Master's Degree Dissertation

Cost-effectiveness of first-line treatment options and treatment sequencing in advanced renal cell carcinoma

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I formally declare that I have written the submitted piece of work independently. I did not use any outside support except for the quoted literature and other sources mentioned in the paper.

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Abstract

Continued cancer research allows for the development of novel and potentially superior treatments and management approaches. The recent identification of the role of the immune system in cancer has led to the development of agents targeting the anti-tumor immune response, bringing increased survival and improved patient quality of life. However, these agents, known as immune checkpoint inhibitors (ICIs), also bring additional costs associated with the drug itself and management of immune-associated safety events. Despite the approval of three ICI-based combinations for the first-line treatment of advanced renal cell carcinoma (aRCC), the question remains as to which of the three options is the most cost effective and whether these new agents are more cost-effective overall for society. Further, given that most patients progress on first-line therapy, there is motivation in clinical practice to save ICIs as second-line salvage therapy, retaining the current non-ICI first-line standard of care. A Markov model was created comparing the cost-effectiveness of these 3 ICI-based options and the current first-line standard of care in the context of multi-line treatment. The model included direct medical costs, utilities associated with progression-free survival and progressive disease, and commonly used second-line treatment options for patients who progressed on the first-line treatment options. Incremental cost-effectiveness ratios (ICERs) were calculated for all 4 first-line treatment options assessing cost (US dollars) per quality-adjusted life year (QALY). Avelumab + axitinib was the more cost effective first-line option and ICI-based combination. Only nivolumab + ipilimumab exceeded the selected willing-to-pay threshold of $100,000 USD/QALY. In summary, ICI-based combinations, in particular avelumab + axitinib, are also cost-effective first-line options in the treatment of aRCC.

Introduction

In 2019, renal cell carcinoma (RCC) is expected to be the 8th most common cancer in the US, with 73,820 new cases and 14,770 deaths expected in the US alone.[1] Despite the commonality of this malignancy and a clear biological understanding of disease initiation and progression, treatment options have been less than optimal due to limited efficacy and high toxicity. Although localized RCC is managed through surgical resection, advanced disease, which is no longer localized to the origin site in the kidney, requires systemic therapy.[2] The realization that RCC was an immunogenic tumor led to the introduction of historical immunotherapy, such as interleukin-12, to enhance the anti-tumor immune response and patient survival.[3] However, these therapies were highly toxic and treatment efficacy can not be maintained with dose reduction to mitigate toxicity.[4] The appreciation that RCC progression is in part driven through increased angiogenesis led to the approval of tyrosine kinase inhibitors (TKIs),[3] which are still considered the standard of care (SOC) in RCC across treatment lines 20 years later.[2,5] Inhibitors targeting other key signaling pathways such as the PI3K–Akt–mTOR have also been approved and are commonly used to treat RCC as later-line therapy.[2] Although these targeted therapies have prolonged overall survival (OS) and progression free survival (PFS) with a good safety profile,[5] many patients progress or relapse and thus other treatment options are being investigated.[3]

In the last five years, the field of oncology has experienced a dramatic shift with the discovery of immune checkpoint expression on tumor cells, allowing the tumor to go undetected by the immune system, leading to progression and patient death.[3] Immune checkpoint inhibitors (ICI) have shown significant impact in melanoma and NSCLC, with the belief that a cure for cancer has finally been reached.[3] However, as not all tumor types and not all patients respond equally to these inhibitor due to differential tumor and patient biology, ICI-based combinations have been explored[6] where the other drug is used to poise the immune system for tumor destruction once the checkpoint is inhibited.[7] Alternatively, the combination of different checkpoint inhibitors blocking different avenues of tumor-mediated immune suppression are also in use.[3] Both immune checkpoint monotherapy and combination therapy have shown promise in aRCC with four treatment options approved by the FDA in the last few years.[4,6,8,9]

The significant benefit of ICIs also comes with the cost of the drug itself and intravenous administration.[10] In addition, these drugs bring novel safety concerns,

known as immune-related adverse events, which occur due to normal tissue expression of these immune checkpoints.[10] The most common irAEs include hypertension, diarrhea and hepatoxicity and the irAEs that have been reported range in severity from mild (Grade 1-2) to significant (Grade 3-4), requiring different management according to intensity and type.[10] In ICI-based combinations, these irAEs may combine with toxicities of the other agent, further affecting patient quality of life and management costs.[3,10]

There is also concern as to the placement of these new agents within current management guidelines and treatment sequencing. Although three ICI-based combinations have been approved as first-line (1L) therapy,[2] additional guidance as to which option to use and when, and whether ICIs should be adopted in the 1L setting or used as salvage therapy in the 2L when patients progress is necessary.[4,6] Given that these options seem to have similar effects on patient survival, cost-effectiveness analysis may help clarify the treatment landscape.

This study will investigate the cost-effectiveness of the three currently approved ICI- based combinations, avelumab+ axitinib, pembrolizumab + axitinib, nivolumab + ipilimumab, in comparison to the TKI SOC, suntinib, which acts as a small molecule (SM) to inhibit vascular endothelial growth factor (VEGF) in patients with aRCC. All three approved ICI-based combinations are included to properly assess the benefit, given that each brings varying clinical benefit and costs associated with management. The three pivotal randomized controlled trials (RCT) used to support this analysis included the preferred option for next line of treatment, allowing assessment of sequencing starting with either ICI or a VEGF TKIs and then switching to a VEGF TKI, an mTOR inhibitor or an ICI. Data will be reported as incremental cost-effectiveness ratios (ICERs) in US dollars (USD).

Methods

Model overview

In order to assess cost-effectiveness of the currently approved 1L ICI-based options for patients with aRCC, avelumab + axitinib, pembrolizumab + axitinib and nivolumab + ipilimumab, a Markov model was employed to accurately reflect the chronic nature of the disease. Transition probabilities were constant throughout the model given that the focus is on 1L treatment. Key data used for the model was taken from the pivotal RCTs underlying FDA approvals, JAVELIN Renal 101,

KEYNOTE426 and CheckMate-214.[8,9,11] This model is depicted via a tree diagram (Supplemental Figure 1), starting with a decision node including the option of the three checkpoint inhibitors and the SOC, sunitinib, as the VEGF TKI comparator. Sunitinib was also used as the comparator in all three pivotal RCTs used in the model, with data reported from the study with avelumab + axitinib used as the base case. The subtree of each of the four treatment options starts with a Markov node with transitions to PFS, progressive disease (PD) or death. As all the RCTs are powered to assess for PFS with treatment, all patients start in the PFS subgroup (probability=1), then moving to PD or death over time. For patients that progress, additional subtrees to investigate 2L treatment benefit and associated costs were built using the two most common subsequent treatments identified in each of the 1L pivotal RCTs, and data from the respective RCTs supporting these 2L treatments. Rewards (costs and utilities) were assigned to the appropriate states.

Model outcomes include costs calculated in 2019 USD, and quality adjusted life years (QALYs). A 7-year time span was used to adequately assess patient response to 1L and 2L treatments with a cycle length of 6 weeks, reflective of the interval between patient assessment that is commonly used in the trials and in clinical practice. The model was built and run using the TreeAge Pro software. ICERs were calculated between options in comparison to sunitinib as the SOC. Discounting was not included. The perspective was that of the US society and the willing-to-pay (WTP) threshold was set to $100,000 USD in line with other studies in the field.

Transition probabilities

Efforts to calculate the transition probabilities for PFS, PD and death were made and given the lack of ability in R programming and challenges with the modeling software, placeholder values were used simply to allow for model execution and application of key concepts. Thus, all output data and assessment are mere estimates and would be repeated with correct transition probability values if the study were for publication. Transition to 2L therapy was based on the rate of patients who were treated with that therapy after progression in the pivotal RCTs.

Cost and utilities

The study included direct medical costs associated with the drug and with the management of a given health state. Drug costs and drug administration costs were extracted from Medicare (administration code 96413 for avelumab, pembrolizumab

and nivolumab and codes 96417 and 96514 for ipilimumab).[12] Treatment costs were modified to reflect dosing according to the 6-week cycle. It was assumed that patients in the PFS state continued to receive treatment and thus incur drug and safety-associated costs. Patients who transitioned to the PD state were only assigned drug and safety-associated costs for the initial cycle, after which disease progression would have been identified through assessment and treatment would have been stopped for most patients, as reported in the pivotal RCTs. [8,9,11] Costs associated with the management of each state, i.e. PFS or PD, regardless of treatment were previously reported and include office visits, community nurse visits, scans (CT and MRI), blood and metabolic test and associated materials according to US-based management guidelines.[13] No costs were assigned to the death state.

Costs associated with specific adverse events (AEs) were taken from a primary analysis by Wong et al. who reported safety-associated costs for patients with several cancers, including RCC.[14] Safety events were defined in this study in the same way as the pivotal RCT trials used in this analysis. In the publication by Wong et al, costs for US healthcare management were determined through the use of medical claims databases (Truven Health Analytics MarketScan1).[14] These costs were then adjusted to the model cycle length and based on the 6-week probabilities inferred from the adverse reaction (AR) rates reported in the US Prescribing Information of each treatment used.[15-20] AR rates were used, as opposed to AE rates, as ARs reflect drug-associated responses whereas AEs merely record any safety event occurring within the RCT, whether associated with the drug or not. The total sum of the AR costs, both low grade (Grade 1-2) and high grade (Grade ≥3), were associated only with any state in which treatment was administered for simplification. Low- and high-grade costs were kept separate for sensitivity analysis given the different impact of adverse event severity on costs.

Utilities assigned to PFS and PD states were previously published in studies in this space, reflecting the differential benefit of ICIs in comparison to VEGF TKIs SMs.[21,22] Similar values for ICIs were reported in a second study and these values were used for the sensitivity analysis (uPDs, uPFSs).[22] Key values included in the study are listed in Table 1.

Table 1. Key Values Used in the Model.

Tree	Utilities[21,22]	Costs per cycle[12-20]
Avelumab + axitinib	uPD= 0.66	Cost of PD= $141.54
	uPFS= 0.78	Cost of PFS= $89.89
		Cost of AE Grade 1-2= $2172 Cost of AE Grade ≥3= $1818.9 Cost of drug= $38616.08
Sensitivity analysis	uPDs= 0.65 uPFSs=0.73	Cost of AE Grade 1-2= $1522.63 Cost of AE Grade ≥3= $1707.88
Pembrolizumab + axitinib	uPFS= 0.78	Cost of PD= $141.54
	uPFS= 0.78	Cost of PFS= $89.89
		Cost of AE Grade 1-2= $955.60 Cost of AE Grade ≥3= $1255.00 Cost of drug= $38442.34
Sensitivity analysis	uPDs= 0.65 uPFSs=0.73	Cost of AE Grade 1-2= $1522.63 Cost of AE Grade ≥3= $1707.88
Nivolumab + ipilimumab	uPD= 0.66	Cost of PD= $141.54
	uPFS= 0.78	Cost of PFS= $89.89
		Cost of AE Grade 1-2= $995.60 Cost of AE Grade ≥3= $1255.00 Cost of drug= $218896.34
Sensitivity analysis	uPDs= 0.65 uPFSs=0.73	Cost of AE Grade 1-2= $473.93 Cost of AE Grade ≥3= $204.95
Sunitinib	uPD= 0.61	Cost of PD= $141.54
	uPFS= 0.69	Cost of PFS= $89.89
		Cost of AE Grade 1-2= $4404.07 Cost of AE Grade ≥3= $2500.11 Cost of drug= $17879.56
Sensitivity analysis		Cost of AE Grade 1-2= $1373.19 Cost of AE Grade ≥3= $1874.57
Cabozantinib	uPD= 0.61	Cost of PD= $141.54
	uPFS= 0.69	Cost of PFS= $89.89
		Cost of AE Grade 1-2= $1992.06 Cost of AE Grade ≥3= $1658.1
		Cost of drug= 23505.13

Everolimus	uPD= 0.61	Cost of PD= $141.54
	uPFS= 0.69	Cost of PFS= $89.89
		Cost of AE Grade 1-2= $2883.49 Cost of AE Grade ≥3= $361.69
		Cost of drug= 20484.56
Nivolumab	uPD= 0.65	Cost of PD= $141.54
	uPFS= 0.73	Cost of PFS= $89.89
		Cost of AE Grade 1-2= $2315.97 Cost of AE Grade ≥3= $472.36
		Cost of drug= $86342.02

Sensitivity analysis

Analysis through TreeAge Pro software and subsequent univariate sensitivity analyses were performed. According to TreeAge Pro, the variables with the main effect on uncertainty included the utility values and costs of treatment. This was thus followed-up with a univariate analysis to further probe the impact of these variables.

For the univariate sensitivity analysis, utilities associated with ICI PFS and PD were replaced with those reported by Edwards et al.[22] As costs of drugs and drug administration do not change, costs of management of safety events were altered replacing values for ARs with those of the AEs reported for each of the pivotal RCTs.[8,9,11]

Results

Costs and QALYs associated with each of the 1L treatment options are included in Table 2. Both costs and QALYs were higher with ICI-based treatment options. When all four options were considered equally using no treatment as the comparator (ICER1), avelumab + axitinib had the lowest costs per QALY of all treatments. When sunitinib was used as the comparator for the ICER (ICER2) given that suntininb is the current SOC (Table 2), avelumab + axitinib also had the lowest ICER of all ICI-based treatment options. Only the nivolumab + ipilimumab option was above the WTP threshold of $100,000 USD.

Table 2. Markov Model Output from Main Analysis and Univariate Sensitivity Analysis.

Data summary						
	QALYs	Costs	Costs/ QALY* (ICER1)	ΔQALYs (vs sunitinib)	ΔCosts (vs sunitinib)	ICER2 (vs sunitinib)
Avelumab + axitinib	4.02	121533	30232.09	1.3	25008.83	19279.44
Pembrolizumab + axitinib	5.98	197519	33029.93	3.25	100994.83	31006.87
Nivolumab + ipilimumab	2.95	493103	167050.12	0.22	396578.83	1731762.15
Sunitinib	2.723	96524	35450.03	-	-	-
Sensitivity Analysis 1						
	QALYs	Costs	Costs/ QALY* (ICER1)	ΔQALYs (vs sunitinib)	ΔCosts (vs sunitinib)	ICER2 (vs sunitinib)
Avelumab + axitinib	3.87	121533	31403.88	1.15	25008.83	21800.34
Pembrolizumab + axitinib	5.76	197519	34291.49	3.04	100994.83	33252.87
Nivolumab + ipilimumab	2.83	493103	174241.34	0.11	396578.83	3700243.53
Sunitinib	2.72	96524	35450.03	-	-	-
Sensitivity Analysis 2						
	QALYs	Costs	Costs/ QALY* (ICER1)	ΔQALYs (vs sunitinib)	ΔCosts (vs sunitinib)	ICER2 (vs sunitinib)
Avelumab + axitinib	4.02	118849	29564.42	1.3	22324.83	17210.33
Pembrolizumab + axitinib	5.98	195233	32647.65	3.25	98708.83	30305.03
Nivolumab + ipilimumab	2.95	489973	165989.7	1.07	393448.83	1718094.21
Sunitinib	2.723	88264	32416.34	-	-	-

*This value is also used to represent the ICER in comparison to no treatment option, when all four 1L options are being compared.

Sensitivity analysis

Analysis through TreeAge Pro as well as subsequent univariate sensitivity analyses were performed. According to TreeAge Pro, the variables with the most effect on uncertainty in comparing avelumab + axitinib and of nivolumab + ipilimumab were utility for the health states associated with ICIs and costs of both combinations. In comparison of avelumab + axitinib and pembrolizumab + axitinib, key variables impacting the model were health states associated with ICIs, and costs of both treatments. When comparing avelumab + axitinib with sunitinib, the variables impacting the model were costs of the avelumab + axitinib combination and of sunitinib, utilities of the SM health states nh, costs of Grade 1-2 AEs with sunitinib and cost of nivolumab, a common subsequent treatment following sunitinib.

Varying the utilities associated with PFS and PD with ICIs (Sensitivity Analysis 1) and the costs associated with AEs (Sensitivity Analysis 2) did not change the outcome of the analysis.

Discussion

The costs of cancer diagnosis and management in the US continue to increase due to novel treatment options and management approaches accompanying a better understanding of tumor biology and technological advances.[23,24] Accordingly, health economic assessments, particularly cost-effectiveness analyses are becoming more common.[24] In these assessments, models project the ICER for treatment options or scenarios over a specific time horizon based on mathematical extrapolation of the reported survival benefit to calculate expected costs and quality of life impact beyond the limited span of the clinical trial.[24] Although the benefit of these models are numerous, there are a number of necessary over-simplifications given data availability and to allow for practical and applicable conclusions.[24] For example, these models do not necessarily reflect real-world conditions and thus continue to assess efficacy as opposed to effectiveness.[24] These studies are also often limited by published data that is often no longer current by the time the study goes to print.[24]

Several simplifications were employed in this model for analysis. Specifically, treatment was modeled as continuous when patients were in the progression-free state. However, in reality, treatment may be limited to a certain duration due to discontinuations or toxicities, or stopped if patients show lack of disease signals.[23] Further, the probability of AR/AE occurrence was assumed to be constant overtime, where it is known that some immune-associated AEs occur within a specific time

frame after treatment initiation and have a specific duration.[10] A Markov process, with varying rates over time, would have been a better way to model the safety, and safety-associated costs with these treatments. In addition, utilities for ARs/AEs were not included and probabilities of ARs/AEs were incorporated into costs only. Alternatively, another Markov model could have been created assessing not only transition through states associated with treatment efficacy but also with safety. Finally, only two subsequent lines of therapy were included when assessing the impact of the 1L treatment options, where in reality there may be up to twenty.

As ICIs are a relatively new addition in the cancer treatment landscape, key data points impacting variables and model structure are immature. For example, further development of utility values in this space is necessary.[24] Some studies suggest that utility and disutility values should also be refined based on PRO and clinician input, which would help maintain a societal perspective in assessment.[24] One downside to ICIs is the intravenous injection every few weeks as compared to daily oral administration of small molecules. This can impact treatment adherence and thus associated effectiveness and safety.[26] The utility values used were not specific to each treatment option but to the drug class itself, and thus should reflect key differences between ICIs and SM such as safety and administration route. Values used in other studies of the cost-effectiveness of ICIs have been reported to range from 0.52-0.89 for PFS and from to PD 0.28-0.8, thus the values used in this study (0.78 for PFS and 0.66 for PD) are within commonly used ranges in cancer studies.[24] However, utility values specific to each 1L treatment for aRCC would help better assess which option is most cost effective.

A main limitation of this study was the availability of cost data for all safety events. As some costs could not be determined, the impact of some ARs/AEs on cost-effectiveness could not be determined. Although most agents in this class have similar safety signals, the incidence varies and so this omission likely does impact overall cost calculations. Despite what is commonly seen in the literature, all safety events were considered (all grades) in this study, as the costs associated with management of low-grade events may be significant.

This study used a WTF threshold of $100,000 USD/QALY for ICERs based on previous studies in this space.[25] The US does not have a standard WTP threshold but common ranges include $50,000-150,000 USD/QALY.[24,25] Although conclusions cannot be drawn from this study, the data suggests that avelumab + axitinib, followed by a 2L VEGF TKI, is the most cost-effective option. More accurate utility

values and cost data may have led to a different outcome favoring another treatment option. Nivolumab + ipilimumab was the only option over the WTP threshold, and even with extending the threshold to 150,000 USD/QALY this combination would be above the threshold at $167050.12/QALY when the four treatment options are compared (comparator of no treatment) and $1731762.15/QALY in comparison to sunitinib. This is likely due to the increased costs of a combination of two ICIs (nivolumab and ipilimumab) as opposed to the other options of an ICI with a VEGF TKI.

Variable uncertainty was assessed through sensitivity analyses, but model uncertainty was not directly evaluated. As stated, the model was built based on the outcomes of pivot RCTs and US-based guidelines for management (i.e. for discontinuations and safety events) but was not altered to address the potential over-simplifications. Additional complexity, although a more accurate representation of the real-world experience, may overcomplicate the study and restrict applicability.

In patient treatment, ICIs are thought to be particularly beneficial due to durable response rates observed in some patients after many years of follow-up.[3] Although a 7-year time horizon was used, this study does not adequately assess this benefit as long-term data was not available in this indication for any of the three ICI-based combinations. Thus, longer-term efficacy analyses would also potentially impact the outcome of the study.

Although cost-effectiveness studies are becoming increasingly common, the FDA does not take cost-effectiveness into account in drug approvals and Medicare is currently prohibited from making reimbursement and coverage decisions based on cost-effectiveness.[25] Other reports have suggested that current cost-effectiveness approaches and ICERs have limited uptake in the US as they do not consider that patient's autonomy and physician-patient shared-decision making, both highly valued in American culture.[24] Accordingly, setting a cost-effectiveness threshold for ICERs in US-based studies may be useful from an theoretical standpoint, but may not be practical or may not capture society's willingness to pay. Thus, despite the limitations of this study, and even with accurately derived transition probabilities, the potential impact of this study is unknown given the current atmosphere. However, as the cost of cancer management care continues to increase, and with continued approval of new therapeutic options, US healthcare systems may move to limit funding and such studies may be essential.

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