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First-Line Lenvatinib plus Pembrolizumab or Everolimus versus Sunitinib for Advanced Renal Cell Carcinoma: A United States-based Cost-effectiveness Analysis

Running Head: The LP or LE for aRCC

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ABSTRACT

Introduction: The CLEAR trial indicated that Survival benefits were generated with lenvatinib plus pembrolizumab (LP) or everolimus (LE) than with sunitinib for advanced renal cell carcinoma (aRCC). However, the high cost of immuno-target and dual-targeted treatment, we assessed the cost-effectiveness of lenvatinib plus pembrolizumab or everolimus in the first-line setting for treatment of patients with aRCC from the United States (US) payersø perspective.

Methods: A comprehensive Markov model was developed to evaluate the cost and effectiveness of LP or LE in first-line therapy for aRCC. We estimated life years (LYs), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs). Utility values and direct costs

related to the treatments were gathered from the published studies. Then, one-way and probabilistic sensitivity analyses were performed. Additional subgroup analyses were considered.

Results: Treatment with LP and LE provided an additional 0.67 QALYs (0.62 LYs) and 0.66 QALYs (0.90 LYs) compared with sunitinib, resulting in ICER of $131,656 per QALY and 201,928 per QALY, respectively. The most influential factor in this model was the cost of pembrolizumab with LP. Probabilistic sensitivity analysis showed there was a 58.97% and 28.91% probability that LP and LE were cost-effective at WTP values of $150,000 per QALY in the US. Subgroup analyses demonstrated that LP was more cost-effective for patients from Western Europe and North America, intermediate risk of the International risk group of Metastatic Renal Cell Carcinoma Database Consortium (IMDC), favorable and intermediate risk group of Memorial Sloan Kettering Cancer Center (MSKCC) and PD-L1 combined positive score greater than or equal to 1%.

Conclusion: From the perspective of the US payer, LP is a cost-effective option as first-line treatment for patients with aRCC at a WTP threshold of $150,000 per QALY, but LE is the opposite.

Key words: advanced renal cell carcinoma, lenvatinib, pembrolizumab, everolimus, cost-effectiveness analysis

1. Introduction

In the United States (US), kidney cancer is the second most common genitourinary cancer, accounting for more than 76,000 new cases and 13,000 deaths in 2021[1]. Renal cell carcinoma (RCC) accounts for up to 85% of kidney cancers and about 17% of patients have distant metastatic disease at diagnosis, with a 5-year survival rate of 11.7%[2, 3].

Recently, because of the improvement in survival and quality of life, treatment with immune checkpoint inhibitors (ICIs), either as a dual combination or in combination with vascular epithelial growth factor (VEGF) inhibitors, may replace sunitinib and become a standard modality for advanced renal cell carcinoma (aRCC). Approved treatments in the first-line setting include VEGF inhibitors (lenvatinib, axitinib, sunitinib, pazopanib, cabozantinib) and ICIs (pembrolizumab, nivolumab, ipilimumab).

Lenvatinib is an oral multikinase inhibitor that targets VEGF. Pembrolizumab is a human immunoglobulin G4 monoclonal antibody that binds to the programmed death 1 receptor. Everolimus is an oral protein kinase inhibitor of the mammalian target of rapamycin (mTOR) serine/threonine kinase signal transduction pathway. The combination regimens of lenvatinib plus pembrolizumab or everolimus showed survival benefits for aRCC according to previous studies[4, 5]. In the first-line treatment of patients with aRCC, the CLEAR randomized clinical trial demonstrated that lenvatinib plus pembrolizumab (LP) significantly prolonged overall survival (OS hazard ratio [HR] for death, 0.66; 95% confidence interval [CI], 0.49 to 0.88; p=0.005) and the progression-free survival (PFS 23.9 vs 9.2 months; HR for disease progression or death, 0.39; 95% CI, 0.53 to 0.80; p < 0.001) than sunitinib. Lenvatinib plus everolimus (LE) also improved the PFS (14.7 vs 9.2 months; HR, 0.65; 95% CI, 0.53 to 0.80; p < 0.001), however, no OS benefit was observed (HR for death, 1.15; 95% CI, 0.88 to 1.50; p=0.30). In addition, LP and LE were associated with a higher incidence of grade 3 or higher adverse events than sunitinib (82.4% and 83.1% vs 71.8%)[6]. Subsequently, LP was approved as the first-line treatment for patients with aRCC in all International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk by the National Comprehensive Cancer Network (NCCN) in March 2021[7].

Even though the LP treatment is effective and safet in patients with aRCC. ᵛjgtg"ku"uvkm"c"itgcv"pggf"qh"cuuguukpi"ᵛjg"ftwiᶿu"emkpkecn"dgpghkv"cv"c" reasonable cost when it is taken into account the high cost of recently approved novel drugs. Therefore, our goal was to evaluate the cost-effectiveness of adopting newer but more costly treatment strategies such as LP as the first-line treatment of aRCC htqo"c"WU"rc{gtuᶿ perspective.

2. Methods

2.1.Model structure

A comprehensive Markov model and decision tree were developed to evaluate the costs and effectiveness of the different first-line treatments of patients with aRCC. The decision trees included three treatments: (1) LP group: lenvatinib plus pembrolizumab; (2) LE group: lenvatinib plus everolimus and (3) sunitinib group. The Markov model included three health states to replace the disease course of aRCC: PFS, progressive disease (PD), and death (eFigure 1 in the supplementary material). All patients started state with PFS and were treated with three treatment strategies until disease progression or intolerable toxicity and adverse effects. Upon PD or severe adverse events (AEs), both patients could receive subsequent treatment until death. Our Markov cycle length in the model was 6 weeks and outcomes were developed over 20 years boundaries given that more than 99% of the cohort died. We adopted the costs and effects of a 3% discount rate per year[8]. The outputs included the total cost, life-years (LYs), quality-adjusted LYs (QALYs), and incremental cost-effectiveness ratios (ICERs). We also focused on subgroups and conducted a cost-effectiveness analysis. The model structure and data were based on the results of the CLEAR trial[6] and were obtained

from US publicly available databases and published literature. The Markov model was using TreeAge Pro 2020 (TreeAge Software, Williamstown, MA, https://www.treeage.com).

2.2. Model survival and progression risk estimates

The transition probabilities of death in any state from aRCC for each treatment strategy were estimated based on the OS and PFS curves of the CLEAR trial. We applied the GetData Graph Digitizer (version 2.26; http://www.getdata-graph-digitizer.com/index.php) to collect the data points from the OS and PFS curves and these data points were then used to fit parametric survival models. Parametric models include the Weibull, Exponential, Gompertz, Log-logistic, and Log-pqt o cn" fkuvtkdwvkqpu0" Ceeqt fkp i "vq" cm" cu r gevu. "Cmckm gøu" kphqt o cvkqp" etkvgt kqp"]CKE_"cpf" Bayesian information criterion [BIC] are selected to evaluate the fitting degree of the alternative model. Weibull survival curves which were flexible and widely used were matched to the number of patients in the three states over time, as it can monotonically increase or decrease the hazard function, it is suitable for estimating the event that occurs in the early follow-up work period. The survival model selection was shown in previously published research[9]. A detailed description of the survival model selection was shown in eTable 2 and eFigure 2 in the supplementary material. Then, we used Weibull distribution to operate in R and we got the two-rctc o gvgt."ujcrg"* +"cpf"uecng"* +."yjkej"ygtg" estimated from this fit and applied to Kaplan-Meier curves using the R (version 4.0.2, http://www.r-project.org) and the method proposed by Hoyle and Henley[10] (Table 1).

The time-dependency transition probabilities(tp) are essential in the model analysis. Tp in each Markov cycle was calculated based on the following formula: The Markov cycle is u and the arrival at state t after u Markov cycles is tu was calculated with the following formula: ᴠr*ᴠw+?3" "gzr} *ᴠ" "w+ " " ᴠ ¡"* "@"2." "@"2+[11]

2.3.Utility estimates

The utility was used to estimate the consumer's quality of life (QoL) and reflected the impacts of the disease-related health state (0 for worst health to 1 for perfect health). We used previously published utilities of 0.76 and 0.66[12]as the mean health utility value for the PFS and the PD state, respectively. The utility value of the first-line treatment using sunitinib was 0.73[13]. We also consider the disutility values of 3/4 adverse events (AEs) in our analysis[12-16] (Table 1).

2.4.Cost inputs

Direct medical costs included drug costs, AEs costs (assuming that AEs appeared only one model cycle in the PFS and the PD state)[13, 17, 18], administration costs[13] follow-up, monitoring costs, and terminal care costs[19] (Table 2).

Based on the CLEAR trial, the patients in the LP group: lenvatinib was administered at a dose of 20 mg orally once daily for each 21day treatment cycle, and pembrolizumab was administered at a dose of 200 mg intravenously on day 1 of each 21day cycle. The patients in the LE group: lenvatinib was administered at a dose of 18 mg and everolimus was administered at a dose of 5 mg orally once daily for each 21-day

cycle. The patients in the sunitinib group: sunitinib was administered at a dose of 50 mg orally once daily for 4 weeks of treatment followed by 2 weeks with no treatment. 60% of patients in the LP group, 68.8% of patients in the LE group, and 81.2% of patients in the sunitinib group discontinued study treatment. Then, according to the NCCN guidelines and the CLEAR trial, these patients continued to receive nivolumab and cabozantinib until after death, with each patient receiving terminal care. In the LP, LE, and sunitinib group, 13.6% 51.4%, and 53.1% of patients received nivolumab, respectively; 50.7%, 40.8%, and 41.4% of patients received cabozantinib, respectively.We assumed the patient is 65 years of age, has a weight of 70kg, a height of 70, and a body surface area of $1.84m^2$[20]. The price was derived from the Centers for Medicare & Medicaid Services[21] and the drug price inquiry website[22] (Table 1). The follow-up costs covered fees for computed tomography or magnetic resonance imaging (every 8 weeks from the date of randomization during treatment cycles)[6]. Grade 1/2 events were considered manageable within standard patient monitoring and the correlation with QoL was low[12]. Thus, we included only the cost of managing grade 3/4 AEs (a frequency of greater than 5%) in the model, which had notably different probabilities between the arms of the CLEAR trial. AEs costs were derived from previously published studies[13, 17]. All costs associated with healthcare services were inflated to 2021 values according to the US consumer price index. Information on these costs was obtained, shown in Table 2.

2.5.Sensitivity analysis

We used a series of sensitivity analyses to predict the uncertainty of the model results. One-way sensitivity analysis was conducted within a variance of 20% from their baseline values according to varied values of a certain parameter within its defined range and the established approaches to examine the individual effects of this parameter on the ICERs[8, 23]. We also conducted probabilistic sensitivity analyses by

performing 10,000 Monte Carlo simulations, and the probabilistic sensitivity analysis was completed to assess the variations in multiple parameters at once[19]. A cost-effectiveness acceptability curve of each treatment strategy was evaluated as being the most cost-effective at a certain WTP threshold.

We also considered all patient subgroups of the CLEAR trial. Due to insufficient data for each patient subgroup, we adopted the same baseline sunitinib survival curve for all patients in the sunitinib group, and their LP and LE group survival curves were produced based on the subgroup-specific HRs according to the approach taken by Hoyle et al.[24] for the absence of OS and PFS curves for each patient subgroup.

3. Results

3.1. Base case results

The model projected that the life expectancy of patients receiving LP and LE was 5.98   LYs and 6.26 LYs, which were 0.62 LYs and 0.90 LYs more than those receiving sunitinib, respectively. Accounting for QOL, Patients receiving LP and LE received 4.16 and 4.15 QALYs, which were 0.67 QALYs and 0.66 QALYs more than those receiving sunitinib, respectively. The use of LP and LE cost an additional \$88,597 and \$132,300, resulting in an ICER of \$131,656 and \$201,928 per QALY (\$144,724 and \$147,000 per LY) compared with sunitinib (Table 2).

3.2. Sensitivity analysis

The one-way sensitivity analyses (Figure 1) indicated that the greatest influence of variables on the ICER in LP compared with sunitinib was the cost of pembrolizumab (ranging from \$41.29 to \$61.94, with the ICER increasing from -\$483.16 per QALY (dominated) to \$264,928 per QALY),

Weight decrease	7,439.210	5951.368	8927.052	[18]	Gamma
Proteinuria	0	0	0	[18]	Gamma
Decreased appetite	7,064.170	5651.336	8477.004	[18]	Gamma
Fatigue	0	0	0	[13]	Gamma
Stomatitis	121.140	96.912	145.368	[18]	Gamma
Anemia	70.520	56.416	84.624	[17]	Gamma
Lipase increased	0	0	0	[18]	Gamma
Amylase increased	0	0	0	[18]	Gamma
Asthenia	6,172.460	4937.968	7406.952	[18]	Gamma
Lipase increased	0	0	0	[18]	Gamma
Amylase increased	0	0	0	[18]	Gamma
Hypertriglyceridemia	75.330	60.264	90.396	[18]	Gamma
Platelet count decreased	9,709.000	7767.200	11650.800	[17]	Gamma

Thrombocytopenia	9,709.000	7767.200	11650.800	[17]	Gamma
Neutrophil count decreased	36,106.000	28884.800	43327.200	[17]	Gamma
Neutrophil	36,106.000	28884.800	43327.200	[17]	Gamma
Follow-up and monitoring per cycle	442.3	353.8	530.8	[19]	Gamma
Administration per cycle	144.0	115.2	172.8	[13]	Gamma
Terminal care per cycle	11,227	8981.6	13472.4	[18]	Gamma

Table 2. Baseline results.

Parameters	Lenvatinib plus Pembrolizumab	Lenvatinib plus Everolimus	Sunitinib
LYs	5.98	6.26	5.36
QALYs	4.16	4.15	3.49
Total cost $	1,120,020	1,163,723	1,031,423
ICER $/LY [a]	144,724	147,000	-
ICER $/QALY [b]	131,656	201,928	-
WTP $/QALY	100,000-150,000	-	-

[a] Compared to Sunitinib ($/LY).

[b] Compared to Sunitinib ($/QALY).

Abbreviation: ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year; WTP, willingness-to-pay.

Table 3. Results of subgroup analyses of lenvatinib plus pembrolizumab group.

Subgroup	Simple size		OS HR (95% CI)	PFS HR (95% CI)	ICER	Cost-effectiveness probability at WTP	
	LP	Sunitinib				$100,000/QALY	$150,000/QALY
Age							
65y	194	225	0.63(0.41-0.95)	0.37(0.28-0.49)	187,842	15.89%	32.66%
65y	161	132	0.61(0.40-0.95)	0.43(0.31-0.61)	166,368	19.08%	39.52%
Sex							
Male	255	275	0.70(0.49-0.99)	0.38(0.30-0.49)	168,327	21.59%	38.02%
Female	100	82	0.54(0.30-0.94)	0.42(0.27-0.66)	181,285	13.63%	35.19%
Geographic region							
Western Europe and Nort	198	199	0.68(0.46-1.00)	0.42(0.32-0.57)	144,422	22.49%	51.67%

h America						
Rest of the world	157	158	0.63(0.40-0.99)	0.36(0.26-0.49)	159,621	15.16%	46.58%
MSKCC risk group						
Favorable	96	97	0.86(0.38-1.92)	0.36(0.23-0.54)	94,083	49.46%	56.89%
Intermediate	227	228	0.66(0.47-0.94)	0.44(0.34-0.58)	145,780	23.26%	42.30%
Poor	32	32	0.50(0.23-1.08)	0.18(0.08-0.42)	291,025	3.18%	11.84%
IMDC risk group						
Favorable	110	124	1.15(0.55-2.40)	0.41(0.28-0.62)	Dominated[a]	-	-
Intermediate	210	192	0.72(0.5-1.05)	0.39(0.29-0.52)	143,804	23.61%	51.19%
Poor	33	37	0.30(0.14-0.64)	0.28(0.13-0.60)	237,919	4.65%	14.52%
Baseline Karnofsky performance-status score						
100-90	295	294	0.88(0.47-1.67)	0.38(0.3-0.48)	159,230	24.15%	40.01%
80-70	60	62	0.56(0.40-0.79)	0.44(0.36-0.74)	182,444	12.08%	34.69%

No. of organs with metastases

1	97	108	0.88(0.47-1.67)	0.46(0.30-0.71)	Dominated[a]	-	-
×4	254	246	0.56(0.40-0.79)	0.46(0.28-0.47)	200,719	12.31%	31.04%

PD-L1 combined positive score

1%	107	119	0.76(0.46-1.27)	0.40(0.27-0.58)	138,093	24.37%	54.59%
< 1%	112	103	0.50(0.28-0.89)	0.39(0.26-0.59)	177,592	13.87%	36.65%

[a] Subgroup analyses were dominated either due to their lower health benefits and higher costs or because they were not considered cost-effective since the ICER far exceeded the WTP threshold of the US.

Abbreviation: LP, Lenvatinib plus Pembrolizumab; CI, confidence interval; ICER, incremental cost-effectiveness ratio; OS HR, overall survival hazard ratio; PFS HR, progression-free survival hazard ratio; WTP, Willingness-to-pay; QALY, quality-adjusted life-year; MSKCC, Memorial Sloan Kettering Cancer Center; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PD-L1, programmed cell death-Ligand 1.