

Cost-Effectiveness of Avelumab Maintenance Therapy for
Advanced or Metastatic Urothelial Carcinoma in Japan

by

Hiroyuki Hata

21MP207

Master's Capstone Report submitted in partial satisfaction of the

requirements for the degree of

Master of Public Health

at

St. Luke's International University

Graduate School of Public Health

Supervisor: Prof. Sachiko Ohde

13/JAN/2023

Abstract

Background: The late stage of Urothelial Carcinoma (UC) has no other effective treatment than the old type of chemotherapies (standard chemotherapy) such as Cisplatin + Cyclophosphamide + Doxorubicin (CISCA) therapy and Gemcitabine + Cisplatin (GC) therapy. In this regard, the effectiveness of the avelumab first-line maintenance therapy was previously assessed by the JAVELIN Bladder 100 (JB100) study, and its cost-effectiveness has been proved in several developed countries. However, it has not been researched in Japan yet. The present analysis assessed the cost-effectiveness of avelumab + Best Supportive Care (BSC) vs. BSC alone in the Japanese healthcare setting.

Methods: A partitioned survival model was applied to investigate the cost-effectiveness of avelumab as a first-line maintenance therapy among patients in the late stage of UC. Locally advanced or metastatic Urothelial Carcinoma (la/mUC) patients were targeted for this study. Clinical parameters were referred from the JB100 study, which is in its phase 3 trial. Because the Programmed Cell Death Ligand 1 (PD-L1) sensitivity testing is currently not reimbursed in Japan, the cost-effectiveness of avelumab was calculated among patients with UC and PD-L1 from the JB100 study. The time horizon was life years, and the utility score was from a published study. Cost was based on the national health insurance. The assumption was based on the inputs of a urologist. Discontinue rate was set at 0% as this research assumed all patients completed all treatments. ¥7,500,000 per Quality-Adjusted Life Years (QALYs) was defined as the threshold of willingness to pay. The primary endpoint was the Incremental Cost-Effectiveness Ratio (ICER). One-way sensitivity analysis was performed for assessing analysis robustness.

Results: For all patients, ICER was ¥10,711,738/QALY. On the contrary, for PD-L1 positive patients, ICER was ¥4,094,355/QALY at the willingness-to-pay threshold of ¥7,500,000/QALY. One-way sensitivity analysis showed that the ICER of the avelumab maintenance therapy was stable, but not the cost of avelumab.

Conclusion: The avelumab maintenance therapy with BSC was cost-effective for PD-L1 positive la/mUC patients in the Japanese national health insurance setting.

Keywords: Avelumab; Cost-effectiveness; Partitioned Survival model; Carcinoma Programmed cell Death Ligand 1; Maintenance therapy; Best Supportive Care

List of abbreviations

BC	Bladder Cancer
BCG	Bacillus Calmette-Guérin
UC	Urothelial Carcinoma
M-VAC	Methotrexate + Vinblastine + Doxorubicin + Cisplatin
CISCA	Cisplatin + Cyclophosphamide + Doxorubicin
GC	Gemcitabine
OS	Overall Survival
AE	Adverse Event
ICI	Immune Checkpoint Inhibitors
la/mUC	locally advanced or metastatic Urothelial Carcinoma
JB100	JAVELIN Bladder 100 trial
NCCN	National Comprehensive Cancer Network
PD-1/L1	Programmed Death-1/ Programmed cell Death Ligand-1
JSCO	Japan Society of Clinical Oncology
CEA	Cost-Effectiveness Analyses
PD-L1	Programmed cell Death ligand 1
BSC	Best Supportive Care
ICER	Incremental Cost-Effectiveness Ratio
WTP	Willingness-to-Pay
GDP	Gross Domestic Product
OWSA	One-Way Sensitivity Analysis
PSM	Partitioned Survival Model

PD	Progress Disease
PFD	Progression-Free Disease
PartSA	Partitioned Survival Analysis
OS	Overall Survival
PFS	Progression-Free Survival
ISPOR	the International Society for Pharmacoeconomics and Outcomes Research
EV	Enfortumab Vedtin
NHI	National Health Insurance
MHLW	Ministry of Health, Labour and Welfare
KEGG	Kyoto Encyclopedia of Genes and Genomes
UTI	Urinary Tract Infection
QoL	Quality of Life
HR-QoL	Health-Related QoL
ICER	Incremental Cost-Effectiveness Ratio
LYs	Life Years
QALYs	Quality-Adjusted LYs
C2H	Core 2 Health
R&D	Research and Development

Contents

1. INTRODUCTION.....	7
1.1. Background Information.....	7
1.2. Objectives	10
2. METHODS.....	11
2.1. Decision Tree and State Model.....	11
2.2. Partitioned Survival Model.....	12
2.3. Clinical Inputs.....	14
2.4. Cost Inputs	17
2.5. Utility Inputs	20
2.6. Analysis.....	20
3. RESULTS.....	21
3.1. Base-Case Analysis.....	21
3.2. Sensitivity Analysis	22
4. DISCUSSION	23
4.1. Limitations	25
4.2. Implications for Practice	25
4.3. Conclusions.....	26
5. References	27

1. INTRODUCTION

1.1. Background Information

Bladder Cancer (BC) has the 10th highest incidence rate, which and accounts for 3.0% of the solid tumour types [Bill & Melinda Gates Foundation, 2019]. The main cause of BC is smoking (50% of attributable risk factor) and represents the second highest tumour type followed by lung cancer [JSCO, 2022]. The mortality rate of BC is only 2.1% due to effective therapies, such as surgery and the intravesical instillation of Bacillus Calmette-Guérin (BCG) (attenuated *Mycobacterium bovis*) into the bladder for earlier stages of BC [JSCO, 2022]. Most of BCs are categorised as Urothelial Carcinoma (UC), and the incidence rate for males is 3.7 times the rate of females [JSCO, 2022].

Although the overall mortality rate is not high, there are some challenges for treatment strategies. For instance, the late stage of UC only has a standard type of chemotherapy, which has limited efficacy and higher Adverse Event (AE) rates [JSCO, 2022]. Although, Methotrexate + Vinblastine + Doxorubicin + Cisplatin (M-VAC) therapy could show its efficacy in a single-arm study without a phase 3 trial, the JSCO guideline recommended it for stage 4 of UC as the only choice [Sternberg, 1985] [Sternberg, 1989]. Subsequently, this therapy was shown in few randomized studies to prolong survival significantly more than cisplatin monotherapy [Loehrer, 1992] or Cisplatin + Cyclophosphamide + Doxorubicin (CISCA) therapy until 1999 [Logothetis, 1990] [JSCO, 2022]. Later on, Gemcitabine + Cisplatin (GC) therapy was shown to be effective in the phase 3 trial, which showed the same level of Overall Survival (OS) and less incidence of AEs and treatment-related deaths such as decrease in grade three or above of neutrophil count, febrile neutropenia, and mucositis, This therapy also became the first choice for the first-line stage 4 of UC [Maase, 2000]. However, the AE incidence rate and severity are still higher than recent molecular targeted therapies or

immune check point inhibitors when it was compared with recent molecular targeted therapies or immune check point inhibitors (ICIs) [JSCO, 2022]. On the other hand, ICIs have been successfully developed in cancer immunotherapy, and their clinical introduction is progressing in various tumours including bladder cancer, which results in significant changes [JSCO, 2022].

One example of ICI is avelumab, which was proved to be effective as a first-line maintenance therapy after the standard chemotherapy and to improve the survival of locally advanced or metastatic Urothelial Carcinoma (la/mUC) patients in the JAVELIN Bladder 100 trial (JB100) [Powles, 2020]. On the other hand, even though platinum-based therapy has been shown to improve OS, most of patients experience Progression Disease (PD) within approximately nine months after completion [JSCO, 2022], which led to short median OS among la/mUC patients [JSCO, 2022]. Therefore, effective maintenance therapy following platinum-based therapy has been warranted [JSCO, 2022].

Furthermore, the National Comprehensive Cancer Network (NCCN) bladder cancer guideline recommends either the combo of gemcitabine and cisplatin or gemcitabine and carboplatin for cisplatin-eligible patients and for cisplatin-ineligible patients, respectively, followed by the avelumab maintenance therapy as a stage four bladder cancer systemic therapy option for the stage four of bladder cancer patients [NCCN, 2021]. Moreover, the Japanese clinical practice guidelines for bladder cancer recommends the avelumab maintenance therapy for la/mUC patients as a grade “A” of certainty of the evidence and strength of recommendation “1” with the reference of the JB100 study by Powles, et al, 2020 [JSCO, 2022]. However, treatment costs of Programmed Death-1/ Programmed cell Death Ligand-1 (PD-1/L1) agents including avelumab are considered expensive than traditional chemotherapy drugs.

Cost-Effectiveness Analyses (CEA) performed in some developed countries reported the

avelumab maintenance arm than the BSC alone arm. For example, Peng et al (2021) reported a US-based CEA study which showed avelumab plus Best Supportive Care (BSC) therapy to be more cost-effective compared with the BSC-alone therapy as a first-line maintenance therapy. In this study, the Incremental Cost-Effectiveness Ratio (ICER) was \$122,653/QALY for all patients and \$106,223/QALY for PD-L1 positive patients at the Willingness-to-Pay (WTP) threshold of \$150,000/QALY [Peng, 2021]. Moreover, four conference posters were presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Europe, which is one of the most famous HTA conferences, in 2021 and 2022. These studies reported the cost-effectiveness of the avelumab maintenance therapy in the UK, Finland, Taiwan, and France. The results of these studies are shown below.

- A) The UK showed the cost-effectiveness for NICE setting [Critchlow, 2021].
- B) Finland showed significant clinical efficacy and potential cost-effectiveness with an ICER of more than three times lower than the Gross Domestic Product (GDP) per capita per QALY [Karttunen, 2021].
- C) Taiwan showed the cost-effectiveness of avelumab maintenance therapy with an ICER of the avelumab maintenance therapy, which was less than half of the threshold [Chang, 2021].
- D) France showed the cost-effectiveness of avelumab maintenance therapy with an ICER of €145,626/QALY for a WTP threshold of €300,000/QALY [Plessala, 2022].

Lin, et al. (2022) reported another US-based CEA study, in which the avelumab maintenance therapy was not cost-effective even for all la/mUC patients and for PD-L1 positive la/mUC patients. The high cost of avelumab was due to the higher weight of American patients (70kg to 100kg) compared with Japanese patients due to their diet and

cultural differences in the study [Lin D., 2022]. Additionally, Xie et al (2022) reported another CEA study conducted in the US and China. This study also concluded that the avelumab maintenance therapy was not cost-effective for la/mUC patients in neither country and even for PD-L1 positive patients. The study stated that cost of avelumab maintenance therapy might have been overestimated. Although in the US study, the total cost of the therapy was far away from the cost-effective range, in China, the avelumab maintenance therapy would be cost-effective if the estimated costs were 86.24% and 82.17% cheaper for all la/mUC patients and for PD-L1 positive la/mUC patients, respectively, than the current price at the current China's WTP, which is \$30,447.09 [Xie, 2022]. Therefore, the efficacy and cost-effectiveness of the avelumab maintenance therapy with the PD-L1 status were reported with some challenges.

On the other hand, the cost-effectiveness of the avelumab maintenance therapy in Japan has not been reported to date. Additionally, PD-L1 susceptibility testing is not reimbursed for UC treatment in Japan. Therefore, this study assessed the cost-effectiveness of avelumab maintenance therapy for all la/mUC patients and those with positive PD-L1 in Japan.

1.2. Objectives

To assess the cost-effectiveness of avelumab maintenance therapy with BSC versus BSC alone on the locally advanced or metastatic Urothelial Carcinoma patients in Japan.

- Primary Outcome: Incremental Cost-Effectiveness Ratio (ICER) value of Avelumab
- Secondary Outcomes: Costs, Quality-Adjusted Life Years (QALYs)

2. METHODS

The present CEA was implemented with a decision tree and a Partitioned Survival Model (PSM). Clinical inputs were based on the JB100 study, and the time horizon was life years. Utilities were referred from the most recent published US study [Lin D., 2022]. Then, One-Way Sensitivity Analysis (OWSA) was also performed in this research. TreeAge Pro 2020 software was chosen for this CEA analysis and one-way sensitivity analysis.

2.1. Decision Tree and State Model

A decision tree is defined as a non-parametric supervised learning algorithm. This is for regression and classification tasks and has hierarchical data structure with root nodes, leaf nodes, internal nodes, and branches [IBM, 2022]. In the present analysis, the avelumab maintenance therapy, which was defined as “chemotherapy followed by avelumab + BSC” was compared with BSC-alone therapy, which was defined as “chemotherapy followed by BSC” for all la/mUC patients with unknown PD-L1 status as scenario 1 (Fig 1). A state model explains the process of one type of record [IBM, 2022]. For instance, Progress Disease (PD), Progression-Free Disease (PFD), and death were recorded in the following order: Patients were first in the PFD status, then they either continued in the PFD status, move to PD or died (Fig 1). In scenario 2, this analysis was limited to PD-L1 positive la/mUC patients to compare the avelumab maintenance therapy versus BSC-alone therapy. The state model of scenario 1 is the same as scenario 2 (Fig 2).

Fig 1: Decision Tree & State Model of la/mUC Avelumab vs. BSC Therapies for All la/mUC Patients (Scenario 1)

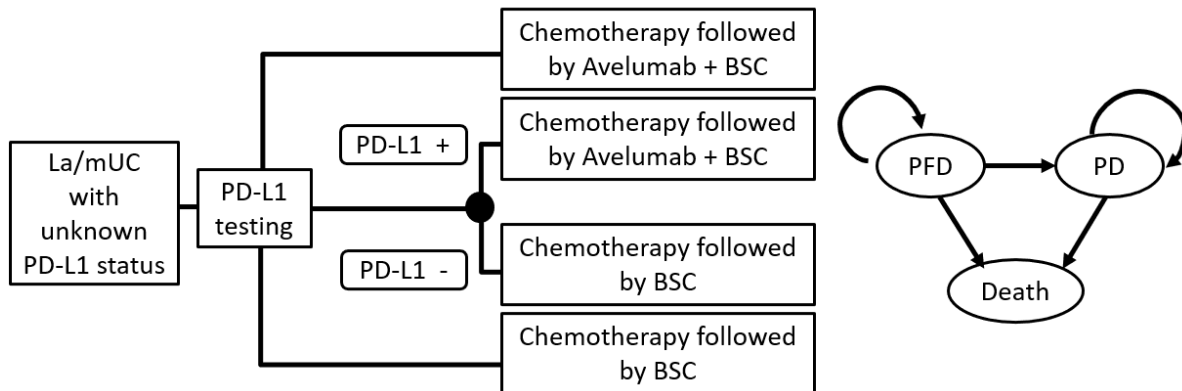
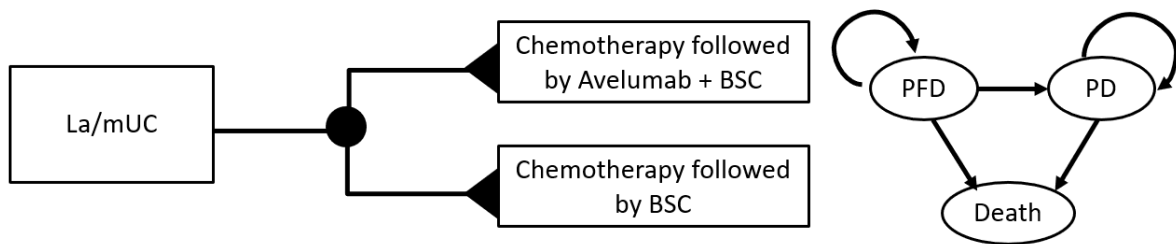


Fig 2: Decision Tree & State Model of la/mUC Avelumab vs. BSC Therapies for PD-L1 Positive la/mUC Patients (Scenario 2)



2.2. Partitioned Survival Model

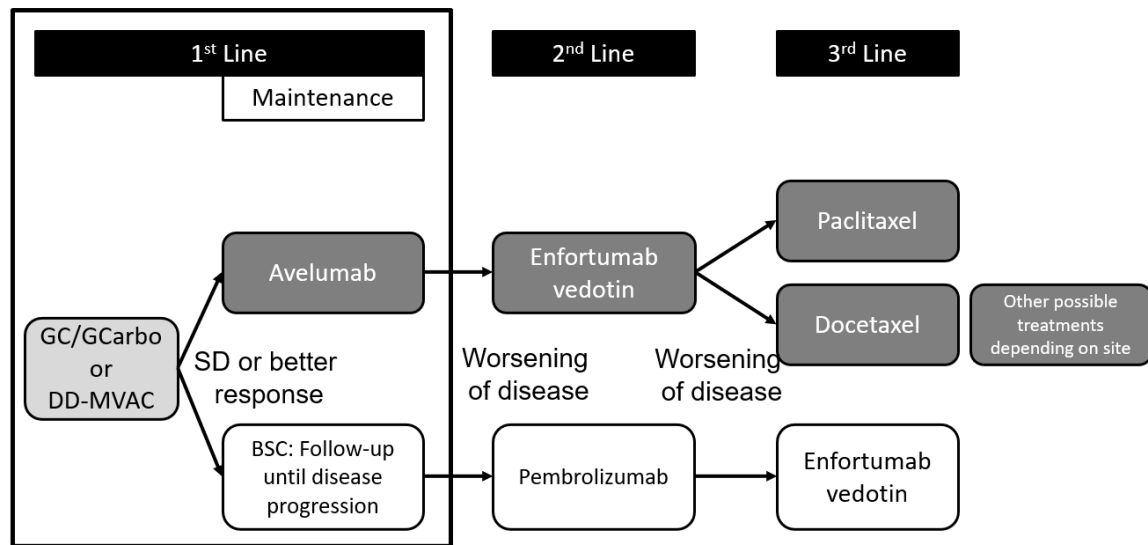
PSM is an economic model that uses Partitioned Survival Analysis (PartSA). The PartSA model follows a theoretical cohort over time as it evolves across exhaustive and mutually exclusive health states [YHEC, 2022]. In contrast to the Markov model, the PartSA model enables us to deal with time points consecutively [JPMA, 2020]. Also, the percentage of the cohorts in each condition is based on parametric survival equations for the PartSA model [YHEC, 2022].

In the PartSA model, the Overall Survival (OS) curve of the subject group directly estimates the proportion of people alive over time [Woods, 2022]. Generally speaking, the

PSM fits anti-cancer drugs modeling since different survival equations for OS and PFS can be directly used into the model. [YHEC, 2022].

In the present analysis, PartSA fits well since OS and PFS data are available from the JB100 study. In the JB100 study, la/mUC patients first take Gemcitabine (GC) plus Cisplatin or GC plus Carboplatin. Then, they take avelumab plus BSC or BSC alone as a first-line maintenance therapy until disease progression. When the patients' condition are getting worse, they move on to the second line. For the avelumab maintenance therapy arm, Enfortumab Vedtin (EV) is generally used for the second line. For the BSC-alone arm, pembrolizumab is used. Then, when these patients become worse, they move on to the third line, either paclitaxel or docetaxel for the avelumab maintenance arm or EV for the BSC-alone arm (Fig 3). In this analysis, the model included both the first line and the first-line maintenance phase, and AE management fees. These treatment costs were calculated until 6 months for both treatment arms in all la/mUC patients and PD-L1 positive la/mUC patients. The goal is to assess the pure cost-effectiveness of the avelumab maintenance therapy with avoiding any patients would not be shifted to the second line therapy.

Fig 3: Treatment Flow of la/mUC Patients



Source: Oncologist Input

2.3. Clinical Inputs

All key clinical inputs such as OS and PFS are from the JB100 study. The algorithm to estimate the parameters beyond the observational time horizon is from the Kaplan-Meier curve [Guyot, 2012]. According to Peng, et al (2021), in the JB100 study, the OS and PFS of the avelumab plus BSC arm and the OS of the BSC arm fitted for lognormal distribution, and the PFS of the BSC arm fitted for log-logistic in overall and PD-L1 positive la/mUC population when they considered the survival functions of generalized gamma, exponential, log-logistic, lognormal and the Weibull model [Peng, 2021].

In all la/mUC patients, the Mu and Sigma of the OS of BSC's lognormal distribution were 2.78046 and 1.07231; those of the PFS of the avelumab plus BSC's were 1.757201 and 1.246729; and those of the OS of the avelumab plus BSC's were 3.114915 and 1.063164, respectively (Table 2). In the PD-L1 positive la/mUC patients, the Mu and Sigma of the OS of the BSC's lognormal distribution were 2.849133 and 1.041593; those of the PFS of the avelumab plus BSC's were 1.973356 and 1.328816; and those of the OS of the avelumab plus

BSC's were 3.394345 and 1.12443, respectively (Table 2). The Lambda and Gamma of BSC's PFS in all la/mUC patients' log-logistic distribution were 0.1167864 and 1.986459; those of the PFS of BSC in PD-L1 positive la/mUC patients were 0.1050369 and 1.933245, respectively (Table 2) [Peng, 2021].

The clinical inputs for time horizon were estimated with the Kaplan-Meier estimation method which was created by Guyot [Guyot, 2012].

Table 1: Clinical Parameters Table

Parameters	Expected value
All patients with unknown PD-L1 status urothelial cancer	
Log-logistic distribution for PFS in BSC arm	Lambda: 0.1167864 Gamma: 1.986459
Lognormal distribution for OS in BSC arm	Mu: 2.78046 Sigma: 1.07231
Lognormal distribution for PFS in avelumab plus BSC arm	Mu: 1.757201 Sigma: 1.246729
Lognormal distribution for OS in avelumab plus BSC arm	Mu: 3.114915 Sigma: 1.063164
Subpopulation with known PD-L1-positive status urothelial cancer	
Log-logistic distribution for PFS in BSC arm	Lambda: 0.1050369 Gamma: 1.933245
Lognormal distribution for OS in BSC arm	Mu: 2.849133 Sigma: 1.041593
Lognormal distribution for PFS in avelumab plus BSC arm	Mu: 1.973356 Sigma: 1.328816
Lognormal distribution for OS in avelumab plus BSC arm	Mu: 3.394345 Sigma: 1.12443

2.4. Cost Inputs

This model focused on treatment drug cost with the AE management fee, but excluded administration, premedication and so on because there is no big difference of these costs for each arm and because it simplifies the model. All drug costs were adjusted to the April 2021 National Health Insurance (NHI) price (薬価: Yakka) fee schedule. The cost of Gemcitabine plus Cis-platin or Carbo-platin as the first-line chemotherapy had not considered these costs since they were charged in both arms. After the chemotherapy, the first-line maintenance therapy was conducted for the avelumab plus BSC arm and the BSC-alone arm. The cost of avelumab (Bavencio) was calculated with the dosage of 10mg/kg, every 2 weeks [Merck Biopharma, 2022]. This model used 50kg as the body weight as defined by the MHLW when they list a new drug in the NHI price list [Yakuji Nippo, 2020]. When this model considered the NHI monthly price which was multiplied NHI daily price by the days of one month., one month represents 30.4375 days. This value comes from the calculation $(365 \text{ days} \times 3 \text{ years} + 366 \text{ days}) / (12 \text{ month} \times 4 \text{ years})$. The NHI price of avelumab is ¥195,785 as of April 2022 [KEGG, 2022]. Its daily price is ¥34,962 and the monthly price is ¥1,064,144 (Table 4). For the BSC, this model chose ¥1, instead of ¥0 since BSC is almost nothing as a treatment in la/mUC, and ¥0 was not set by the “TreeAge” software due to technical reasons.

The AE management fee was also included in the model. According to Powles et al. (2020), the JB100 study reported that the mainly reported AE was Urinary Tract Infection (UTI) and Anemia, and the incidence rate of grade 3 or above was 4.4 % and 3.8% for the avelumab maintenance arm and 2.6% and 2.9% for BSC alone arm, respectively [Powles, 2020]. Hale et al. (2020), reported that the management annual cost of UTI and Anaemia were \$7,272.84 and \$7,534.01, respectively [Hale, 2020]. The money exchange rate was referred to as “\$1.00 = ¥142” in January 2023 from the Bank of Japan [BoJ, 2023]. Therefore, the cost of monthly AE management fee was added for each arm. The formulas are

listed below.

- UTI in the Avelumab Maintenance arm: $\$7,272.84 \times 142 \times 4.4\% / 12 \text{ months} = \text{¥}3,787/\text{month}$
- UTI in the BSC-Alone arm: $\$7,272.84 \times 142 \times 2.6\% / 12 \text{ months} = \text{¥}2,238/\text{month}$
- Anemia in the Avelumab Maintenance arm: $\$7,534.01 \times 142 \times 3.8\% / 12 \text{ months} = \text{¥}3,388/\text{month}$
- Anemia in the BSC-Alone arm: $\$7,534.01 \times 142 \times 2.9\% / 12 \text{ months} = \text{¥}2,585/\text{month}$

Hence, the cost of grade three or above of UTI was ¥3,787/month for the avelumab maintenance therapy arm and ¥2,238/month for the BSC-alone therapy arm (Table 3). The cost of grade three or above of Anemia was ¥3,388/month for the avelumab maintenance therapy arm and ¥2,585/month for the BSC-alone therapy arm (Table 3). These costs were included as the monthly costs of the model.

Table 2: Monthly NHI Price of Avelumab

Compound Name	Product Name	NHI Price per unit (in JPY)	Dose per vial/tablet (mg)	Dose and administration	Dose / kg	Body weight (kg)	Dose per standard cycle	Cycle (days)	NHI Price / Day	NHI Price /Month (30.4375 days)
Avelumab	Bavencio	195,785	200	10mg/kg, every 2 weeks	10	50	500	14	34,962	<u>1,064,144</u>

Table 3: AE Management Cost

\$1.00 = ¥142	Annual Cost (\$)	Annual Cost (¥)	Cost (\$)/Month	Cost (¥)/Month
Infection	\$7,272.84	¥1,032,743	\$606	¥7,172
Anemia	\$7,534.01	¥1,069,829	\$628	¥7,429

Grade \geq 3	Avelumab Incidence %	BSC Incidence %	Avelumab Arm Cost/Month (¥)	BSC Arm Cost/Month (¥)
UTC	4.4%	2.6%	<u>¥3,787</u>	<u>¥2,238</u>
Anemia	3.8%	2.9%	<u>¥3,388</u>	<u>¥2,585</u>

2.5. Utility Inputs

Because there was no data for Quality of Life (QoL) in the JB100 study, Health-Related QoL (HR-QoL) scores, which are between “0” (death) to “1” (perfect health), were referred from a published article by Lin (2022). The utility score of PFS was 0.718 and that of PD was 0.604 (Lin, 2022).

2.6. Analysis

In terms of the base-case analysis, the primary end point was the Incremental Cost-Effectiveness Ratio (ICER). Life Years (LYs), Quality-Adjusted LYs (QALYs), and total cost were calculated as the secondary end points. The discount rate of 2% was applied for this model as the base case [C2H, 2022]. The threshold of WTP was set at ¥7,500,000 per QALY as this model is for an anti-cancer drug [MHLW, 2020]. The ICER was calculated with the following formula:

$$ICER = (C_1 - C_0)/(E_1 - E_0) = \Delta C/\Delta E$$

C_1 : the cost of avelumab plus BSC arm

C_0 : the cost of BSC-alone arm

E_1 : the effectiveness of avelumab plus BSC arm

E_0 : the effectiveness of BSC-alone arm

The next step consisted of a one-way sensitivity analysis. It was performed using a range of variation for each parameter. Each parameter was tested with a plus and minus ten percent increase and decrease, respectively.

3. RESULTS

The results are described in two parts: base-case analysis and sensitivity analysis.

3.1. Base-Case Analysis

Table 4 lists the results of the baseline analysis for the cost-effectiveness of the avelumab maintenance arm. This model provided the ICER of ¥10,711,738/QALY with 1.297 QALYs for the avelumab maintenance arm compared with the BSC-alone arm at the WTP threshold of ¥7,500,000/QALY for all la/mUC patients. For the PD-L1 positive la/mUC patients, these results shifted to the ICER of ¥4,094,355/QALY with 2.246 QALYs for the avelumab maintenance arm compared with the BSC-alone arm (Table 4).

Table 4: Base Case Results for All Patients and PD-L1 Patients

All la/mUC /Treatment Arm	Total Cost	Incremental Cost	Total QALY	Incremental Effectiveness	ICER
BSC alone	¥2,255,272		12.566		
Ave + BSC	¥16,152,348	¥13,897,076	13.863	1.297	<u>10,711,738</u>
PD-L1 + la/mUC /Treatment Arm	Total Cost	Incremental Cost	Total QALY	Incremental Effectiveness	ICER
BSC alone	¥2,446,595		13.001		
Ave + BSC	¥11,663,313	¥9,196,718	15.247	2.246	<u>4,094,355</u>

3.2. Sensitivity Analysis

A one-way sensitivity analysis was performed to analyze which parameter would have a larger impact on the ICER for all la/mUC patients (Fig 4). It showed that the avelumab's cost had a significant impact on the ICER and the BSC's cost, avelumab's PFS rate, rate of avelumab's OS, and BSC's PFS rate had following impacts on the ICER. Furthermore, the sensitivity analysis for PD-L1 positive la/mUC patients (Fig 5) showed the same trend which shows that avelumab's cost is the key to this model.

Fig 4: One-Way Sensitivity Analyses Results of Avelumab + BSC vs. BSC alone in All la/mUC Patients

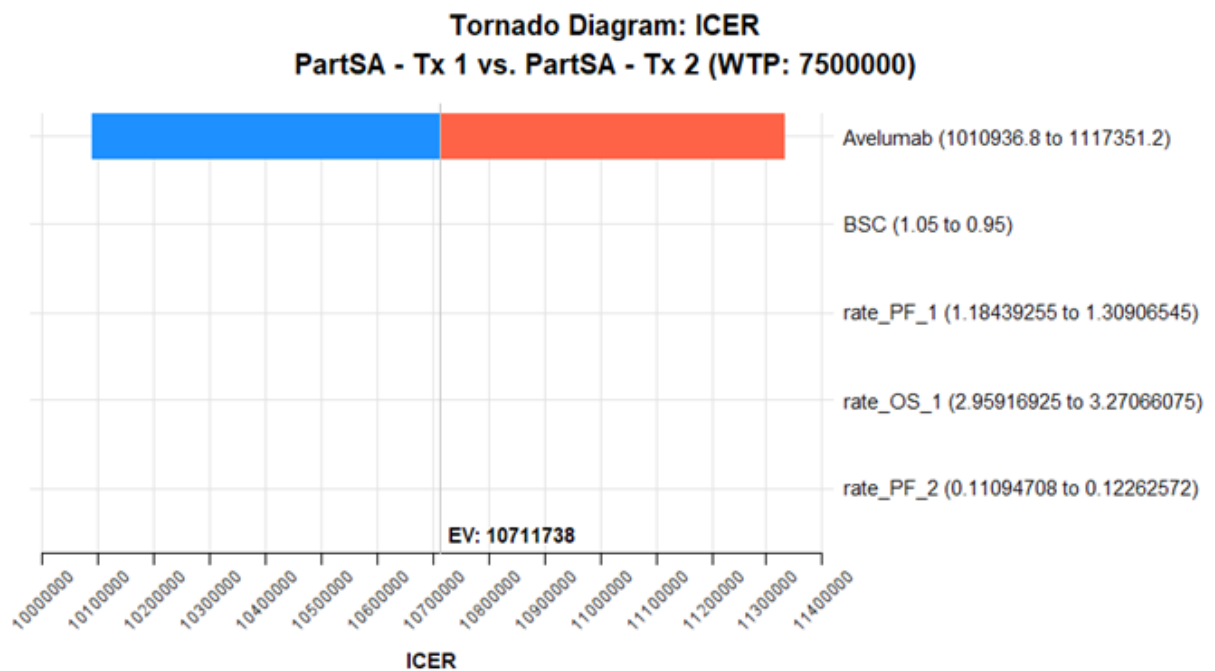
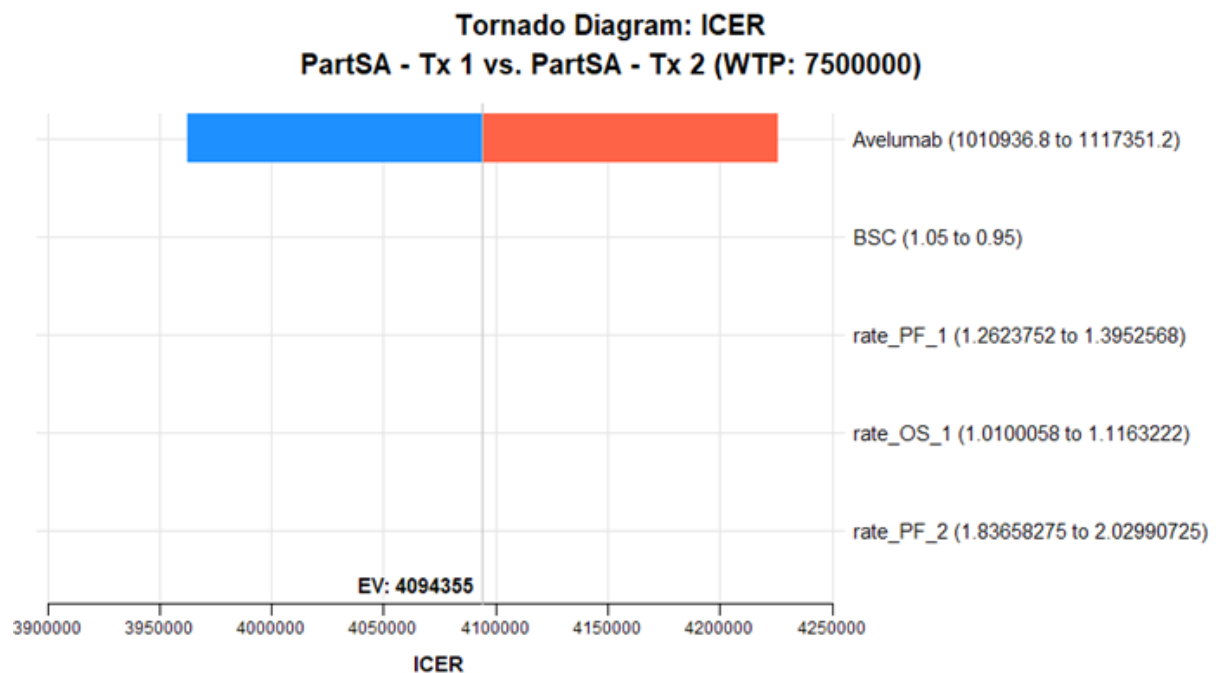


Fig 5: One-Way Sensitivity Analyses Results of Avelumab + BSC vs. BSC alone in PD-L1 Positive Ia/mUC Patients



4. DISCUSSION

Our analysis evaluated the cost-effectiveness of the avelumab maintenance therapy in Japan, which is an unmet medical need. Japan has a universal coverage health care system (NHI system) [JMA, 2023] and a growing population of elderly people, which is already larger than other countries [Globalnote, 2022]. This is probably the main reason that the health care total costs are boosted by using expensive drugs in Japan compared with other developed countries.

Therefore, CEA studies of expensive drugs such as avelumab in Japan could be considered good benchmark models for many countries since the number of elderly people will also increase in other developed countries in the near future.

By referencing the clinical outcome from the JB100 study, the present research showed

that the avelumab maintenance therapy plus BSC was not a cost-effective strategy for all la/mUC patients at a WTP threshold of ¥7,500,000/QALY, compared with the BSC-alone therapy. However, the avelumab maintenance therapy plus BSC was a cost-effective strategy for PD-L1 positive la/mUC patients at a WTP threshold of ¥7,500,000/QALY compared with the BSC-alone therapy. Currently, the sensitivity test of PD-L1 is not reimbursed for la/mUC patients, but the result of this test is very important for estimating the efficacy and cost-effectiveness of the avelumab maintenance therapy for la/mUC patients. Additionally, the cost of avelumab has the strongest influence for the model.

Even though huge different points exist in cancer treatment and outcomes between countries, the social and economic burden of cancer in most of the countries are of concern [Guyot, 2012]. The access for cutting-edge oncology agents especially PD-1/L1s is challenging because it is expensive to maintain a sustainable national health insurance system [Luengo-Fernandez, 2013]. This issue is a concern to developed countries since the price, demand, and actual usage of these new drugs continue to increase [Guyot, 2012]. Therefore, the high cost of cutting-edge oncology drugs must be considered from the health economy point of view and the point of keeping the profitability of pharmaceutical companies for continuing the next generation of Research and Development (R&D), which also increases the cost dramatically, is also considered. Pricing is needed to consider the real clinical value and maintain its profitability for sustaining the sustainable supply and future R&D. Previous CEA studies reported that the avelumab maintenance therapy was cost-effective for la/mUC patients, especially for PD-L1 positive la/mUC patients. On the other hand, two studies that did not find avelumab maintenance therapy to be cost-effective suggested that one reason might be how the total cost of avelumab is calculated in terms of length of treatment, body weight based dosage and so on. [Lin D., 2022] [Xie, 2022].

The ICER value of the avelumab maintenance therapy in Japan is mainly affected by the

length of treatment and body weight. The present research concludes that avelumab is cost-effective for PD-L1 positive la/mUC patients. This result could be utilized for including PD-L1 Susceptibility Testing in the NHI reimbursement list for la/mUC treatment. This result may lead to a higher clinical efficacy outcome, and lower ICER value which indicates cost-more effective even the current avelumab price was kept in the real world setting in Japan and other developed countries whose elderly population is also on the increase.

4.1. Limitations

Some limitations exist in this research. At first, the estimation of the OS and PFS data which were referred from JB100 after the observation period might add uncertainties for the result since it was from the parametric distribution. Second, because of lacking the QoL-related data in the JB100 study, the utility input was referred from a published data (Lin, 2022), but the one-way sensitivity analysis concluded the utility input has minor impact for the results. Third, only UTI and Anemia, which have the highest and second highest incident rates, considered their management fees; the rest of the AEs management costs were not considered in this model. This might have biased the results. Finally, future treatments should have massive impact on clinical inputs. Randomized controlled trials consider these major issues and would lead to uncertainties of this analysis. Even though these limitations exist, the results of this research might help improve la/mUC treatment strategies.

4.2. Implications for Practice

The present result supports that the avelumab maintenance therapy has the position of the “1” level recommendation with grade “A” of certainty of evidence in the Japanese clinical practice guidelines for bladder cancer as a 1st line maintenance therapy, especially for PD-L1

positive la/mUC patients. In terms of PD-L1 negative la/mUC patients, there is a room to consider the avelumab's cost-effectiveness.

4.3. Conclusions

The avelumab maintenance therapy plus BSC was cost-effective for la/mUC patients with PD-L1 positive compared with the BSC-alone therapy at the WTP threshold of ¥7,500,000/QALY.

5. References

1. JSCO, 2022. *Cancer Clinical Practice Guideline*. [Online]
Available at: <http://www.jsco-cpg.jp/bladder-cancer/>
2. Sternberg CN, Yagoda A, Scher HI, et al, 1985. *Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium.*, Hagerstown, MD US: J Urol 133 : 403-407, 1985.
3. Sternberg CN, Yagoda A, Scher HI, et al, 1989. *Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium Efficacy and patterns of response and relapse*, Atlanta, GA US: J Urol 133 : 403-407, 1985.
4. Loehrer PJ, Sr., Einhorn LH, Elson PJ, et al, 1992. *A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma : a cooperative group study.* , Hagerstown, MD US: J Clin Oncol 10 : 1066-1073, 1992
5. Logothetis CJ, Dexeus FH, Finn L, et al, 1990. *A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors.* , Alexandria, VA US: J Clin Oncol 8 : 1050-1055, 1990
6. Powles T., Park S.H., Voog E., Caserta C., Valderrama B.P., Gurney H., Kalofonos H., Radulović S., Demey W., Ullén A., Loriot Y., Sridhar S.S., Tsuchiya N., Kopyltsov E., Sternberg C.N., Bellmunt J., Aragon-Ching J.B., Petrylak D.P., Laliberte R., Wang J., Huang B., Davis C., Fowst C., Costa N., Blake-Haskins J.A., Pietro A., and Grivas P., 2020. *Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma*, Waltham, MA: N Engl J Med 2020; 383:1218-1230.
7. NCCN, 2021. *NCCN Guidelines for Patients Bladder Cancer 2021*. Plymouth Meeting,

MA: National Comprehensive Cancer Network.

8. Peng Y, She Z, Peng L, Liu Q, Yi L, Luo X, Li S, Wang L, Qin S, Wan X, Tan C., 2021.

Cost-Effectiveness of Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma in the United States, Berlin, DE: Adv Ther Dec;38(12):5710-5720.

9. Critchlow, et al., 2021. *Modeling Health-Related Outcomes With Avelumab as a First-Line Maintenance Treatment Following Chemotherapy vs. Best Supportive Care (BSC) for*

Patients With Locally Advanced or Metastatic Urothelial Cancer in the UK. [Online]

Available at: <https://www.ispor.org/heor-resources/presentations-database/presentation/euro2021-3409/112140>

[Accessed on: 09 JAN 2023].

10. Karttunen, et al., 2021. *Cost-Effectiveness of Avelumab as First-Line Maintenance*

Treatment for Locally Advanced or Metastatic Urothelial Carcinoma in Finland. [Online]

Available at: <https://www.ispor.org/heor-resources/presentations-database/presentation/euro2021-3409/112147>

[Accessed on: 09 JAN 2023].

11. Chang, et al., 2021. *Cost-Effectiveness Analysis of Avelumab Plus Best Supportive Care (BSC) vs BSC Alone as a First-Line (1L) Maintenance Treatment for Patients With Locally*

Advanced or Metastatic Urothelial Carcinoma in Taiwan. [Online]

Available at: <https://www.ispor.org/heor-resources/presentations-database/presentation/euro2021-3407/112259>

[Accessed on: 09 JAN 2023].

12. Plessala et al., 2022. *Cost-Effectiveness Analysis of Avelumab Plus Best Supportive Care (BSC) As First-Line Maintenance Treatment in Locally Advanced or Metastatic Urothelial*

Carcinoma (La/mUC) in France. [Online]

Available at: <https://www.ispor.org/heor-resources/presentations->

database/presentation/euro2022-3566/119386

[Accessed on: 09 JAN 2023].

13. 4. Lin D., Luo S., Lin S., Zhong L., Zhou W., Gu D., Huang X., Chen Q., Xu X., Wen X., 2022. *Avelumab Maintenance Treatment After First-line Chemotherapy in Advanced Urothelial Carcinoma -A Cost-Effectiveness Analysis*, Cambridge, MA: Elsevier ISSN 1558-7673, <https://doi.org/10.1016/j.clgc.2022.10.001>.

(<https://www.sciencedirect.com/science/article/pii/S1558767322002087>).

14. Xie Q., Zheng H., Chen Y., Peng X., 2022, *Cost-Effectiveness of Avelumab Maintenance Therapy Plus Best Supportive Care vs. Best Supportive Care Alone for Advanced or Metastatic Urothelial Carcinoma*, Front Public Health. 2022 Apr 27;10:837854.

15. IBM, 2022. *Decision Trees*. [Online]

Available at: <https://www.ibm.com/topics/decision-trees>

16. IBM, 2022. *State models*. [Online]

Available at: <https://www.ibm.com/docs/en/rational-clearquest/8.0.1?topic=schemas-working-state-models>

17. YHEC, 2022. *York Health Economics Consortium*. [Online]

Available at: <https://yhec.co.uk/glossary/partitioned-survival-model/>

18. JPMA, 2020. *Problems of Survival Analysis in Cost-Effectiveness Analysis*. [Online]

Available at:

https://www.jpma.or.jp/information/evaluation/results/allotment/lofurc000000a1dj-att/c_e_a_problems_01.pdf

[Accessed on: 12 JAN 2023].

19. Woods, e. a., 2022. *TSD 19: Partitioned survival analysis as a decision modelling tool*.

[Online]

Available at: <https://www.sheffield.ac.uk/nice-dsu/tsds/partitioned-survival-analysis>

20. Guyot, P., Ades, A., Ouwers, M.J., Welton N.J., 2012. *Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves*, London, UK: BMC Medical Research Methodology 12, 9.
21. Merck Biopharma, 2022. *Package Insert: Bavencio*. [Online]
Available at: https://www.bavencio.jp/product/package_insert.pdf
22. Yakuji Nippo, 2020. *薬価基準制度 2020*. Tokyo, Japan: Yakuji Nippo.
23. KEGG, 2022. *Prescription Drug: Bavencio*. [Online]
Available at: https://www.kegg.jp/medicus-bin/japic_med?japic_code=00067176
24. Hale O., Patterson K., Lai Y., Meng Y., Li H., Godwin J. L., Moreno B. H., Mamtani R., 2020. *Cost-effectiveness of Pembrolizumab versus Carboplatin-based Chemotherapy as First-line Treatment of PD-L1–positive Locally Advanced or Metastatic Urothelial Carcinoma Ineligible for Cisplatin-based Therapy in the United States*, Philadelphia, PA US: Clinical Genitourinary Cancer. Vol. 19, Issue 1, 2021, e17-e30.
25. Bank of Japan, 2023. *Reporting Ministerial Ordinance Rate (January 2023)*. [Online]
Available at: https://cotoha-ipf.miraitranslator.com/loggedin/translate_text.php
[Accessed on: 12 JAN 2023].
26. C2H, 2022. *Guideline for Preparing Cost-Effectiveness Evaluation to the Central Social Insurance Medical Council*. [Online]
Available at: https://c2h.niph.go.jp/tools/guideline/guideline_en.pdf
27. MHLW, 2020. *Cost-effectiveness evaluation system (summary)*. [Online]
Available at: https://www.mhlw.go.jp/stf/newpage_13559.html
28. JMA, 2023. *The standard of care and medical expenses in Japan and other countries*. [Online]
Available at: <https://www.med.or.jp/people/info/kaifo/compare/>
[Accessed on: 23 JAN 2023].

29. Globalnote, 2022. *Global Aging Rate (Percentage of Elderly Population), Ranking and Transition by Country*. [Online]

Available at: <https://www.globalnote.jp/post-3770.html>

[Accessed on: 23 JAN 2023].

30. Luengo-Fernandez R, Leal J, Gray A, Sullivan R., 2013. *Economic burden of cancer across the European Union a population-based cost analysis*, London, UK: Lancet Oncology 2013 Nov;14(12):1165-74.