Economic Evaluation of Nivolumab plus Ipilimumab in Advanced Renal-Cell Carcinoma in Japan

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Background

In the current clinical guideline in Japan, nivolumab plus ipilimumab combination therapy (NIV+IPI) is recommended as the first-line therapy for patients with advanced renal cell carcinoma (aRCC) in International Metastatic RCC Database Consortium (IMDC) intermediate or poor risk. Although NIV+IPI has been found to be efficacious in Phase III RCT(CheckMate 214),its cost-effectiveness is not necessarily clarified in Japan. The aim of this study is to assess whether this combination therapy is cost-effective for patients with aRCC, comparing with standard therapy in Japanese settings in order to to contribute to health policy decision making in Japan.

Methods

Model-based cost-effectiveness analysis

A model-based, cost-effectiveness analysis (CEA) was conducted to evaluate the cost-effectiveness of NIV+IPI compared to sunitinib (SUN) from the perspective of Japanese healthcare payer. We modeled the Japanese patients with aRCC assuming the CheckMate 214. A partitioned survival analysis (PartSA) model was developed to predict long-term costs and quality adjusted life years (QALYs) associated with each therapy. In the PartSA, the prognosis of patients with aRCC was modeled into three states of "progression-free survival (PFS)", "progression of disease (PD)", and "death". Outcomes (costs, life years, and quality-adjusted life years) are evaluated for each health state. We did the modeling according to the following steps:

1. The probability of death and risk of progression were derived from the overall survival (OS) and PFS curves published in the CheckMate 214. Data points were extracted from published survival curves by using WebPlotDigitizer (Version 4.5). Construct pseudo patient-level survival time data from the image data of the Kaplan-Meier curves (PFS and OS) and the number-at risk-table obtained in the CheckMate 214.
2. Use pseudo patient-level data to model parametric survival functions (exponential function, Weibull function, lognormal function, log-logistic function,
3. Gompertz function, and generalized gamma function), using Stata 16 (Stata Corp LLC. College Station, TX, USA) .
4. Choose the optimal function for base-case analysis determined based on visual inspection, statistics such as AIC (Akaike Information Criteria) and BIC (Bayesian Information Criteria) and Japanese epidemiology data (5/10-year survival rate for patients with aRCC).
5. Calculate the expected long-term costs and QALYs by multiplying the estimated patient proportion with the cost per cycle and utility weight of each condition.
6. Calculate the ICER based on the estimated expected costs and expected QALYs as follows:
   ICER＝($Cost_{NIV+IPI}$-$Cost_{SUN}$)/($QALY_{NIV+IPI}$-$QALY_{SUN}$).

For the base case, we evaluated the ICER of NIV+IPI in aRCC patients with IMDC intermediate/poor risk. In addition, scenario analysis was performed in patients with IMDC favorable risk and patients in the intention-to-treat (ITT) analysis.

A willingness to pay (WTP) threshold of $US 75,000 per QALY gained was used as the acceptable level of ICER. The time horizon was set to 42 years. Based on the guideline for the cost-effectiveness evaluation in Japan, a discount rate of 2% per annum was applied to long-term costs and QALYs. The cycle length of the model was defined as 1 month. The model was developed and analyzed using TreeAge Pro 2021(R1.2).

Table.1 Parameter settings

Parameters		NIV+IPI arm		SUN arm	
Cost(US$)		estimate	plausible range	estimate	plausible range
PFS state	drug costs of NIV (per administration)	3,504	3,154-3,855		
	drug costs of IPI (per administration)	9,872	8,885-10,860		
	drug costs of SUN (per month)	※		5,643	5,079-6,207
	medical costs (per month)	2,590	2,209-2,971	1,847	1,672-2,023
PD state	medical costs (per month)	8,306	7,307-9,304	6,238	5,947-6,529
terminal medical costs (per case)		29,123	25,484-32,762	29,123	25,484-32,762
Utility					
PFS		0.793	0.714-0.872	0.754	0.679-0.829
PD		0.702	0.632-0.772	0.707	0.636-0.778

US$1=JPY100
※We set the drug price US$3,504 per administration. We used 3,504×2=US$7,008 for the first cycle and fourth cycle and after. We used US$3,504 only in the second and third cycles.

Utility and cost inputs

In this analysis, the utility weights for PD and PFS were derived from the report of technology appraisal by the National Institute for Health and Care Excellence (NICE) (Table 1). In this model, the following cost parameters were set:
(1) drug costs for PFS in each group, (2) medical costs for PFS in each group, (3) medical costs for PD in each group, and (4) terminal medical costs in each group (Table 1). Drug costs for PFS were estimated based on the drug price standard and clinical practice in Japan. Other cost parameters were estimated using the JMDC claims database provided by Japan Medical Data Center Co.,Ld. (JMDC). We analyzed the claims data on 4,141 patients with RCC (ICD-10: C64) from January 2005 to June 2018.

Sensitivity analysis

One-way sensitivity analysis was performed on the parameters set in the model. 95% confidence intervals were used for the plausible range for cost parameters except for the drug costs in PFS. For other parameters, ±10% were applied. Based on the guideline in Japan, 0%~4% were used for discount rate.

Results

Base case analysis

The results of base case analysis were shown in Table 2. The average survival time in the PFS state was 4.429 years in the NIV+IPI arm and 2.350 years in the SUN arm, respectively. Compared with SUN, NIV+IPI therapy incurred an additional cost of US$ 306,491 and conferred an additional 1.34 QALYs. This resulted in an ICER of US$228,278 per QALY gained. Scenario analysis showed that the ICER on NIV+IPI was estimated to be US$578,587 and US$ 243,385 per QALY in patients with IMDC favorable risk and ITT population, respectively.

Table.2 Base case results

	Duration in PFS (yr)	Duration in PD (yr)	LY	Incremental LY	QALY	Incremental QALY	Cost (US$)	Incremental cost (US$)	ICER (US$/QALY)
Base Case result(Intermediate/Poor)									
SUN arm	2.35	1.56	3.91	-	2.67	-	331,408	-	-
NIV+IPI arm	4.43	1.36	5.79	1.88	4.01	1.34	637,899	306,491	228,278
Scenario analysis (Favorable Risk)									
SUN arm	4.25	2.68	7.79	-	5.03	-	602,195	-	-
NIV+IPI arm	5.11	3.99	8.24	0.45	5.44	0.41	838,915	236,720	578,587
scenario analysis(ITT population)									
SUN arm	3.00	1.83	4.84	-	3.25	-	398,386	-	-
NIV+IPI arm	4.70	2.04	6.73	1.89	4.55	1.30	714,435	316,049	243,385

Sensitivity analysis

The results of the one-way sensitivity analysis were shown in the tornado diagram of Figure 1. Factors that greatly affected the cost-effectiveness of NIV+IPI were the utility weight of PFS in each group and the drug cost of NIV+IPI group. The most strongly affected the ICER of NIV+IPI was the utility weight of PFS state in NIV+IPI arm. The best case ICER was US$185,368 per QALY and the worst case ICER was US$297,037 per QALY. The ICERs remained higher than US$75,000 per QALY over the full range of model parameters.

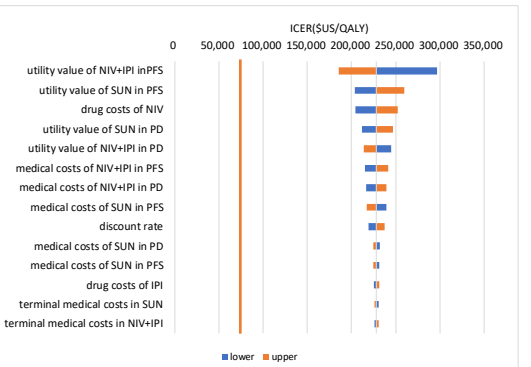

Figure.1 Tornado diagram

Conclusions

Applying the willingness to pay threshold of US$7,5000 per QALY, NIV+IPI therapy might not be cost-effective for the first-line therapy of aRCC. Further research is required on utility of Japanese patients with aRCC.

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