

A Cost-Effectiveness Analysis of First-line Treatments for Advanced Renal Cell Carcinoma: Nivolumab-Ipilimumab vs. Pembrolizumab-Axitinib vs. Sunitinib

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Background

The FDA has recently approved several immune checkpoint inhibitors including nivolumab, ipilimumab, and pembrolizumab in combination therapy as first-line treatment for metastatic clear-cell, renal cell carcinoma (mRCC).

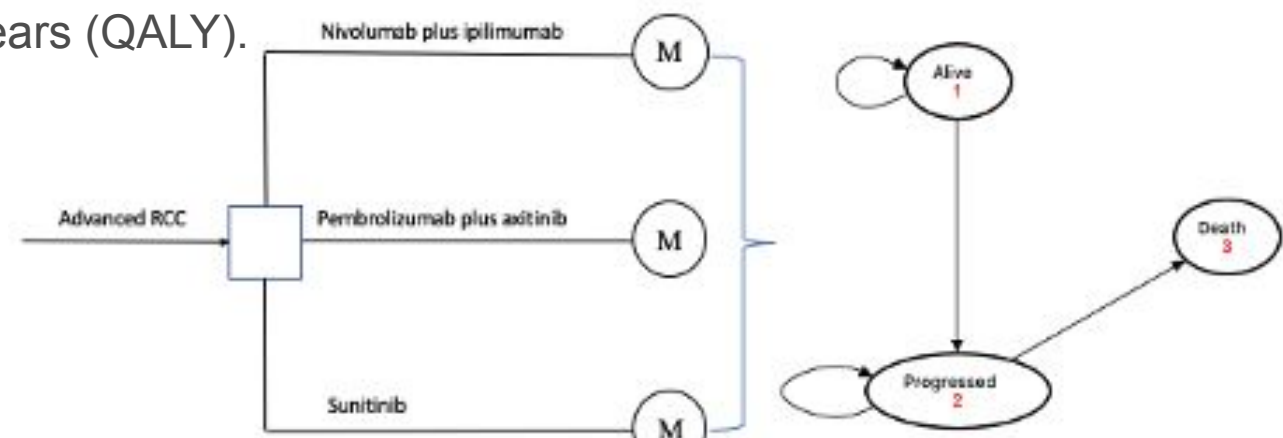
Combination therapies can present an obstacle in clinical decision-making due to variable costs and the propensity for additional side effects. Cost-effectiveness analyses (CEA) such as this one can help elucidate the cost-efficiency of these treatments. This study is the first comparison between nivolumab-ipilimumab, pembrolizumab-axitinib, and sunitinib.

Objective

The objective of this analysis was to compare the lifetime cost-effectiveness among nivolumab-ipilimumab combination therapy, pembrolizumab-axitinib combination therapy, and sunitinib for patients with mRCC from a U.S. medical center perspective.

Methods

- Design:** A three-state Markov model was developed comparing sunitinib, nivolumab-ipilimumab, and pembrolizumab-axitinib cost-effectiveness to one another over a 20-year time horizon. All costs were adjusted to 2019 U.S. Dollars (USD) and were discounted at an annual rate of 3%. The primary outcome is an incremental cost-effectiveness ratio (ICER) using quality adjusted life years (QALY).



- Sample:** Our modeled population included ≥18 year old patients with mRCC from the CheckMate 214 (nivolumab-ipilimumab) and KEYNOTE-426 (pembrolizumab-axitinib) clinical trials, in which both therapies were compared to sunitinib. The nivolumab-ipilimumab group was composed of a lower proportion of favorable risk patients as compared to the pembrolizumab-axitinib group.

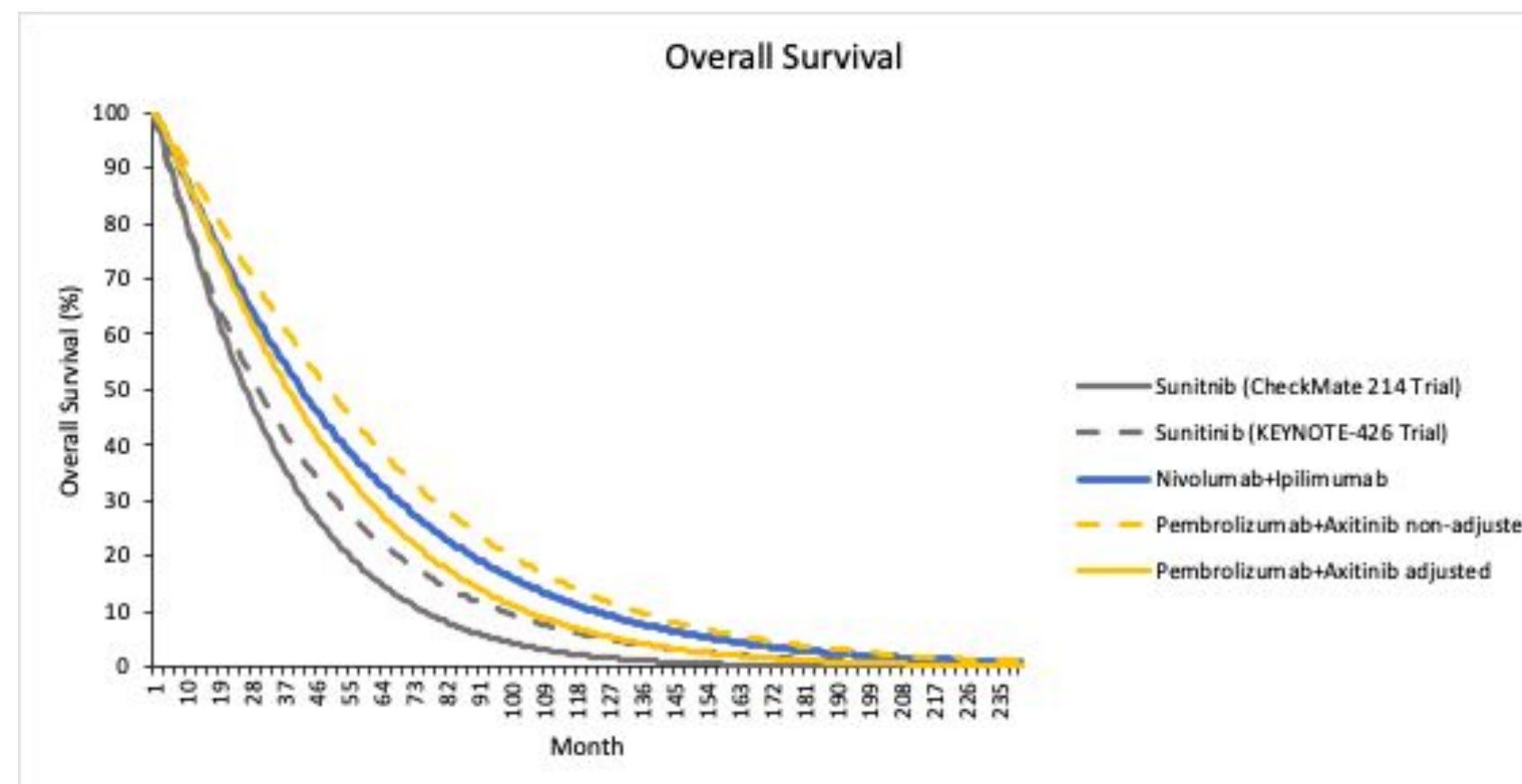
Methods continued

- Comparison:** A matching-adjusted indirect comparison was used to control for differences in patients by standardizing the control and treatment groups based on the ratio of the sunitinib differences in overall survival (OS) and progression-free survival (PFS) in the two trials. We performed two scenarios including unadjusted and adjusted base case analyses.
- Costs:** Costs were included for drug and adverse event (AE) treatments. Drug costs were taken from RED BOOK™ Online 2020 as wholesale acquisition cost (WAC) in USD.
- Outcome/Survival:** OS and PFS monthly data for the three treatment arms were extracted from the clinical trials to calculate monthly transition probabilities.
- Analysis:** Univariate and probabilistic sensitivity analyses of all model variables, including utility and cost of treatment, were performed.

Results

- Nivolumab-ipilimumab was cost-effective (CE) at an ICER of \$34,190 compared to sunitinib, but pembrolizumab-axitinib was not CE with ICER of \$12,630,831 when compared with the next lowest cost treatment (nivolumab-ipilimumab).
- Pembrolizumab-axitinib was also not CE compared to sunitinib.
- After adjustment, the projected life expectancy of patients receiving sunitinib, nivolumab-ipilimumab, pembrolizumab-axitinib was 3.24, 4.21, and 3.25 years, respectively.

Figure 2. Comparison of Adjusted and Non-Adjusted Survival Outcomes



(4) The ICER of both the adjusted and non-adjusted pembrolizumab-axitinib scenario were not CE compared to either sunitinib or nivolumab-ipilimumab, because changes in survival did not offset the high costs of pembrolizumab-axitinib.

Figure 3. Base Case ICER Results

Summary of Cost and Effectiveness					
Parameter	Total Cost (2019 USD)	Incremental Cost (2019 USD)	Total Effectiveness	Incremental Effectiveness	ICER
Comparisons to the least cost option					
Sunitinib	\$241,656		1.98		
Nivolumab-ipilimumab	\$284,683	\$43,028	3.23	1.26	\$34,190
Pembrolizumab-axitinib	\$457,769 (A) \$519,750 (NA)	\$216,113 (A) \$235,067 (NA)	1.99 (A) 2.44 (NA)	0.02 (A) 0.47 (NA)	(A): \$12,630,831 PA ICER (NA): \$594,197
Comparisons between two combination therapies					
Nivolumab-ipilimumab vs. pembrolizumab-axitinib		\$173,085 (A) \$235,067 (NA)		-1.24 (A) -0.79 (NA)	Dominated by Nivolumab-ipilimumab in A and NA scenarios

A: adjusted survival outcomes for pembrolizumab-axitinib; NA: no adjustments for survival outcomes for pembrolizumab-axitinib

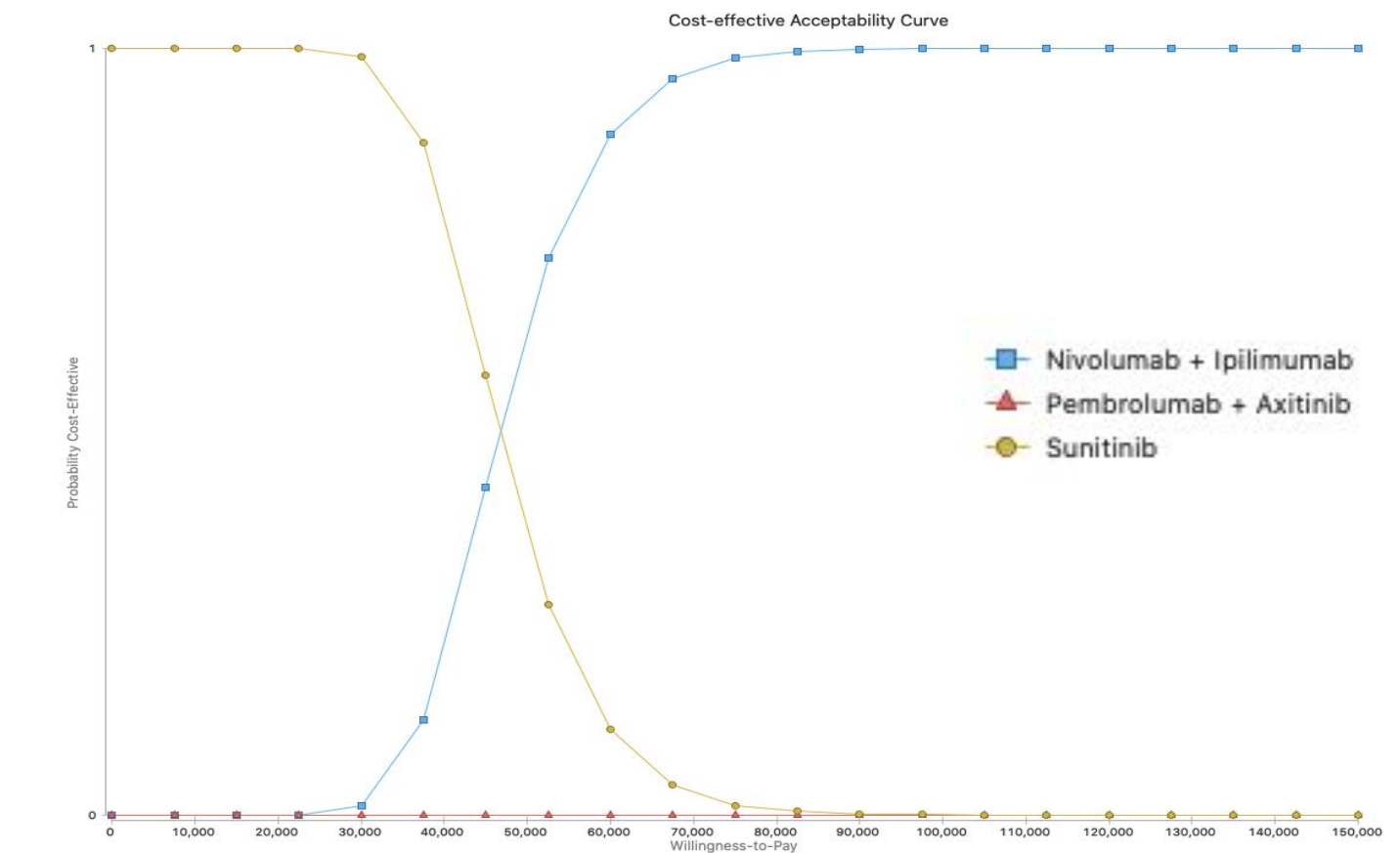
(5) The cost of both combination treatments had the most important impact on the CE as both treatments needed at least 20% price change to cross the CE threshold. Nivolumab-ipilimumab had a cap of length of use in treatment, whereas sunitinib and pembrolizumab-axitinib did not, which contributed to high costs.

Figure 4. One-Way Sensitivity Analysis of Both Scenarios

Variables found to impact cost-effectiveness	Scenario 1 with adjusted OS scenario	Scenario 2 with non-adjusted OS scenario
Cost of pembrolizumab-axitinib	↓ by >37% to be CE compared to sunitinib ↓ by >59% to be CE compared to nivolumab-ipilimumab	↓ by >20% to be CE compared to sunitinib ↓ by >45% to be CE compared to nivolumab-ipilimumab
Cost of nivolumab-ipilimumab	↑ by <59% to remain CE compared to pembrolizumab-axitinib	↑ by <50% to remain CE compared to pembrolizumab-axitinib

CE: cost-effectiveness using WTP of \$150,000 (standard for oncology products)

Figure 5. Cost-Effectiveness Acceptability Curve of Adjusted Scenario



(6) Nivolumab-ipilimumab is more likely to be cost-effective when the willingness-to-pay (WTP) threshold is greater than \$34,190, whereas sunitinib has a higher likelihood below that level. Pembrolizumab-axitinib is never cost-effective within the \$150,000 WTP range due its high costs and relatively low effectiveness.

Conclusions

- The base-case model indicated that nivolumab-ipilimumab was the most cost-effective treatment option for mRCC compared with pembrolizumab-axitinib and sunitinib.
- While the NCCN guidelines show all three options as first-line treatment for mRCC, our findings suggest nivolumab-ipilimumab would save patients and health systems from costly alternatives while improving outcomes.
- Our conclusions agree with CEAs completed previously. Two comparisons of nivolumab-ipilimumab vs. sunitinib ranging from \$85,506 (Wu et al. 2018) to \$108,363 (Wan et al. 2019). Our ICER was lower, because it was the only study done in the U.S. rather than China after the price was determined.
- One study by Chen et al. (2019) also found pembrolizumab-axitinib not cost-effective compared to sunitinib, but for patients/payers in China (ICER: \$178,725/QALY in 2019 USD).
- Our study is the only one that compared the CE of nivolumab-ipilimumab and pembrolizumab-axitinib, showing that pembrolizumab-axitinib was not CE.
- Pembrolizumab-axitinib could be CE if the drug costs were lowered. This study can help direct clinical decision-making in the treatment of mRCC.