Cost-Effectiveness of Paclitaxel + Ramucirumab Combination Therapy for Advanced Gastric Cancer Progressing After First-Line Chemotherapy in Japan

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ABSTRACT

Purpose: The combination of paclitaxel + ramucirumab is a standard second-line treatment in patients with advanced gastric cancer. This therapy has been associated with increased median overall survival and progression-free survival compared with those with paclitaxel monotherapy. We evaluated the cost-effectiveness of paclitaxel + ramucirumab combination therapy in patients with advanced gastric cancer, from the perspective of health care payers in Japan.

Methods: We constructed a Markov model to compare, over a time horizon of 3 years, the costs and effectiveness of the combination of paclitaxel + ramucirumab and paclitaxel alone as second-line therapies for advanced gastric cancer in Japan. Health outcomes were measured in life-years (LYs) and quality-adjusted (QA) LYs gained. Costs were calculated using year-2016 Japanese yen (¥1 = US $17.79) according to the social insurance reimbursement schedule and drug tariff of the fee-for-service system in Japan. Model robustness was addressed through 1-way and probabilistic sensitivity analyses. The costs and QALYs were discounted at a rate of 2% per year. The willingness-to-pay threshold was set at the World Health Organization's criterion of ¥12 million, because no consensus exists regarding the threshold for acceptable cost per QALY ratios in Japan's health policy.

Findings: Paclitaxel + ramucirumab combination therapy was estimated to provide an additional 0.09 QALYs (0.10 LYs) at a cost of ¥3,870,077, resulting in an incremental cost-effectiveness ratio of ¥43,010,248/QALY. The incremental cost-effectiveness ratio for the combination therapy was >¥12 million/QALY in all of the 1-way and probabilistic sensitivity analyses.

Implications: Adding ramucirumab to a regimen of paclitaxel in the second-line treatment of advanced gastric cancer is expected to provide a minimal incremental benefit at a high incremental cost per QALY. Based on our findings, adjustments in the price of ramucirumab, as well as improves in other clinical parameters such as survival time and adverse event in advanced gastric cancer therapy, are needed. (*Clin Ther*. 2017;▮:▮▮▮–▮▮▮)

Key words: cost-effectiveness, gastric cancer, Markov model, paclitaxel, ramucirumab.

INTRODUCTION

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer-related mortality worldwide.[1] In Japan, gastric cancer is the leading cause of death, based on a sample of >50,000 deaths in 2010.[2] Furthermore, according to the Survey of National Medical Care Insurance Services, medical expenses arising from gastric cancer treatment accounted for ~10% of the medical expenses for all cancers in 2009.[3] Thus, gastric cancer is an important health economic issue in Japan.

Although surgery is the most efficient treatment of operable cancer, recurrence may result in cases with

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poor prognoses. As an important component of therapy for resectable gastric cancer, adjuvant chemotherapy may improve patient outcomes.[4,5] According to the Japanese Gastric Cancer Association's 2014 gastric cancer treatment guideline,[6] both capecitabine + oxaliplatin and S-1 are recommended as adjuvant treatments of gastric cancer. Despite treatment, many patients experience disease progression or recurrence. In the majority of patients in Japan, disease progresses within 6 months following first-line chemotherapy, and many patients remain candidates for second-line chemotherapy.[7] However, there are few treatment options after the failure of first-line therapy.[8]

Recently, targeted therapies have been developed to provide alternative treatment options for gastric cancer. Ramucirumab is a fully human immunoglobulin G_1 monoclonal antibody against vascular endothelial growth factor (VEGF) receptor 2. Working as a receptor antagonist, ramucirumab prevents ligand binding and receptor-mediated pathway activation in endothelial cells. VEGF- and VEGF receptor 2–mediated signaling and angiogenesis seem to play an important role in the pathogenesis of gastric cancer. In patients with gastric cancer, higher circulating and tumor concentrations of VEGF are associated with increased tumor aggressiveness and reduced survival.[9]

Paclitaxel + ramucirumab combination therapy has been shown to be more effective than paclitaxel monotherapy in treating patients with advanced gastric cancer progressing at 4 months after first-line chemotherapy. A randomized clinical trial conducted by Wilke et al,[10] the RAINBOW (Paclitaxel Plus Ramucirumab Versus Placebo Plus Paclitaxel in Patients With Previously Treated Advanced Gastric or Gastro-Oesophageal Junction Adenocarcinoma) trial, involving 665 adult patients with advanced gastric or gastroesophageal junction cancer, demonstrated that, compared with paclitaxel alone, paclitaxel + ramucirumab combination therapy was associated with significantly increased progression-free survival (PFS; median, 4.4 vs 2.9 months) and overall survival (OS; median, 9.6 vs 7.4 months). Wilke et al[10] concluded that this combination could be regarded as a new standard second-line treatment in patients with advanced gastric cancer.

However, ramucirumab therapy markedly increases the cost of the entire treatment process for gastric cancer. To this point, no study has examined the cost-effectiveness of paclitaxel + ramucirumab combination therapy in Japan. The aim of this study was to evaluate the cost-effectiveness of paclitaxel + ramucirumab combination therapy for advanced gastric cancer progressing after first-line chemotherapy from the perspective of health care payers in Japan.

MATERIALS AND METHODS

Target Population and Treatment Strategies

We compared the cost-effectiveness of 2 treatment strategies from the perspective of health care payers (patients, health insurers, and the government) in Japan:

Strategy 1: Paclitaxel + Ramucirumab Combination Therapy

Patients received paclitaxel 80 mg/m^2 IV on days 1, 8, and 15, and ramucirumab 8 mg/kg IV on days 1 and 15, of a 28-day cycle.

Strategy 2: Paclitaxel Monotherapy

Patients received paclitaxel 80 mg/m^2 IV on days 1, 8, and 15 of a 28-day cycle.

Analyses

For this analysis, the Markov model consisted of a hypothetical cohort of 60-year-old men weighing 65 kg, with a body surface area of 1.72 m^2, who had advanced gastric cancer progressing after first-line chemotherapy with S-1 + cisplatin for *HER2*-negative gastric cancer, and capecitabine + cisplatin and trastuzumab for *HER2*-positive gastric cancer. With both strategies, third-line therapy was assumed to be irinotecan, and the rate of third-line therapy was assumed to be 0.5 based on data from the RAINBOW study.[10] With each treatment, patients were treated until progression.

Disease Modeling

For the analysis, we constructed a Markov model including 3 health states: PFS, disease progression, and death (Figure 1). Patients move from 1 state to another during each cycle duration of 1 month. The time horizon of 3 years was adopted to reflect the limited remaining life of the patients. Weibull curves were extrapolated to fit to Kaplan–Meier survival curves. The scale (λ) and shape (γ) parameters were determined using the method for estimating the underlying survival distribution from a Kaplan-Meier graph.[10,11] These parameters were used for measuring the probability of transition during cycle *t*, according to

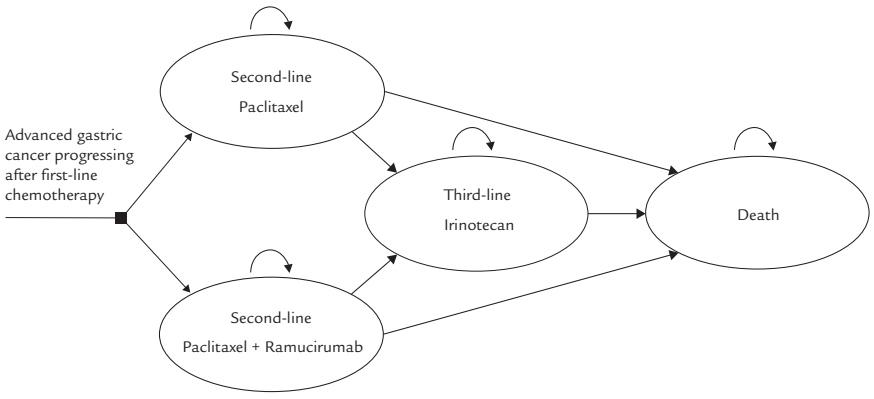

Figure 1. Markov model for cost-effectiveness analysis.

the formula $P(t) = 1 - \exp[\lambda(t-1)^{\gamma} - \lambda t^{\gamma}]$.[12] The fitted Weibull curves are provided in Figure 2.

OS is a clinical parameter that includes death unrelated to gastric cancer. Therefore, we did not include background mortality in the simulation.

Costs

Costs were estimated from the health care payer's perspective; therefore, only direct medical costs were included. The medical costs considered in this model included drugs and outpatient chemotherapy (Table I). The drug costs of ramucirumab and paclitaxel were calculated based on the assumed body weight (65 kg) and body surface area (1.72 m^2). The costs related to outpatient chemotherapy included the outpatient service fee, the IV drip fee, laboratory testing, and diagnostic imaging. The costs of terminal and best supportive care were expected to be similar with both strategies, so they were not included in this analysis. Costs were calculated using year-2016 Japanese yen (¥1 = US $17.79) according to the social insurance reimbursement schedule and drug tariff of the fee-for-service system in Japan, which excludes inpatient treatment at large hospitals.[13,14]

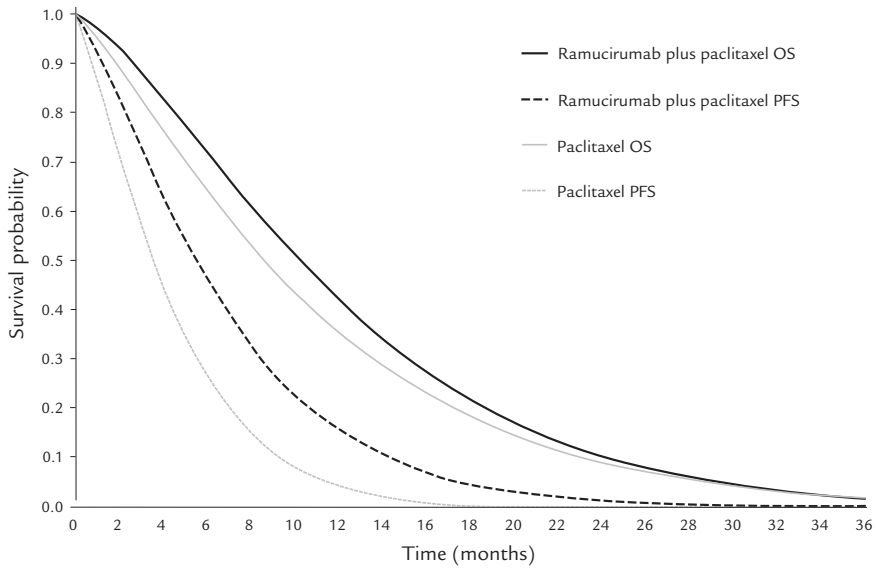

Figure 2. Estimated Weibull survival curve. OS = overall survival; PFS = progression-free survival.

Table I. Cost and number of applications of health care services. Data are given per annum.

		Paclitaxel + Ramucirumab		Paclitaxel		Irinotecan	
Parameter	Unit Cost, ¥	n	Price, ¥	n	Price, ¥	n	Price, ¥
Drug cost							
Ramucirumab 100 mg 5.2 V	391,378	16	6,262,048	–	–	–	–
Paclitaxel 100 mg 1.4 V	30,899	15	463,491	15	463,491	–	–
Irinotecan 40 mg 7 V	28,714	–	–	–	–	27	775,278
Granisetron hydrochloride 1 mg 1 A	1,485	–	–	–	–	27	40,095
Dexamethasone 6.6 mg 1 V	335	16	5,360	15	5,025	27	9,045
Famotidine 20 mg 1 A	232	16	3,712	15	3,480	–	–
Sodium chloride 50 mL	220	31	6,820	15	3,300	27	5,940
Dexamethasone 4 mg 4 T	143	–	–	–	–	27	3,866
Sodium chloride 250 mL	130	31	4,030	15	1,950	27	3,510
Diphenhydramine hydrochloride 10 mg 1 T	29	16	464	15	435	–	–
Outpatient chemotherapy							
CT scan with contrast medium	15,900	0.5	7,950	0.5	7,950	0.5	7,950
Contrast medium	9,500	0.5	4,750	0.5	4,750	0.5	4,750
IV drip fee	7,250	16	116,000	15	108,750	27	195,750
CT scan diagnostic fee	4,500	0.5	2,250	0.5	2,250	0.5	2,250
Administration fee for chemotherapy	4,000	12	48,000	12	48,000	12	48,000
Laboratory test fee	2,010	16	32,160	15	30,150	27	54,270
Biochemical test diagnostic fee	1,440	12	17,280	12	17,280	12	17,280
Immunology test diagnostic fee	1,440	12	17,280	12	17,280	12	17,280
Blood test diagnostic fee	1,250	12	15,000	12	15,000	12	15,000
Outpatient service fee	730	16	11,680	15	10,950	27	19,710
Prescription fee	420	–	–	–	–	27	11,340
Laboratory test administration fee	400	12	4,800	12	4,800	12	4,800
Total cost per annum	–	–	7,023,075	–	744,841	–	1,236,114
Total cost per patient cycle (mo)	–	–	585,256	–	62,070	–	103,010

A = Ampule; T = Tablet; V = Vial.

Health-Related Utility

The primary measures of effectiveness in the present analysis were life-years (LYs) and quality-adjusted (QA) LYs gained. To estimate the total QALYs in the Markov model, survival time was adjusted by health-related quality of life. We used previously published mean utility values of 0.741 and 0.581 in patients with PFS and progressive disease, respectively.[15,16]

Cost-Effectiveness Analysis

Cost-effectiveness was evaluated using the incremental cost-effectiveness ratio (ICER)—the ratio between cost increments and QALY increments. In this analysis, the willingness-to-pay (WTP) threshold was set at ¥12 million/QALY gained based on a recent recommendation from the World Health Organization.[17] In this approach, the WTP threshold is calculated as 3-fold the national annual gross domestic product per capita. We performed a base-case analysis that incorporated the baseline parameters. The costs and QALYs were discounted at a rate of 2% per annum in the base-case analysis, based on the Guideline for the Economic Evaluation of Healthcare Technologies in Japan.[18]

Sensitivity Analysis

Several sensitivity analyses were performed to evaluate the uncertainty and robustness of the model. For these sensitivity analyses, we selected the parameters to cover all potential areas of uncertainty, such as the survival curves for PFS and OS, drug costs, and health-related utility values. One-way sensitivity analyses assessed the effects of varying key model parameters on the ICER. Drug costs were varied within a range of ±20%, except for the cost of subsequent therapy, which was varied by ±50% because of the high variability of this cost. Utility values were varied within a range of ±10%. The rate of third-line therapy was fluctuated from 0.25 to 0.75, and the discount rate was varied from 0.00 to 0.05.

A probabilistic sensitivity analysis was also performed to assess the impact of sensitivity on the model parameters using Monte Carlo simulation with 10,000 samples. We used the standard normal distribution for the Weibull parameters, the γ distribution for the cost parameters, the β distribution for the utility parameters, and the triangle distribution for the rate of third-line therapy. For each run of the simulation, input values for the parameters were drawn at random from appropriate distributions. The Weibull parameters of the curves for PFS and OS were generated using the Cholesky decomposition.

Additionally, a threshold analysis was performed to determine the cost-effectiveness price of ramucirumab when WTP is ¥12 million. All of the analyses were performed using TreeAge Pro software version 2016 (TreeAge, Williamstown, Massachusetts).

RESULTS

Base-Case Results

The base-case model results are presented in Table II. Compared with paclitaxel monotherapy, paclitaxel + ramucirumab combination therapy was associated with a gain of 5 weeks of life (0.10 LY). When adjusted for quality of life, paclitaxel + ramucirumab combination therapy was associated with a gain of 0.09 QALY. The incremental cost of paclitaxel + ramucirumab combination therapy was ¥3,870,077 in 3 years. Therefore, the ICER for paclitaxel + ramucirumab combination therapy compared with paclitaxel monotherapy was ¥43,010,248/QALY.

Sensitivity

The results of the 1-way sensitivity analyses are presented in a tornado diagram (Figure 3). The parameters with the greatest influence on the ICER were the cost of ramucirumab and the utility value for PFS. Across broad variations in the values of each parameter, the ICER remained >¥12 million/QALY. The cost of paclitaxel and the cost of post-progression care had minor influences on the ICER.

The results of the probabilistic sensitivity analyses are shown in the cost-effectiveness acceptability curve in Figure 4. The curve shows the probability that paclitaxel + ramucirumab combination therapy would be cost-effective with increasing values of WTP. These results demonstrated a probability near 0% that paclitaxel + ramucirumab combination therapy is cost-effective at WTP values of <¥12 million/QALY gained. There was an 80% probability that paclitaxel + ramucirumab combination therapy would be cost-effective at a WTP threshold of ~¥50 million/QALY.

The results of the threshold analysis are shown in Figure 5. The estimated threshold value of ramucirumab was ¥22,866 per 100 mg when paclitaxel + ramucirumab combination therapy was compared with paclitaxel monotherapy in the base case.

Table II. Base-case results.

Strategy	Total Cost, ¥	LYs	QALYs
Paclitaxel	621,913	0.92	0.60
Paclitaxel + ramucirumab	4,491,989	1.03	0.69
Treatment difference	+3,870,077	+0.10	+0.09
Paclitaxel + ramucirumab ICER, ¥	–	37,322,767	43,010,248

ICER = incremental cost-effectiveness ratio, LY = life-years gained, QALY = quality-adjusted life-years gained

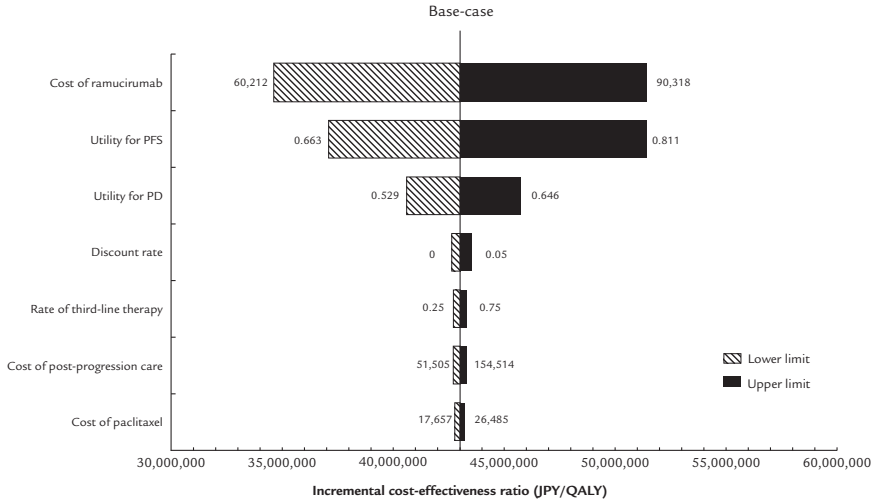

Figure 3. Tornado diagram for 1-way sensitivity analyses. JPY = Japanese yen; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-years gained.

DISCUSSION

We performed a cost-effectiveness analysis of ramucirumab added to a regimen of paclitaxel therapy for advanced gastric cancer. The combination therapy provided modest incremental benefits at high incremental costs per QALY. In the best-case scenario for the most sensitive variable in the 1-way sensitivity analyses, the ICER remained >¥12 million/QALY gained. The probabilistic sensitivity analyses revealed that the probability of paclitaxel + ramucirumab combination therapy being cost-effective was 0% at a WTP threshold of ¥30 million/QALY. The findings from this uncertainty analysis suggest a high likelihood that ramucirumab exceeds the usually accepted value of cost-effective incremental costs of treatment.

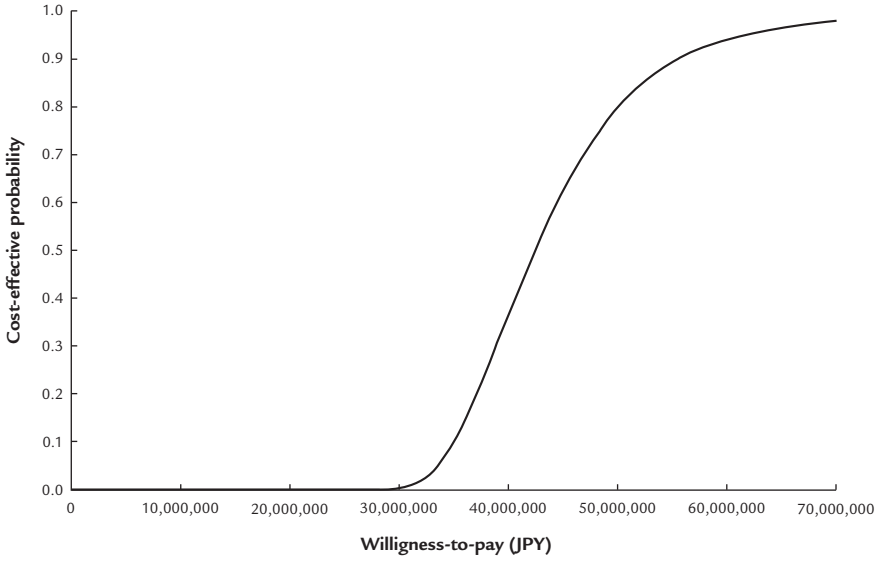

Figure 4. Cost-effectiveness acceptability curve for probabilistic sensitivity analyses.

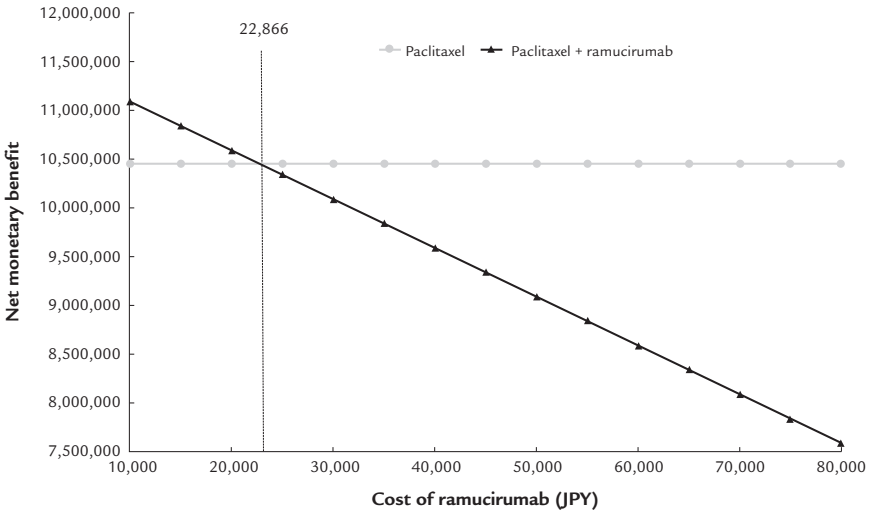

Figure 5. Results of the threshold analysis for the cost of ramucirumab.

In the era of precision medicine, the needs of patients with advanced gastric cancer or other malignancies warrant the development of new therapeutic technologies. However, with the dramatic rises in drug prices in the past several decades, the use of new treatments should be tailored to those patients who are likely to benefit.

A previous study analyzed the cost-effectiveness of ramucirumab for advanced gastric cancer in different settings.[16] In that study, from the United Kingdom, the estimated year-2015 ICER of the combination of ramucirumab and paclitaxel was £273,657 to £392,108, and the investigators did not recommend ramucirumab alone or with paclitaxel for advanced gastric cancer previously treated with chemotherapy. However, evidence from that study may not be applicable to the population in Japan, given the differences in epidemiologic characteristics and in the health care systems.

No consensus exists regarding the threshold for acceptable cost per QALY ratios in Japan's health policy. Therefore, we adopted the World Health Organization's criterion: An intervention is considered cost-effective if the ICER for QALY is 1- to 3-fold the gross domestic product per capita. Based on this standard, we concluded that paclitaxel + ramucirumab combination therapy would not be cost-effective for treating advanced gastric cancer in Japan.[17] This conclusion is considered robust based on the results from our sensitivity analyses. Using the results of the threshold analysis, the acceptable price of ramucirumab was estimated at ¥22,866 per 100 mg. This price is ~30% of the current price of ¥75,265 per 100 mg. Therefore, a price reduction would be necessary for ramucirumab to be considered cost-effective by commonly applied thresholds.

The RAINBOW study[10] reported that the prevalences of grade 3 or 4 adverse events were higher with paclitaxel + ramucirumab combination therapy. These adverse events included grade 3 or 4 neutropenia and leucopenia, as well as grade 3 hypertension, abdominal pain, and fatigue. However, we did not include additional costs or disutility related to adverse events in our model, because the impact of these factors on the ICER was considered slight and there were no available data. There were also no available data on health-related utility scores or health care resource utilization after progression in Japan. Although we performed sensitivity analyses to evaluate the influence of uncertain parameters on our results, this is a limitation of our study.

Shitara et al[19] compared the outcomes of patients from Japan versus the West using data from the RAINBOW study. They concluded that tolerability and PFS were seen in both populations. However, they reported that the rate of post-discontinuation therapy was higher in the population from Japan (75.0%) than in the population from the West (37.2%). Additionally, a greater percentage of patients in the population from Japan than in the population from

the West received fourth-line therapy or subsequent lines of therapy. The 6-month survival rate was 94.1% with combination therapy versus 71.4% with paclitaxel monotherapy in the population from Japan. In the population from the West, these rates were 66.0% and 49.0%, respectively. The differences between patient characteristics may have contributed to the longer OS in the patients from Japan.

Several studies have attempted to estimate the cost-effectiveness of treatments in patients with gastric cancer in Japan.[20,21] Shiroiwa et al[20] estimated the cost-effectiveness of trastuzumab + chemotherapy for human epidermal growth factor 2–positive advanced gastric cancer based on data from the ToGA trial (Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer).[22] They found that, in comparison with chemotherapy alone, trastuzumab + chemotherapy was cost-effective for the subgroup with immunohistochemistry analysis scores of 3+. Hisashige et al[21] found that adjuvant S-1 therapy for curatively resected gastric cancer is likely cost-effective and concluded that this therapy can be accepted for wide use in Japan.

In 2014, the revised version of the Japanese Gastric Cancer Association's guideline on the treatment of gastric cancers was released. This guideline recommends paclitaxel + ramucirumab combination therapy as a standard second-line regimen for advanced gastric cancer. The prevalence of gastric cancer is higher in Japan than in the United States or Europe.[23] In our view, the use of chemotherapy with ramucirumab for advanced gastric cancer could cause increasing medical expenses in Japan in the near future.

In the current environment, costly drugs face few barriers to being introduced into health insurance and adopted by physicians. In February 2017, as a special case, the price of nivolumab, which is used for treating non–small cell lung cancer and malignant melanoma, was slashed in half (from ¥729,849 to ¥364,925 per 100 mg) by Japan's government, because national health financing was being burdened by the consumption of the drug.

The processes of new drug approval and price revision based on cost-effectiveness will be introduced into Japan's health care system by the Ministry of Health, Labour and Welfare in 2018. Data from the present study provide a starting point for discussing this process.

The proper pricing of expensive drugs based on cost-effectiveness is an important health problem in Japan. Based on our findings, Japan's government may need to adjust the price of ramucirumab, as well as other clinical interventions, in advanced gastric cancer therapy.

CONCLUSIONS

Our study demonstrates the high incremental cost and low incremental benefit of paclitaxel + ramucirumab combination therapy. Therefore, paclitaxel + ramucirumab combination therapy appears not to be a cost-effective therapy for advanced gastric cancer in Japan. The economic burden of advanced gastric cancer is significant in Japan. Future economic evaluations of advanced gastric cancer need to include the indirect costs to society of this combination therapy.

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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