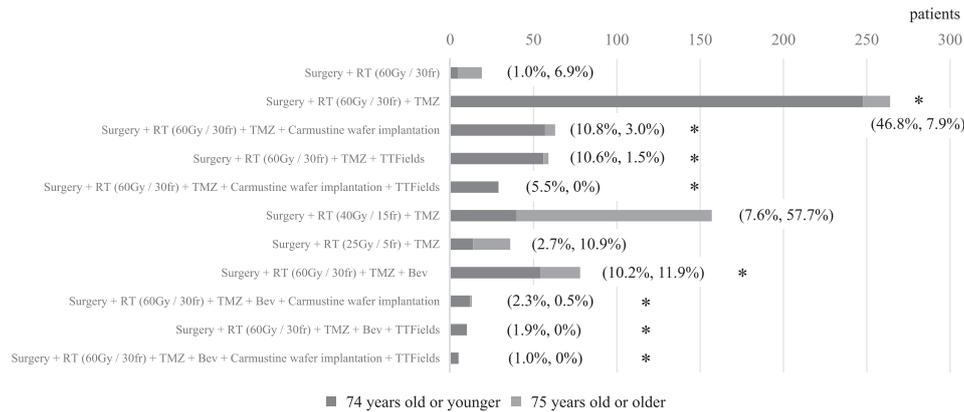
(RT) (60 Gy/30 fr) + TMZ,' (248/530 cases, 46.8%), which is the standard treatment for non-elderly patients with GBM. The next most used regimen was 'Surgery + RT (60 Gy/30 fr) + TMZ' plus (1) carmustine wafer implantation or (2) TTFields, or (3) BEV, which were almost equally used. In contrast, the most used regimen for GBM in patients aged  $\geq 75$  years was 'Surgery + RT (40 Gy/15 fr) + TMZ' (117/203 cases, 57.7%), which is the standard treatment for elderly patients with GBM. The next most used regimens were 'Surgery + RT (60 Gy/30 fr) + TMZ plus BEV' (24/203 cases, 11.9%), and 'Surgery + RT (25 Gy/5 fr) + TMZ' (22/203 cases, 10.9%), which were performed as clinical trials. 'Carmustine wafer implantation' and 'TTFields' tended not to be used in elderly patients with GBM. Overall, the percentages of carmustine wafer implantation, TTFields, and BEV used were 110/733; 15.0%, 103/733; 14.1%, and 106/733; 14.5%, respectively.

#### Comparison of the cost of each treatment regimen used for newly diagnosed GBM

The cost of treatment for eight of the 11 regimens for GBM used in the survey was investigated (Table 3). Among all 733 GBM patients, 521 patients (71.1%) were in the 'high-cost medical care'

group, while 116 (15.8%) were in the 'ultra-high-cost medical care' group. As divided to age groups, 471/530 (88.9%) patients  $\leq 74$  years belonged to the 'high-cost medical care' group, while 112/530 (21.1%) were in the 'ultra-high-cost medical care' group. Among patients  $\geq 75$  years, 50/203 (24.6%) were in the 'high-cost medical care' group, compared to 4/203 (2.0%) in the 'ultra-high-cost medical care' group with a low percentage.

The total cost of 'Surgery + RT (60 Gy/30 fr) + TMZ', the standard treatment for GBM in non-elderly patients as initial treatment, was 7.50 million JPY, including 1.32 million JPY for surgery and 1.00 million JPY for radiation therapy. One course of maintenance therapy cost 0.15 million JPY per month for TMZ maintenance therapy. The cost of 'Surgery + RT (60 Gy/30 fr) + TMZ (standard of care)' for the first 6 months, 1 year, and up to 12 courses of TMZ maintenance therapy is shown in Table 3. Adding carmustine wafer implantation to the standard treatment of GBM in non-elderly patients increased the cost by 1.24 million JPY for initial treatment, adding TTFields increased the cost by 1.44 million JPY per month, and adding BEV increased the cost by 0.22 million JPY per a month. 'Surgery + RT (60 Gy/30 fr) + TMZ' (standard of care), adding 'TTFields regimen,'



**Fig. 1.** The proportion of each regimen for newly diagnosed GBM, selected by JCOG-participating physicians, according to the age group. Percentages show the proportion of patients receiving the regimen in each age groups (<75 years or > 75 years). The bold star highlights the regimens with high- or ultra-high- cost.

**Table 3.** Total cost of each treatment regimen and monthly cost for newly diagnosed GBM.

Treatment	Surgery cost (million JPY)	Cost for the first 6 months of treatment (including 3 courses of TMZ maintenance therapy) (million JPY)	Cost for the first 1 year of treatment (including 9 courses of TMZ maintenance therapy) (million JPY)	Cost for initial treatment without recurrence +12 courses of TMZ maintenance therapy (million JPY)	Cost per month (million JPY)	high-cost medical care	ultra-high-cost medical care
Surgery + RT (60Gy/30fr) + TMZ (Standard of care) (JCOG0911)	1.32	7.95	8.85	9.3	0.74	○	
Surgery + RT (60Gy/30fr) + TMZ + Carmustine wafer implantation (JCOG1703)	1.32	9.19	10.09	10.54	0.84	○	
Surgery + RT (60Gy/30fr) + TMZ + TTFields	1.32	12.27	21.81	26.58	1.82	○	○
Surgery + RT (60Gy/30fr) + TMZ + Carmustine wafer implantation + TTFields	1.32	13.51	23.05	27.82	1.92	○	○
Surgery + RT (60Gy/30fr) + TMZ + BEV	1.32	8.61	10.83	12.31	0.9	○	
Surgery + RT (60Gy/30fr) + TMZ + BEV + Carmustine wafer implantation	1.32	9.85	12.07	13.55	1.01	○	○
Surgery + RT (60Gy/30fr) + TMZ + BEV + TTFields	1.32	12.93	23.79	29.59	1.98	○	○
Surgery + RT (60Gy/30fr) + TMZ + BEV + Carmustine wafer implantation + TTFields	1.32	14.17	25.03	30.83	2.09	○	○

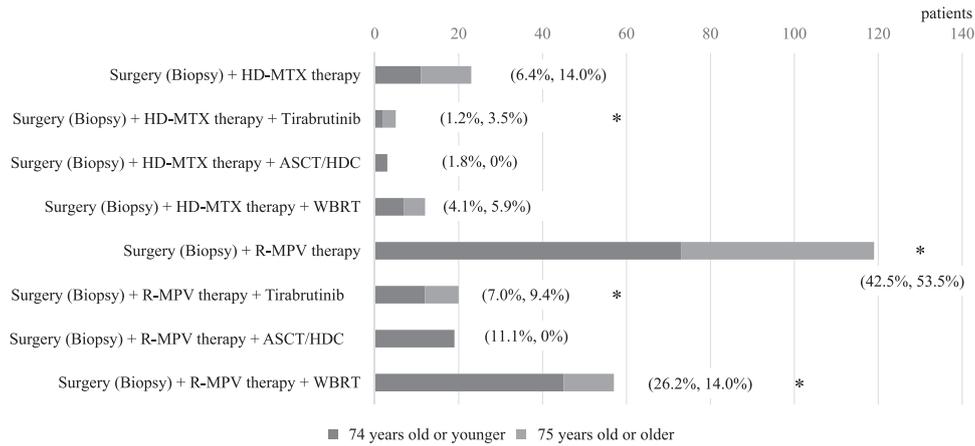
Abbreviation: RT, radiation therapy; TMZ, temozolomide; TTFields, tumor-treating fields; BEV, bevacizumab; JCOG, Japan Clinical Oncology Group.

‘carmustine wafer implantation + TTFields regimen,’ ‘BEV + carmustine wafer implantation + TTFields regimen,’ ‘BEV + carmustine wafer implantation + TTFields regimen,’ and ‘BEV + carmustine wafer implantation + TTFields regimen’ were regimens for ultra-high-cost medical care.

**Results of a survey of treatment regimens used for PCNSL**

A total of 258 PCNSL cases were reported, of which 172 were reported in patients aged ≤74 years and 86 were reported in patients

aged ≥75 years. The proportions of elderly and non-elderly patients in each treatment regimen for PCNSL are shown in Fig. 2 and Table 2. ‘Surgery (biopsy) + R-MPV therapy’ was the commonly used regimen for patients with PCNSL of all ages (119/258 cases, 46.1%). As the European Association of Neuro-Oncology guidelines state that RT should be avoided in elderly patients with PCNSL (13), ‘Surgery (biopsy) + R -MPV therapy + WBRT’ was the second most common treatment regimen. Autologous stem cell transplantation high-dose chemotherapy was not performed in patient with PCNSL aged >75 years.



**Fig. 2.** The proportion of each regimen for newly diagnosed PCNSL, selected by JCOG-participating physicians, according to the age group. Percentages show the proportion of patients receiving the regimen in each age groups (<75 years or > 75 years). The bold star highlights the regimens with high- or ultra-high-cost.

**Table 4.** Total cost of each treatment regimen and monthly cost for newly diagnosed PCNSL.

Treatment	Surgery (biopsy) cost (million JPY)	Cost for the first 6 months of treatment (Cost for initial treatment without recurrence) (million JPY)	Cost per month (million JPY)	high-cost medical care	ultra-high-cost medical care
Surgery (biopsy) + HD-MTX therapy (Previous standard of care, JCOG1114)	0.2	2	0.33		
Surgery (biopsy) + HD-MTX therapy + Tirabrutinib	0.2	4.73	0.79	○	
Surgery (biopsy) + HD-MTX therapy + WBRT	0.2	2.9	0.48		
Surgery (biopsy) + R-MPV therapy	0.2	6.4	1.07	○	○
Surgery (biopsy) + R-MPV therapy + Tirabrutinib	0.2	8.22	1.37	○	○
Surgery (biopsy) + R-MPV therapy + WBRT (Standard of care)	0.2	7.9	1.32	○	○

Abbreviation: HD-MTX, high-dose methotrexate; WBRT, whole brain radiotherapy; R-MPV, rituximab, methotrexate, procarbazine, and vincristine; JCOG, Japan Clinical Oncology Group.

**Comparison of the cost of each treatment regimen used for PCNSL**

The total cost of six of the eight regimens for PCNSL used in the survey was investigated (Table 4). Among the 258 patients with PCNSL, 201 (77.9%) were in the ‘high-cost medical care’ group, while 196 (76.0%) were in the ‘ultra-high-cost medical care’ group. Among patients ≤74 years, 132/172 (76.7%) were in the ‘high-cost medical care’ group, compared to 130/172 (75.6%) in the ‘ultra-high-cost medical care’ group. In contrast, among patients ≥75 years, 69/86 (80.2%) were in the ‘high-cost medical care’ group, compared to 66/86 (76.7%) in the ‘ultra-high-cost medical care’ group.

The most frequently used regimen at the JCOG-BTSG-registered centers was ‘Surgery (biopsy) + R-MPV therapy,’ with a total cost of 6.4 million JPY and 1.07 million JPY per month. The cost of the stereotactic brain tumor biopsy surgery was 0.2 million JPY. Regarding chemotherapy, MTX therapy (two courses) cost 0.7 million JPY per month, R-MPV therapy (two courses) cost 1.4 million JPY per month, and tirabrutinib cost 0.91 million JPY per month. The three regimens based on R-MPV therapy involved ultra-high-cost medical care, with a monthly cost exceeding 1 million JPY. In contrast, adding tirabrutinib to HD-MTX or R-MPV therapy resulted in an increase in 0.91 million JPY per month.

**Discussion**

Both GBM and PCNSL are rare brain tumors with poor prognoses. Although these tumors are treated with what is considered the standard care, little consideration has been given to the cost of the standard treatment itself, the cost of new drugs added to the standard treatment, and the cost-benefit ratio of these new drugs (14,15). Furthermore, clinical trials for the development of new therapies in Japan have not been conducted in a cost-benefit manner. In this study, we investigated the treatment regimens used for GBM and PCNSL at JCOG-BTSG-registered centers with the most experience in treating brain tumors in Japan and the cost of these regimens.

The standard treatment for GBM is ‘Surgery + RT (60 Gy/30 fr) + 6–12 cycles of TMZ’ (4,16). In our series, this regimen was also the commonly used regimen for GBM patients with 264 of 733 cases (36.0%). In the current study, 15.0% (110/733) of the patients with GBM were treated with carmustine wafer implantation. However, there are not many prospective randomized clinical trials that compare these treatment regimen with groups of patients treated with other agents. Although there are some reports from retrospective studies [17–19], there is still no evidence that carmustine wafer implantation in GBM leads to a prolonged prognosis. We

are currently awaiting the results of a randomized phase III study, JCOG1703 (16), for newly diagnosed maximally resected GBM comparing carmustine wafer implantation followed by chemoradiotherapy with TMZ with chemoradiotherapy alone (16). While it remains to be seen how carmustine wafer implantation during surgery much improves the prognosis for of patients with GBM will improve with carmustine wafer implantation during surgery, we should firmly consider the 1.24 million JPY increase over standard therapy. Therefore, this drug is not generally used for GBM in routine practice before the results of the phase III trial, making it less available than it should be.

For GBM, the following two treatments (TTFields and BEV) are representative of prospective randomized clinical trials. A randomized phase III trial was conducted to evaluate the efficacy of the TTFields in newly diagnosed GBM (20). A total of 695 patients with GBM were randomized to receive TMZ maintenance with TTFields or maintenance with TMZ alone after completion of the initial treatment with the Stupp regimen. In patients with newly diagnosed GBM, the median OS period was significantly prolonged by 4.9 months in the TTFields group compared with TMZ alone (20.9 months vs. 16.0 months). A prolonged OS benefit of 4.9 months for TTFields must be considered for cost-effectiveness, considering that the cost per month for TTFields is 1.44 million JPY. A French research group performed a cost-effectiveness analysis of TTFields (21). The analysis using the Markov model showed that the addition of TTFields to the standard treatment with TMZ increased the life expectancy by 4.08 months (0.34 life-years gained (LYG)) and the cost per patient by €185 476. The incremental cost-effectiveness ratio (ICER) was €549 909/LYG. Therefore, this study emphasizes that the current cost of TTFields has an ICER that is significantly high to be cost-effective. However, other research groups tested different models and concluded that TTF remains a less cost-effective intervention, significantly hindering its dissemination to potentially eligible patients (22). Thus, given that TTFields are costly, there is a difference in opinion as to whether they are cost-effective. In the present study, 14.1% (103/733) of patients with GBM were treated with TTF. In Japan, the use of TTF increases the monthly amount by 1 440 000 JPY, with the ICER estimated at 17280000JPY/LYG (incremental cost: 5875200JPY; incremental effectiveness: 0.34 LYG). Therefore, it is considered to be a less cost-effective treatment since it far exceeds the willingness-to-pay (WTP) threshold in Japan (7.5 million yen/QALY).

In the AVAaglio study, compared chemoradiotherapy with TMZ plus BEV (23) and chemoradiotherapy with TMZ plus placebo in patients with newly diagnosed GBM, the median OS period was not significantly different at 16.8 and 16.7 months, respectively. Another randomized controlled trial of BEV in combination with chemoradiotherapy with TMZ for newly diagnosed GBM is the RTOG0805 trial (24) showed no difference in OS between BEV-treated (median survival, 15.7 months) and placebo-treated patients (median survival, 16.1 months). Therefore, BEV is not considered the standard of care for newly diagnosed GBM worldwide, partly because of the lack of significant OS differences in two large placebo-controlled phase III trials. However, the use of BEV for newly diagnosed GBM has been inconsistently approved by insurance in Japan. Even in the JCOG-BTSG registry, 106/733 (14.5%) patients with newly diagnosed GBM were treated with BEV despite a lack of OS prolongation (Fig. 1). One of the reasons why BEV is often used in Japan is that 49.2% of patients newly diagnosed with GBM in Japan have a Karnofsky performance status (KPS) of  $\leq 70$  and BEV is used to improve performance status of patients. Some patients with GBM with low KPS may benefit from additional BEV treatment

with RT + TMZ, but considering that BEV costs 0.22 million JPY per month, the use of BEV for newly diagnosed GBM should be discouraged, at least for patients with high performance status in Japan.

Three to five cycles of HD-MTX have been the standard care for PCNSL in Japan for a long time (25), and the JCOG-BTSG conducted the JCOG1114 study comparing HD-MTX + WBRT versus HD-MTX + TMZ + WBRT plus adjuvant MTX (26). Based on the results of several clinical trials for PCNSL (8,27,28), R-MPV is considered the standard of care for PCNSL in the JCOG-BTSG, and some clinical trials are ongoing. ‘Surgery (biopsy) + R-MPV therapy’ was the most used regimen at the JCOG-BTSG centers in patients with PCNSL aged  $\leq 74$  years (73/172 cases, 42.5%) and in patients with PCNSL aged  $\geq 75$  years (46/86 cases, 53.5%). R-MPV therapy, the standard treatment for PCNSL, belongs to the ‘ultra-high-cost medical care’ group, indicating that the cost of the standard treatment itself is high. If another therapy is added to this standard therapy, the cost will naturally be even higher. Because there are no results of clinical trials comparing it with R-MPV therapy, it is difficult to discuss the cost-effectiveness of PCNSL treatment regimens; however, there are some reports of the cost-effectiveness of PCNSL treatment regimens (29,30). A retrospective study on the cost-effectiveness of rituximab plus methotrexate with AraC (R-MA regimen) has been reported (30). Thirty-seven patients who received the R-M regimen showed good OS at low costs. The International Extranodal Lymphoma Study Group-32 randomized patients with PCNSL into three groups: methotrexate-AraC, methotrexate-AraC-rituximab, and methotrexate-AraC-thiotepa-rituximab (MATRix) as induction therapy. The MATRix regimen significantly improved complete remission (29). The MATRix regimen had a 3.05 quality-adjusted life year (QALY) gain at an additional cost of \$75 513, with an ICER of \$24 758/QALY gain (29). Thus, the MATRix regimen appears to be the optimal induction therapy for PCNSL patients, both clinically and economically.

In the treatment of newly-diagnosed GBM, TMZ plus BEV had no significant difference in median OS period compared to TMZ alone. Thus, in the present study, if the 76 patients treated with ‘Surgery + RT (60 Gy/30 fr) + TMZ + BEV Surgery + RT (60 Gy/30 fr + TMZ + BEV)’, assuming those patients survived 12 months, the cost of BEV could be reduced by 200.64 million JPY, considering an increase of 0.22 million JPY per month in the cost of BEV. Since Japan’s estimated medical cost in 2022 is 46 trillion JPY, this represents a 0.004% reduction in medical costs.

One limitation is that this survey did not cover all brain tumor treatment centers in Japan, only those registered with the JCOG-BTSG. The treatment selections for malignant brain tumors at non-JCOG participating centers may differ from those at JCOG participating centers that have experts in malignant brain tumors. Therefore, the results may differ if the disease population increases. In addition, because the survey period was limited to 1 year, the possibility of bias cannot be denied. Additionally, individual patient data for GBM and PCNSL were not collected. Thus, this study did not consider information, such as the actual duration of administration, drug discontinuation, or dose reduction in individual cases. Therefore, we may not have been able to accurately assess the cost-benefit ratio of each regimen for each disease. Therefore, future prospective clinical trials on GBM and PCNSL should evaluate treatment regimens and cost-benefits. There are still no ongoing surveys or studies for cost containment for malignant brain tumors. Considering the increasing healthcare costs in Japan, healthcare professionals should have a perspective for cost-effectiveness optimization for malignant brain tumors.

## Conclusions

In the present study, we investigated the types of treatment regimens used for GBM or PCNSL and the proportion of elderly/non-elderly patients in each treatment at JCOG-BTSG-registered centers in Japan and provided information on the cost per month of each treatment regimen and whether it was high-cost or ultra-high-cost medical care. Treatment of malignant brain tumors is generally expensive, and substantial number of patients are treated by high-cost drugs with unproven or denied benefit. Although this study analyzed only survival time, it is important to discuss the maintenance of Performance Status or Quality of life of patients in the future. We believe that the results of this study can be used to design future health economic studies examining the cost-effectiveness of malignant brain tumors, particularly GBM and PCNSL.

## Conflict of Interest

The authors declare that they have no conflicts of interest.

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## Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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## Editorial

# Confronting the problems we had hoped to avoid

**Key words:** cost, immune-checkpoint, inhibitors, target-based, drugs, sustainability, health care, system

As early as 2004, Dr Deborah Schrag of the Memorial Sloan Kettering Cancer Center, New York, warned of the rising costs of cancer care (1). Dr Schrag pointed out that the median survival time of advanced colorectal cancer patients was notably improved, almost doubled in the last decade, thanks to the advent of new anticancer agents, such as irinotecan, oxaliplatin, bevacizumab and cetuximab. However, the progress was accompanied by a 340-fold increase in drug costs (1).

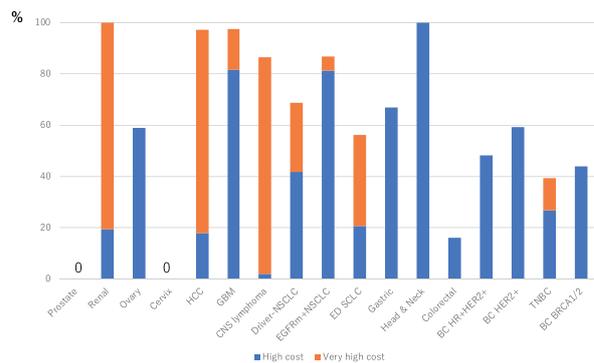
In 2004, some target-based drugs, such as imatinib, gefitinib and erlotinib were available. In retrospect, however, this was just the end of the beginning. The epidermal growth factor receptor (EGFR)-activating mutation, the true target of EGFR tyrosine kinase inhibitors (TKIs), was discovered that year. Anaplastic lymphoma kinase (ALK) fusion in lung cancer was not reported until 2007. In 2004, we did not have, or even know of, immune-checkpoint inhibitors (ICIs). We did not have antibody-drug conjugates. Nor did we know CAR-T.

Even before we began to use the full armamentarium we now have, in 2011, researchers from Europe and North America issued a statement warning that the skyrocketing cost of cancer care would endanger its affordability, even in high-income countries (2). Please note that this was 3 years before nivolumab was launched. They concluded that ‘the cancer profession and industry should take responsibility and not accept a standard evidence base and an ethos of very small benefit at whatever cost; rather, we need delivery of fair prices and real value from new technologies’ (2). Has their recommendation been widely heeded? Probably not.

In Japan, medical costs in 2021 exceeded 45 trillion Japanese yen (JPY), a 4.8% increase compared to 2020 and ~a 35% increase compared to 2004. We used 8.18% of our Gross Domestic Product (GDP) on medical care, which was 7.99% and 6% in 2020 and 2004, respectively (3). Medical costs in Japan have more than tripled since 1986, when one of the authors (H.K.) graduated from medical school, while Japanese GDP has stagnated over the past three decades. When the other author (T.K.) graduated from medical school in 1967, Japan’s medical costs were <4 trillion JPY, ~3.5% of the GDP. Is such an increase sustainable? Definitely not.

But why is this happening? Medical cost increases are mainly driven by two factors: progress in medicine, such as the advent of new drugs, and the aging population. Nobody is to blame for either of them—and nobody can stop them. However, if left unchecked, we will soon witness a total collapse of our healthcare system. The Japanese public insurance system allows us to spend as much money as necessary to treat our patients. Although the Japanese constitution guarantees the right to maintain ‘the minimum’ standard of living, we have provided ‘optimum’ medical care for everyone. It is highly unlikely that we can go on as we have, due, alas, to a lack of money.

**Proportions of patients who receive high-cost treatments**



**Figure 1.** Proportions of patients who receive treatments at monthly costs of 500 000 JPY and 1 000 000 JPY, according to tumor type.

What can we do? To be honest with you, we do not know. Then what should we do? First, we need to understand the situation for what it is. We physicians did not care about money and tried to ignore inconvenient truths. However, understanding ourselves and understanding what we are doing is the first step to we need to take. How much money do we spend on the care of our patients? Unfortunately, we are no longer living in a world where every expense can be justified in the name of ‘patient care’. We need to look at how we can curb this excessive use of resources. But first, we have to understand what we are actually doing.

In a series of articles accompanying this Editorial, nine subgroups of the Japan Cooperative Oncology Group (JCOG) conducted investigations on first-line treatment selections during 2021–2022 and their associated costs in a total of 17 cancer types (4–12). A total of 15 564 patients (29% of them are aged 75 years old or more) were surveyed in probably one of the largest surveys of this kind in the 2020s and certainly the first ever in Japan. Although there are substantial variations according to each specific cancer, we could observe several common features from the data.

First, the monthly cost is high both in absolute and relative terms. Among the 17 tumor types, a median of 59% of the patients (1QR: 44% to 3QR: 87%) received treatments with monthly costs of 500 000 JPY or more. A total of 17% of the patients received treatments with monthly costs of 1 000 000 JPY or more (Fig. 1). As compared to conventional chemotherapy, which was the standard of care 10–15 years ago, there were 10- to 50-fold cost increases.

Elderly patients received high-cost treatments less frequently, although this was apparently due to concerns over toxicities rather than cost. In fact, high-cost regimens such as nivolumab +

ipilimumab in non-small cell lung cancers (7) or nivolumab/pembrolizumab in head and neck cancers (12) are more frequently used in patients of 75 years or older.

Some 'effective' drugs such as androgen receptor signaling inhibitors for prostate cancer and CDK4/6 inhibitors for breast cancer are used for extended periods, because of longer progression-free survival, leading to high total (not only monthly) costs (4,11). This kind of phenomenon was previously reported on pertuzumab, an anti-HER2 antibody (13).

The 'benefits' of the high-cost treatments were highly variable. It could be substantial (such as EGFR-TKIs in EGFR-mutated non-small cell lung cancer), marginal [such as nivolumab to gastric cancer (8)], or nonexistent [such as bevacizumab to glioblastoma (11)]. In most of the cases, lack of adequate benefit does not affect the drug price, since it is the result of an indication-extension trial, and the price had already been determined at the original indication approval.

Oftentimes, more than one drugs of the same class are available. This includes androgen receptor signaling inhibitors for prostate cancer (4), ICIs and TKIs for renal cell carcinoma (4), ICIs for hepatocellular carcinoma (6), ICIs, TKIs and anti-vascular-endothelial growth factor antibodies for lung cancers (7), CDK4/6 inhibitors for breast cancer (10,14) and anti-EGFR and anti-VEGR antibodies in colon cancer (9). Drug prices can vary greatly among the same class, despite exhibiting the same efficacy and toxicities. This again is mainly a result of an indication-extension trial and the price having already been determined at the time of the original indication approval. For example, both ramucirumab and bevacizumab are available for second-line treatments for colorectal cancers, with almost identical efficacy and toxicities, but ramucirumab is many times more expensive than bevacizumab (15–17). The use of ramucirumab in colorectal cancers is strongly discouraged in the literature (15,16), with the speculation that the pharmaceutical company wants to maintain the high price for the lead indication of gastric cancer (17).

We all sense that cancer care is unsustainable and soon to become unaffordable, but there is no easy way out. We are very reluctant to discuss cost-effectiveness. For example, suppose you find a report that the incremental cost-effectiveness ratio for the treatment you are going to give to your patient is 500 000 US dollars per quality-adjusted life year, far exceeding the willing-to-pay threshold of any country, including Japan. But could you 'abandon' the patient, just because it is too expensive? Could you explain this to your patient? Human life is 'priceless', isn't it? How can we balance our duties to patients versus society? (18,19) In addition, cost-effectiveness analyses reports are not reliable. Industry-sponsored studies are far more likely to give 'cost-effective' reports (20). What can we believe?

Still, there should be something we could do, or at least something we could start with. For example, we could move away from the idea of 'care at any cost' and stop using expensive drugs, which provide no clear additional benefit. This can be done without any discussion on cost-effectiveness, since there is no (additional) 'effectiveness'. These drugs include bevacizumab for glioblastoma [as one of the JCOG reports pointed out (11)], or ramucirumab for colorectal cancer (15–17). Ramucirumab can be substituted with bevacizumab, or even better, by bevacizumab biosimilar, which is a much less expensive alternative, without any compromise in efficacy.

As a next step, perhaps we could initiate some discussions. Panitumumab and cetuximab, both anti-EGFR antibodies, are used in Ras sarcoma virus (RAS)-wild colorectal cancer, with similar efficacies (9). Panitumumab is double the price of cetuximab. The only difference appears to be that panitumumab is administered

bi-weekly, whereas cetuximab is given weekly. Does this difference, which amounts to a matter of convenience for the patients, justify the huge increase in cost? Or simply, how about giving cetuximab bi-weekly? We have talked about efficacy, toxicity and convenience. It is time to add cost to our list of discussion points.

Last but not the least, we should perform more and more research on treatment optimization. The dosage of modern cancer drugs might be suboptimally determined, by adopting classic dose-increase studies with cytotoxic agents (21). Food and Drug Administration (FDA) has launched an initiative, Project Optimus, to reform the dose optimization and dose selection paradigm (<https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus>). In addition to dose reduction, many trials evaluate de-escalation strategies, including shortened duration, longer intervals and more (21–26). Some studies have been launched in Japan, including those conducted at JCOG (27).

Life is priceless. But our resources are limited. We have to use the limited resources wisely to treat our patients who are all mortal. We used to believe that it was not our responsibility to think about cost, resources, affordability and sustainability. In fact, it is. If we are to avoid the collapse of the Japanese Health Insurance System, we need to start thinking seriously about medical costs. We hope you can agree on this.

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Dr Kunitoh is the Editor-in-Chief, and Dr Kakizoe is the Emeritus Editor-in-Chief of JCO.

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## Clinical Trial Note

# Multi-institutional study of osimertinib dose-optimization in non-small cell lung cancer patients with EGFR activating mutation aged 70 years or older ('MONEY' trial)

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## Abstract

Osimertinib is the standard of care for patients with epidermal growth factor receptor-activating mutation-positive non-small cell lung cancer. Dose-toxicity has been previously reported, but no dose–response data within the range of 20–240 mg daily (mg/d). Thus, the current 80 mg/d dosing might be too high for elderly Japanese patients with an average body weight of only 50 kg, resulting in excessive toxicity and cost. We therefore initiated a study to investigate whether osimertinib at 40 mg/d is non-inferior to 80 mg/d in patients with advanced or recurrent epidermal growth factor receptor-activating mutation-positive non-small cell lung cancer aged  $\geq 70$  years, using a regression discontinuity design. Osimertinib is administered at 40 mg/d for body weight  $\leq 50$  kg, and 80 mg/d for body weight  $> 50$  kg. The primary endpoint is progression-free survival. Sample size is 550 patients, based on a non-inferiority margin of the progression-free survival hazard ratio 1.333, 0.10 one-sided type I error and 80% power.

**Key words:** osimertinib, dose-optimization, non-small cell lung cancer, epidermal growth factor receptor activating mutation, regression discontinuity design

## Introduction

The cost of medical care in Japan is rising steadily, and the sustainability of the healthcare insurance system is a concern (1). In particular, insurance reimbursement for high-cost drugs such as immune checkpoint inhibitors and molecular-targeted drugs is having a significant impact.

Osimertinib, with the fourth highest sales of pharmaceuticals in Japan in 2022 (2), is the standard of care for patients with epidermal growth factor receptor-activating mutation-positive (EGFRm+) non-small cell lung cancer (NSCLC). In the FLAURA trial comparing osimertinib to first-generation EGFR-TKIs, median progression-free survival (PFS) and overall survival (OS) were significantly prolonged with osimertinib relative to first-generation EGFR-TKIs (PFS: 13.9 vs. 10.2 months, OS: 36.8 vs. 31.8 months) (3,4). Furthermore, osimertinib was associated with a lower incidence of skin rash, diarrhoea and liver dysfunction adverse events compared with first- and second-generation EGFR-TKIs, although interstitial lung diseases (ILD) are a concern (5). Therefore, osimertinib is actively administered to elderly patients who would not be suitable for cytotoxic anti-cancer drugs. Since osimertinib was recently approved for 3-year adjuvant therapy (6), further increases in prescriptions are expected in the near future.

Dosage setting in the development of anti-cancer drugs, even for drugs with novel mechanisms of action, is based on conventional escalation studies and maximum tolerated doses. However, this approach could result in excessive dosing of molecular targeted agents such as osimertinib. In Phase I/II study (AURA trial) for NSCLC harbouring EGFRm with disease progression previously treated with EGFR-TKI (7), response rates of osimertinib were similar for 20, 40, 80, 160 and 240 mg daily doses. Regarding safety, adverse events leading to discontinuation were reported in 11.5% of patients on 40 mg daily and 22.7% for 80 mg daily. Furthermore, a pharmacokinetic study analyzing a total of 780 patients from the AURA trial, the AURA2 trial and healthy volunteers showed no evidence of a relationship between osimertinib exposure and probability of objective response, duration of response or best percentage change in target lesion size. However, it showed a linear relationship between exposure and the occurrence of rash or diarrhoea (8). These results suggest that the efficacy of 40 and 80 mg daily is likely to be equivalent, but that toxicity is lower at 40 mg. Although we were unable to find any papers specifically addressing differences in osimertinib toxicity according to patients' body weights (BW), it would be natural to presume that the body size of the patient would be associated with osimertinib PK. Therefore, patients with low BW would likely derive greater benefit (lower toxicities) from lower doses.

Elderly patients are seldom included in clinical trials for drug development, and therefore conventional dosing may be too high for these patients because of concerns about increased toxicity and decreased quality of life (QOL). A Japanese retrospective study of first-line osimertinib therapy in 132 patients aged  $\geq 75$  years reported that 44 (40.9%) required dose reduction because of adverse events, the most common reasons being fatigue, skin rash and diarrhoea (9). The incidence of ILD was 17.4% with 9.1% of patients having Grade 3 or higher, which was more frequent than in the Japanese population in the FLAURA trial (10). The rate of treatment discontinuation because of adverse events was 26.5%. Median PFS was 19.4 months, with no significant difference between patients with or without dose reduction. That study thus suggested that osimertinib 80 mg daily was more toxic and probably overdosed for elderly patients.

Based on the above rationales, we hypothesize that osimertinib at 40 mg daily instead of the current standard dosing of 80 mg daily might improve risk- and cost-benefits with maintaining efficacy in elderly patients, especially those with a low BW. Efficacy and safety of low starting doses of first- and second-generation EGFR-TKIs have been reported, but these were single arm Phase II trials (11–13). It has not been elucidated whether optimizing the dosage of osimertinib ameliorates toxicities, including financial issues, and improves QOL whilst maintaining efficacy.

The main hypothesis of the present study is that osimertinib 40 mg daily is non-inferior to 80 mg daily in terms of PFS in elderly patients with low BW. A randomized controlled trial to test this hypothesis is not feasible because of the large sample size required and patients' reluctance to be randomized. Furthermore, since the objective of this study is to optimize the dose according to BW, it would be inefficient to uniformly randomize all patients. Therefore, we adopted a regression discontinuity design with BW as the continuous assignment variable. The threshold for treatment decision was 50 kg and the usefulness of osimertinib dose optimization in patients weighing 50 kg or less will be examined.

The Japan Red Cross Medical Center Review Board approved the study protocol in July 2023, and patient enrolment began on 20 September 2023. This study has the potential to contribute to reducing toxicity and improving QOL in elderly patients, as well as reducing the cost of medical care. This trial is necessary to move away from the conventional 'more is better' approach to cancer treatment and to take the first step towards more patient-centred and sustainable cancer treatments in an ageing society.

## Protocol digest of this study

### Objectives

The aim of this study was to investigate whether the efficacy of osimertinib 40 mg daily is non-inferior to conventional 80 mg daily in elderly Japanese patients with EGFRm+ NSCLC, with a small body-size.

### Study design

Regression discontinuity design (14–16), with BW as the assignment variable. The threshold for treatment decision is 50 kg. Those who declined to be assigned by BW are to be treated with conventional dose of 80 mg daily ('fuzzy' regression discontinuity), but would be included in the analysis as allocated. The schema of this study is shown in Fig. 1.

### Endpoints

The primary end-point is PFS, defined as the time from receiving the first dose of osimertinib to the diagnosis of disease progression, death from any cause or the last day of follow-up. The secondary end-points are OS, time to treatment failure (TTF), response rate, adverse events and QOL. OS is defined as the time from receiving the first dose of osimertinib to death from any cause, or the last day of follow-up. TTF is defined as the time from receiving the first dose of osimertinib to the diagnosis of disease progression, death from any cause, discontinuation of the protocol treatment or initiation of post-treatment. If none of the above events occurs, TTF is censored at the last day of follow-up. Response rate is defined as the proportion of complete or partial responses amongst the eligible patients, based on Response Evaluation Criteria in Solid Tumors version 1.1. Safety

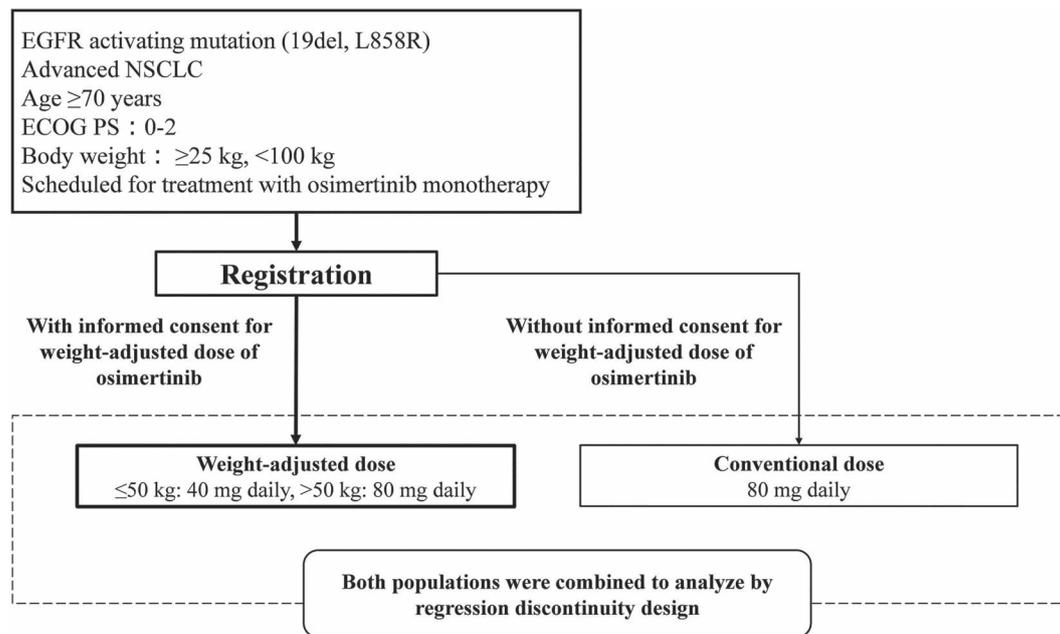


Figure 1. Design of the MONEY trial.

is assessed on the basis of adverse events graded according to the National Cancer Institute-Common Toxicity Criteria version 5.0. QOL is assessed on the basis of EuroQol 5 dimensions 5-level.

### Inclusion criteria

1. Histologically or cytologically confirmed NSCLC.
2. EGFR exon 19 deletion or L858R point mutation-positive (any diagnostic method is acceptable).
3. Clinical Stage IIIB, IIIC without an indication for definitive thoracic radiotherapy, Stage IV or post-operative or post-radiotherapy recurrent disease (the stage will be defined based on the UICC International Union for Tumors Lung Classifications 2017, 8th edition).
4. Patients scheduled for treatment with osimertinib monotherapy.
5. No history of systemic therapy for lung cancer in this study (patients with recurrent disease that worsened during or after adjuvant chemotherapy, excluding EGFR-TKI, can be enrolled).
6. Aged 70 years or older at the time of enrolment.
7. Eastern Cooperative Oncology Group performance status, 0, 1 or 2.
8. BW at least 25 and <100 kg.
9. Patients without measurable lesions are acceptable.
10. No symptomatic brain metastasis, meningeal metastasis or spinal metastasis that requires radiotherapy or surgery.
11. Adequate function of major organs allowing osimertinib treatment.
12. Patients who are currently participating or will participate in other clinical trials or observational studies can participate with permission.
13. Written informed consent.

### Exclusion criteria

1. Infectious disease requiring systemic treatment.
2. ILD on chest computed tomography.
3. History of synchronous or metachronous malignancies that affect the assessment of the primary endpoint.

4. Psychiatric illnesses or symptoms that affect the patient's activities of daily living.
5. Poorly controlled diabetes mellitus, hypertension, congestive heart failure, unstable angina, severe arrhythmia, cerebrovascular disease, etc.
6. Women who are pregnant, possibly pregnant, within 28 days postpartum or breastfeeding.
7. Other ineligible status judged by the attending physician.

### Treatment

Osimertinib monotherapy, with 40 mg daily for those with BW of  $\leq 50$  kg or 80 mg daily for those with BW  $> 50$  kg. Patients who declined to be assigned by BW are to be treated with the conventional dose of 80 mg daily. Osimertinib to be continued until death, disease progression or intolerable toxicity.

### Follow-up

All randomized patients will be followed up for at least 2 years after the completion of patient accrual. Radiographic tumour evaluations are performed and assessed, according to Response Evaluation Criteria in Solid Tumors (version 1.1), by each investigator at least every 12 weeks over the follow-up period.

### Decision rule

If PFS shows no significant discontinuity at the BW 50 kg threshold, osimertinib 40 mg daily would be non-inferior to 80 mg daily and optimal for patients weighting 50 kg or less. Better QOL in the 40 mg group is also anticipated. If non-inferiority is not demonstrated, 80 mg daily dose would remain the standard.

### Statistical considerations

We assume a median PFS of 20 months in both arms and setting a non-inferiority margin at a hazard ratio of 1.333 (ensuring that

the median PFS in the osimertinib 40 mg arm is not shorter than 15 months). Under a 1:1 allocation ratio, an accrual period of 2.5 years, a follow-up period of 2 years, a one-sided significance level of 0.1 and a power of 80%, the required total sample size for a standard randomized controlled trial is 299. Considering the regression discontinuity design, we should multiply the design effect (DE) by the aforementioned sample size of 299. Under the assumption that BW is normally distributed and its median is at the threshold, DE is 1.654 (14). Thus, the required sample size is estimated to be  $299 \times 1.654 = 497$  cases, and we plan to register 550 participants, allowing for a 10% drop-out.

In the analysis of the primary endpoint (PFS), Kaplan–Meier plots will be constructed for each group, and the median survival time and its 95% confidence interval will be calculated. The primary analysis will be conducted fitting a Cox proportional hazards model based on a regression discontinuity design, as follows:

$$b(t) = b_0(t)\exp(\alpha X + \beta Z + \gamma XZ) \tag{A}$$

where  $b(t)$  is a the hazard function at time point  $t$ ,  $b_0(t)$  is the baseline hazard,  $X$  is an indicator variable taking the value 1 for BW to be  $\leq 50$  kg and 0 otherwise.  $Z$  represents the continuous variable of  $\{BW \text{ (kg)} - 50\}$ . The estimate of  $\exp(\alpha)$  is the hazard ratio for the 80 mg group compared with the 40 mg group. The 80% confidence interval for this estimate and the one-sided  $P$  value based on the Wald test with the null hypothesis of a hazard ratio of 1.333 will be computed.

To confirm that the statistical assumptions of the regression discontinuity design are met (15,16), a histogram of BW will be created. Summary statistics for major baseline prognostic factors will be calculated for each group. To assess comparability of two groups at the threshold, we use regression models similar to the model (A) and the balance of prognostic factors at the threshold will be assessed using standardized mean differences (SMDs). Specifically, for each continuous prognostic factor, we use the following linear regression model:

$$E[W|X, Z] = \delta + \alpha X + \beta Z + \gamma XZ \tag{B}$$

where  $W$  is the prognostic factor divided by  $\sqrt{(S_0^2 + S_1^2)}/2$  where  $S_0^2$  and  $S_1^2$  are the standard deviations of  $W$  for the 40 and 80 mg arms, respectively. For each binary prognostic factor, we use the following logistic regression model:logit

$$E[W|X, Z] = \delta + \alpha X + \beta Z + \gamma XZ \tag{C}$$

For model (B), SMD is  $\alpha$ . To calculate SMD for model (C), we define  $p_0$  as  $\text{expit}(\delta)$  and  $p_1$  as  $\text{expit}(\delta + \alpha)$  where  $\text{expit}(k) = 1/(1 + \exp(-k))$ . Then, SMD is calculated by  $(p_1 - p_0) / \sqrt{\{p_1(1 - p_1) + p_0(1 - p_0)\}/2}$ . Similar to models (B and C), categorical factors  $>2$  categories are modelled by multinomial logistic regression and SMDs are calculated using a procedure similar to that of binary factors. For any prognostic factors found to be imbalanced (absolute SMD exceeding 0.25 between groups at the threshold), a post hoc adjusted analysis based on the Cox proportional hazards model will be conducted.

To obtain a valid treatment effect estimate, the assumed model (A) must be correctly specified. As a sensitivity analysis, we also conduct an analysis based on the following Cox model considering possibly

non-linear associations for weight:

$$b(t) = b_0(t)\exp(\alpha X + g_0(Z) + Xg_1(Z))$$

where  $g_0(Z)$  and  $g_1(Z)$  are restricted cubic spline functions whose knots are placed at 0.05, 0.50, 0.95 percentiles for each group.

In the main analysis, we will classify those who declined to the assigned treatment as allocated according to the intention-to-treat (ITT) principle. However, ITT analysis tends to be anti-conservative in demonstrating non-inferiority. Thus, an additional per-protocol analysis will also be conducted.

### Interim analysis and monitoring

All statistical analyses will be conducted at the Department of Health Data Science, Tokyo Medical University. Periodic monitoring will be performed every year by the steering committee to evaluate study progress and to improve the quality of the data. Although no formal interim analysis is planned for this study, the steering committee evaluates the accrual rate, BW distribution, patients' consent status and clinical response to the therapy according to the dose at registration of 100 patients to confirm the feasibility and validity of the study.

### Participant institutions (from north to south)

National Hospital Organization Hokkaido Cancer Center, Akita Kousei Medical Center, Yamagata Prefectural Central Hospital, Tohoku University Graduate School of Medicine, Niigata Cancer Center Hospital, University of Tsukuba Hospital, Tochigi Cancer Center, Dokkyo Medical University Hospital, Gunma Prefectural Cancer Center, National Hospital Organization Shibukawa Medical Center, Kasukabe Medical Center, National Cancer Center Hospital, Toranomon Hospital, Tokyo Saiseikai Central Hospital, Nippon Medical School Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, NTT Medical Center Tokyo, Showa University Hospital, Toho University Omori Medical Center, Japan Red Cross Medical Center, Tokyo Medical University Hospital, Center Hospital of the National Center for Global Health and Medicine, Tokyo Metropolitan Police Hospital, Kyorin University Hospital, Tokai University Hachioji Hospital, Yokohama Municipal Citizen's Hospital, Kanagawa Cancer Center, Fujisawa City Hospital, Kurobe City Hospital, Kanazawa University Hospital, Shinshu University Hospital, Gifu Municipal Hospital, Hamamatsu University Hospital, Nagoya University Hospital, Kansai Electric Power Hospital, Osaka Medical and Pharmaceutical University Hospital, Kansai Medical University Hospital, Hyogo Prefectural Amagasaki General Medical Center, Tottori University Hospital, Okayama University Hospital, Fukuyama City Hospital, Hiroshima Prefectural Hospital, Hiroshima University Hospital, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, National Hospital Organization Shikoku Cancer Center, Ehime University Hospital, Saiseikai Imabari Hospital, National Hospital Organization Kyushu Medical Center, Shin Koga Hospital, Nagasaki University Hospital, National Hospital Organization Okinawa National Hospital.

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## Conflict of interest statement

Yoko Tsukita reports honoraria from AstraZeneca, Taiho Pharmaceutical, Eli Lilly, MSD, Eisai, Chugai Pharmaceutical, Daiichi Sankyo, Bristol-Myers Squibb and Nippon Boehringer Ingelheim outside the submitted work. Yasushi Goto reports grants to institution from Abbvie, Eli Lilly, Pfizer, Bristol Myers Squibb, Ono Pharmaceutical, Novartis, Kyorin, DaiichiSankyo, Novartis and Preferred Network; honoraria and participation on advisory board of Eli Lilly, Chugai, Taiho Pharmaceutical, Boehringer Ingelheim, Ono Pharmaceutical, Bristol Myers Squibb, Pfizer, MSD and Novartis; honoraria from Merck and Thermo Fischer; participation on advisory board of AstraZeneca, Guardant Health Inc., Illumina and DaiichiSankyo; Leadership of Cancer Net Japan, JAMT outside the submitted work. Yukio Hosomi reports honoraria from AstraZeneca, Eli Lilly Japan, Taiho Pharmaceutical, Chugai Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Kyowa Kirin, Nippon Kayaku, Takeda, Eisai, Novartis and Pfizer outside the submitted work. Tomonori Mizutani reports honoraria from Chugai Pharmaceutical and AstraZeneca outside the submitted work. Kageaki Watanabe reports Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Merck Biopharma, MSD, Novartis Pharma, Ono Pharmaceutical, Riken Genesis, Sysmex Corporation and Takeda Pharmaceutical outside the submitted work. Kiyotaka Yoh reports grants to institution from Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Lilly, MSD, Pfizer, Taiho and Takeda; consulting fees from Boehringer Ingelheim; honoraria from Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Janssen, Kyowa Kirin, Lilly, Merck Serono, Novartis, Ono, Otsuka, Taiho and Takeda outside the submitted work. Satoshi Takahashi reports honoraria from AstraZeneca, Bristol Myers Squibb Japan, Chugai Pharma, Kyowa Kirin, Lilly Japan, MSD, Nippon Kayaku, Taiho Pharmaceutical and Takeda outside the submitted work. Kaoru Kubota reports honoraria from Taiho Pharmaceutical, Ono Pharmaceutical, Chugai Pharmaceutical, AstraZeneca, Pfizer, Shionogi, Nihon Kayaku, Kyowa Kirin, Boehringer Ingelheim, Eli Lilly, Bristol-Meyers Squibb, Sawai, Takeda, Merck and Novartis; leadership of Japan Association of Medical Translation outside the submitted work. Hideo Kunitoh reports consulting fees from Daiichi-Sankyo; honoraria from Taiho Pharmaceutical, Daiichi-Sankyo, MSD, Johnson & Johnson and AstraZeneca outside the submitted work.

## Registration number

This trial has been registered in the UMIN Clinical Trials Registry as UMIN000038683.

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医療保障総合政策調査・研究基金事業  
高額医薬品の適正使用の推進のための調査研究  
報告書

令和7年3月

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