Patient Preference and Adherence

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ORIGINAL RESEARCH

Treatment Preferences Among Patients with Renal Cell Carcinoma: Results from a Discrete Choice Experiment

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Introduction: The treatment landscape for advanced/metastatic renal cell carcinoma (aRCC) has evolved quickly with the introduction of immunotherapies as a first-line treatment option. This study examined the preferences of patients with aRCC to better understand the characteristics of preferred treatments and the tradeoffs patients are willing to make when choosing treatment.

Methods and Materials: An online, cross-sectional survey was conducted in the US from May to August 2022 with adult patients with aRCC. A discrete-choice experiment assessed treatment preferences for aRCC. Attributes were identified through literature review and qualitative interviews and included progression-free survival, survival time, objective response rate, duration of response, risk of serious side effects, quality of life (QoL), and treatment regimen.

Results: Survey results from 299 patients with aRCC were analyzed. Patients had a mean age of 55.7 years, were primarily White (50.5%) and were evenly representative of males (49.8%) and females (48.8%). Improvements in all attributes influenced treatment choice. On average, increasing survival time from 10% to 55% was most important, followed by improvements in QoL (ie, from worsens a lot to improves) and improvements to treatment regimen convenience (ie, less frequent infusions). Risk of serious adverse events and increased progression-free time, objective response rate (ORR), and duration of response (DOR) were of lesser importance.

Conclusion: In this study, patients highlighted that improving survival time was the most important and that QoL is also an important consideration. Discussions during treatment decision-making may benefit from broader conversations around treatment characteristics, including impacts on QoL and convenience of the regimen.

Keywords: discrete choice experiment, patient preference, treatment preference, renal cell carcinoma

Introduction

Renal cell carcinoma (RCC) is one of the most common cancers globally, representing an age-standardized incidence rate of 4.6 per 100,000 individuals.[1] Within the United States (US), the incidence rate has steadily increased over the past several decades (7.1 per 100,000 in 1975 to 14.9 per 100,000 in 2016) which has made kidney cancer one of the fastest growing cancers in the US.[2] As a result of this growth, the Surveillance, Epidemiology, End Results (SEER) Program estimated 81,800 new cases in the US in 2023 alone.[3]

About 35% of RCC cases are diagnosed as advanced/metastatic RCC (aRCC).[4] The management of aRCC has progressed toward targeted therapies such as vascular endothelial growth factor receptor tyrosine kinase inhibitors (TKI), mammalian target of rapamycin inhibitors, and immuno-oncology (IO) therapy, with immune checkpoint inhibitors resulting in significant survival benefits.[5–8] In 2018, the US Food and Drug Administration approved ipilimumab (cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] protein inhibitor) and nivolumab (programmed death-1 [PD-1] immune checkpoint inhibitor)[9] to become the first IO-IO combination in treating patients with aRCC with poor or

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intermediate risk status. Following this approval was a paradigm shift to include immune checkpoint inhibitors as first-line therapy for almost all patients with aRCC.[5] Specifically, the National Comprehensive Cancer Network® (NCCN®),[10] European Association of Urology, European Society for Medical Oncology, and the Society for Immunotherapy of Cancer all recommend immune checkpoint inhibitor-based PD-1 and CTLA-4 inhibitors as a backbone of first-line therapy for patients with intermediate or poor risk of survival.[11,12]

As such, multiple treatment options with similar levels of evidence and recommendations are available to aRCC patients. These options differ with respect to clinical, quality of life (QoL), and toxicity outcomes in the first-line setting.[13–15] Although the clinical and safety endpoints assessed in the majority of confirmatory trials may be important from a clinical perspective, patient prioritization of these endpoints may differ.[15,16] While treatment preferences have been examined among patients with RCC,[15,17–20] there is a paucity of data assessing patient preferences for outcomes associated with IO-based combination therapies in aRCC. Therefore, this study aimed to evaluate preferences for different features or outcomes associated with treatments for aRCC including tradeoffs that patients are willing to make when choosing first-line treatment.

Methods

Study Design

An online, cross-sectional survey was conducted in the US from May to August 2022. The survey included a discrete choice experiment (DCE) to assess preferences for treatment in aRCC.[21]

Patients (≥18 years) who were US residents and self-reported a diagnosis of aRCC were eligible; aRCC was defined as cancer that metastasized outside the kidneys. To ensure representation of patients differing in treatment experience, sub-quotas were used to include patients who received different first-line therapies, such as dual IO therapy (IO-IO), IO/-TKI, TKI monotherapy, or patients who received other types of therapies or were treatment naïve. Patients were recruited through patient databases, referrals from patient associations, support groups, healthcare providers, and social media outreach. This study was conducted according to the International Society for Pharmacoeconomics and Outcomes guidelines on conjoint analysis[22–24] and was given exempt determination by Pearl Institutional Review Board (Indianapolis, IN; 16 Feb 2022) in accordance with FDA 21 CFR 56.104 and DHHS 45 CFR 46.104 regulations. All patients agreed to participate via an electronic informed consent and those who completed the survey were compensated.

DCE & Survey Content

The DCE included 12 choice tasks, each showing two treatment profiles that included a combination of treatment characteristics ("attributes") with various levels. The selection of attributes and attribute levels was based on literature focusing on clinical trial endpoints and prescribing information of treatments included in the competitive set (IO-IO, IO/-TKI, and TKI monotherapy).[25–27] The minimum and maximum levels for each attribute represented actual ranges observed for the competitive set. The treatment profiles shown in the DCE included seven treatment attributes with two to five levels each: progression-free time, survival time, objective response rate (ORR), duration of response (DOR), QoL, serious adverse event (SAE), and dosing regimen (Table 1).

Draft attributes were confirmed in cognitive interviews with eight patients. Especially for oncology terms, it is important to ensure that respondents understand the terms being used through qualitative research.[28,29] The interview participants most often mentioned quality of life as important, as well as regimen convenience and minimizing treatment side effects. Nevertheless, participants indicated that they would be willing to have a more inconvenient or aggressive treatment for a treatment with higher effectiveness. The findings informed two attribute revisions: "tumor", within the progression-free time attribute, was replaced with "cancer", and second, out-of-pocket costs was removed as an attribute as the participants noted that this was not meaningful as their treatment was covered by insurance or alternative financial assistance.

In each DCE choice task, patients were asked to review the two treatment profiles and identify which they would choose (Figure 1). The combinations of levels shown for each profile was based on a balanced experimental design with minimal overlap.[24] In a balanced design, all attribute levels are presented an equal number of times. Minimal overlap

Table 1 Attributes and Levels

Attribute	Attribute Description	Level 1	Level 2	Level 3	Level 4	Level 5
Progression-free time	Cancer does not worsen for an average of __ months	8	16	24	–	–
Survival time	__% increase in survival time	10	25	55	–	–
Objective response rate	Tumor shrinks for __ out of 100 people	20	50	70	–	–
Duration of response	If tumor shrinks, response lasts for an average of __	1 year	3 years	6 years	–	–
Quality of life[a]	On average, health-related quality of life __	Worsens a lot	Worsens a little	Stays the same	Improves	–
Serious adverse event	__ out of 100 people have a serious side effect that requires medical intervention or hospitalization	82	65	–	–	–
Dosing regimen	*Only levels are shown*	Oral pills once per day plus 30-min IV infusion every 2 weeks	Oral pills once per day plus 30-min IV infusion every 4 weeks	Oral pills once or twice per day plus 30-min IV infusion every 6 weeks	1-h IV infusion every 3 weeks; after completing 4 doses, 30-min IV infusions every 4 weeks	Oral pills once per day

Notes: [a]To help respondents understand what the "quality of life" attribute represents, respondents completed the NCCN-FACT FKSI-19 (V2) quality of life instrument prior to completing the DCE. The instrument was prefaced with the following text: "Health-related quality of life refers to an individual's physical and emotional well-being. Below are questions used to assess health-related quality of life among patients with renal cell carcinoma".

means that attribute levels repeat within the same choice task a small amount of time, preventing respondents from focusing only on one attribute in each task. Based on a rule of thumb for sample sizes for DCE studies, the target sample size target of 300 respondents was highly robust to estimate preference weights for each attribute level with a high level

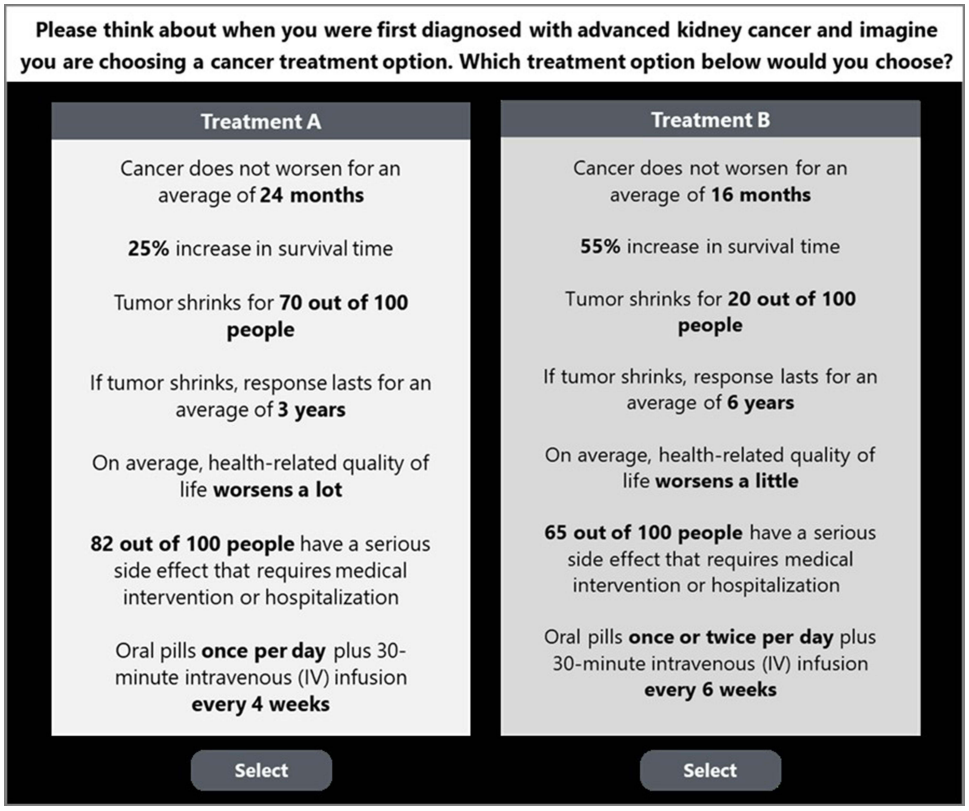

Figure 1 Example Discrete Choice Experiment Task.
Abbreviation: IV, intravenous.

of precision.[30] In addition to DCE, data on demographics and medical history were collected. Health-related QoL was assessed using the NCCN®'s Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – 19-Item Version (FKSI-19).[31]

Statistical Analyses

Descriptive statistics were reported for all survey questions. Categorical variables were described using counts and percentages, and continuous variables were presented using mean and standard deviation (SD). With respect to the DCE, a hierarchical Bayesian logistic regression model was used to estimate preference weights for each attribute level.[23] The Bayes estimation used effects coding for the attribute levels. The results yield a joint posterior distribution of preference weights over the entire sample, including the mean and standard error for each attribute level. This model is "hierarchical" because it has two levels. At the higher level, the model assumes that individuals' preference weights are described by a multivariate normal distribution, and, at the lower level, the individuals' preference weights are governed by a multinomial logistic model.

The differences among preference weights within an attribute represent the strength of preference; the larger the difference, the more influence this change has on treatment choice. Comparing the differences in preference weights between levels across attributes demonstrates the tradeoffs that patients were willing to make when choosing treatment. To further understand the impact of specific attribute levels on treatment choice, preference weights were calculated for three profiles that differed only in two attributes (survival time and regimen). For each profile, the preference weights were summed at an individual level for each attribute level. Mean preference weights were then computed for these summed preference weights and compared across the profiles using paired t-tests.

Each FKSI-19 item was scored on a 0–4-point scale with a total score range of 0–76 where higher scores indicate few to no symptoms and a score of 0 indicates a severely symptomatic patient.[31] Analyses were conducted using SPSS 28.0 and Sawtooth Software Lighthouse Studio 9.13.2.

Subgroup Analyses

Subgroup analyses were performed using ANOVA tests to compare attribute-level preference weights among select subgroups: FKSI-19 score (above versus below median score), race/ethnicity (Asian, Black or African American, Hispanic, White, other, and prefer not to answer), and treatment history (first-line treatments [IO-IO, IO-TKI, TKI monotherapy] and other [first-line treatments not listed and treatment naïve patients]).

Results

Sociodemographic and Disease Characteristics

Of the 331 patients who entered the study, 9 patients withdrew during the screening process, 22 patients did not fulfill the inclusion criteria, and 1 patient was removed for data quality reasons. Thus, 299 patients were included in the final data set and analysis.

Patients had a mean (SD) age of 55.7 (9.4) years with the majority (81.9%) being <65 years old. Patients were evenly distributed between males (49.8%) and females (48.8%). Nearly half were white (50.5%), and 24.8% identified as being of Hispanic, Latino, or Spanish origin. Of those who disclosed their health insurance status (n = 267) and household income (n = 160), most patients reported having private health insurance (69.2%) followed by Medicare (20.7%), and 41.2% reported a household income of $50,000 or higher (Table 2).

Most patients reported a subtype diagnosis of clear cell RCC (85.3%) and perceived their overall health negatively by rating it as "poor" (62.9%) or "fair" (31.4%) at the time of the study. The mean (SD) FKSI-19 score was 33.1 (12.8) indicating that the overall population experienced moderate symptoms. The mean (SD) time since the initial kidney cancer diagnosis was 24.3 (32.2) months, and the time since diagnosis of metastatic disease was 21.2 (24.8) months. Patients were grouped into four categories based on their first-line therapy: IO-TKI combination (29.8%), TKI monotherapy (29.8%), dual immunotherapy (29.4%), and other first-line treatments or treatment-naïve patients (11.0%).

Table 2 Demographic and Health Characteristics

Characteristic		Total Patients (n = 299)
Age, n (%)	<65 years	245 (81.9)
	65–74 years	53 (17.7)
	75–84 years	1 (0.3)
	85+ years	0 (0.0)
Sex, n (%)	Male	149 (49.8)
	Female	146 (48.8)
	Non-binary, other	0 (0.0)
	Prefer not to answer	4 (1.3)
Race, n (%)	White	151 (50.5)
	Black or African American	49 (16.4)
	Prefer not to answer	42 (14.0)
	Native Hawaiian or Pacific Islander	25 (8.4)
	Asian	15 (5.0)
	Other	10 (3.3)
	American Indian or Alaska Native	8 (2.7)
Ethnicity, n (%)	Not of Hispanic, Latino, or Spanish origin	180 (60.2)
	Prefer not to answer	45 (15.1)
	Mexican, Mexican American, Chicano	40 (13.4)
	Cuban	16 (5.4)
	Puerto Rican	14 (4.7)
	Another Hispanic, Latino, or Spanish origin	4 (1.3)
Current health insurance, n (%)	Private or commercial	207 (69.2)
	Medicare	62 (20.7)
	Prefer not to answer	32 (10.7)
	Medicaid	10 (3.3)
	Other	7 (2.3)
	I do not have health insurance	2 (0.7)
Annual Household Income (US), n (%)	Less than $24,999	18 (6.0)
	$25,000 to $49,999	19 (6.4)
	$50,000 to $74,999	26 (8.7)
	$75,000 to $99,999	32 (10.7)
	$100,000 to $124,999	23 (7.7)
	$125,000 to $149,999	11 (3.7)
	$150,000 or more	31 (10.4)
	Prefer not to answer	139 (46.5)

(*Continued*)

Table 2 (Continued).

Characteristic		Total Patients (n = 299)
Type of renal cell carcinoma, n (%)	Clear cell renal cell carcinoma	255 (85.3)
	Papillary renal cell carcinoma	29 (9.7)
	Chromophobe renal cell carcinoma	12 (4.0)
	Other (ie, medullary, etc.)	1 (0.3)
	Unknown/I am not sure	2 (0.7)
	Prefer not to answer	0 (0.0)
Overall health rating*, n (%)	Excellent	0 (0.0)
	Very good	5 (1.7)
	Good	12 (4.0)
	Fair	94 (31.4)
	Poor	188 (62.9)
Treatment History	IO-TKI combination	89 (29.8)
	TKI monotherapy	89 (29.8)
	Dual immunotherapy	88 (29.4)
	Other treatment or treatment-naive	33 (11.0)
Mean time since diagnosed with kidney cancer, months	Mean ± SD	24.3 ± 32.2
Mean time since diagnosed with metastatic kidney cancer, months		21.2 ± 24.8
FKSI Overall score (maximum possible score =76)		33.1 ± 12.8

Note: *Overall health rating is a patient reported single item.
Abbreviations: US, United States; FKSI, Functional Assessment of Cancer Therapy Kidney Symptom Index; IO, immunotherapy; SD, standard deviation; TKI, tyrosine kinase inhibitor.

DCE Attribute-Level Preference Weights

The difference in preference weights within an attribute level represents the strength of preference for that change. The greater the difference among levels within an attribute, the more influence this difference has on treatment choice. In general, for the six attributes that included numeric levels, the preference weights increased linearly as the levels improved (Figure 2).

Based on the difference between mean preference weights within attributes, the most notable improvements were increased survival time from 10% to 55% (difference in mean preference weight = 2.56), change in QoL from "worsens a lot" to "improves" (difference = 2.24), and a reduction in infusion frequency from "oral pills once a day plus 30 minute IV infusion every 2 weeks" to "oral pills once or twice per day plus 30 minutes IV infusion every 6 weeks" (difference = 2.03).

The magnitude of the differences in attribute level preference weights enables the calculation of trade-offs that patients are willing to make in treatment choice. For example, patients were willing to accept a decrease in progression-free time from 24 to 8 months (difference in mean preference weights = 0.51) in exchange for an increase in survival time from 25% to 55% (difference in mean preference weights = 1.49). Further, an improvement in QoL from "worsens a little" to "stays the same" was valued similarly to a decrease in the risk of SAEs from 82% to 65% (difference in preference weights for = 0.82). Also, patients were willing to accept an increase in the risk of a SAE from 65% to 82% (difference in preference weights = 0.82) in exchange for an increase in survival time from 25% to 55% (difference in preference weights = 1.49), as 1.49 is greater than 0.82. As the incremental increase of 1% in survival time was equivalent to a 0.0497 increase in preference weight, and

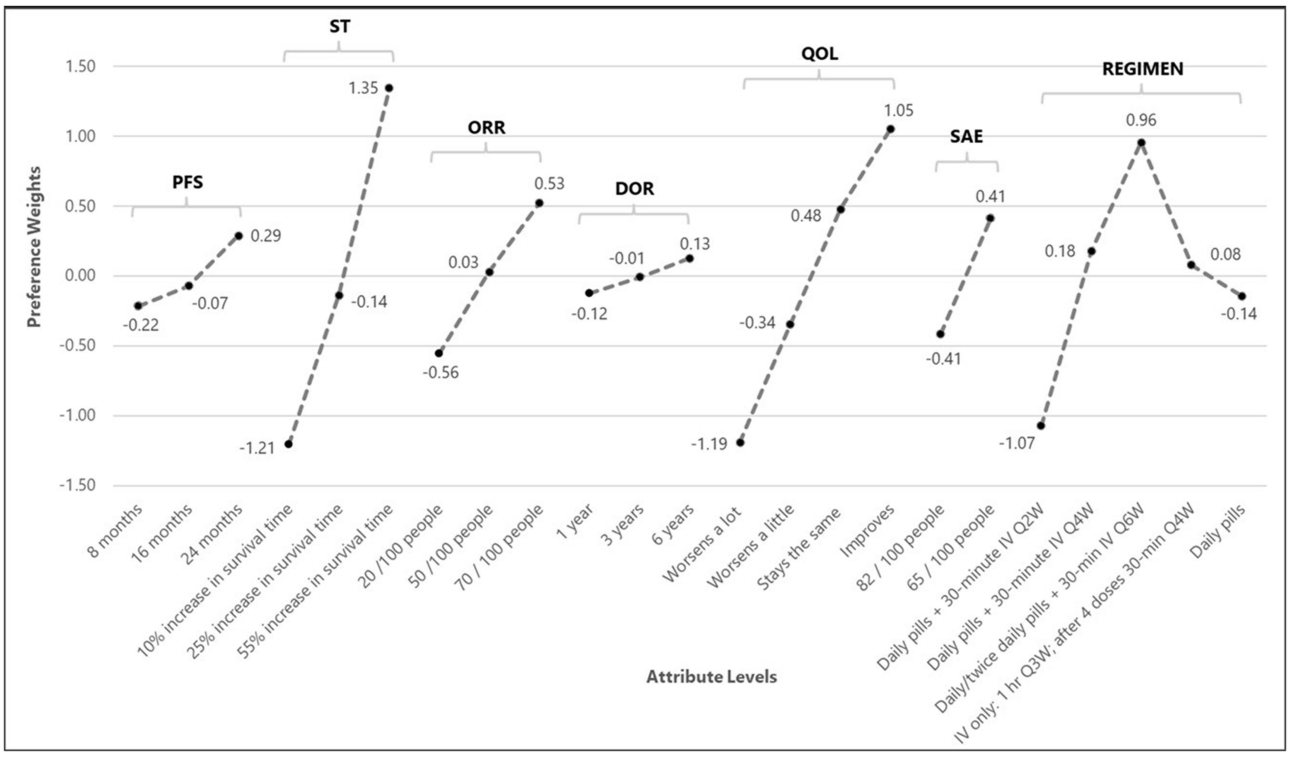

Figure 2 Mean attribute-level preference weights.
Note: Q#W – every (2/3/4/6) weeks.
Abbreviations: PFS, progression-free survival (progression-free time); ST, survival time; QoL, quality of life; SAE, serious adverse event; IV, intravenous.

a decrease in the risk of a SAE of 1% was equivalent to a 0.0482 increase in preference weight, this indicates that each percentage increase or decrease between these two attributes were interchangeable.

Assessing Survival and Treatment Regimen Preferences for Select Treatment Profiles

To better understand tradeoffs between increased efficacy and treatment regimen, preference weights were estimated for three profiles that differed in survival time and regimen (Table 3). Specifically, Profiles A and C both showed an increase in survival time of 55% but had different regimens; Profile A involved an oral pill once per day plus an infusion every 6

Table 3 Preference Weights for Selected Treatment Profiles Comparison

Attribute	Profile A	Profile B	Profile C
Progression free time	24 months	24 months	24 months
Survival time	55% increase	10% increase	55% increase
ORR	70 / 100 people	70 / 100 people	70 / 100 people
DOR	6 years	6 years	6 years
QOL	Improves	Improves	Improves
SAE	65 / 100 people	65 / 100 people	65 / 100 people
Regimen	Pills 1x/2x per day + 30-min IV infusion every 6 weeks	Pills 1x/2x per day + 30-min IV infusion every 6 weeks	Pills 1x per day + 30-min IV infusion every 2 weeks
Summed Preference Weight	4.71	2.16	2.68
Standard Error	0.11	0.12	0.18

Note: All p-values for paired *t*-test comparing groups (A-B, B-C, A-C) were significant.
Abbreviation: IV, intravenous.

weeks, and Profile C had an oral pill plus an infusion every 2 weeks. Profile B had a survival time increase of 10% and a regimen with an oral pill plus an infusion every 6 weeks. Profile A, which had the most favorable survival time and most convenient regimen, was most preferred by patients (overall summed mean preference weight = 4.71). The mean preference weights for Profiles B and C were 2.16 and 2.68, respectively (all profiles differed significantly from each other; $p < 0.05$). Because Profile C had a higher preference weight than Profile B, it indicates that increasing survival time was considered more important in treatment selection than switching the dosing regimen; in other words, improving efficacy had more of an impact on preference score than switching to a more convenient regimen.

Subgroup Analyses

Subgroup analyses examined differences in preference weights among race, type of first-line treatment, and FKSI-19 score. The preference weights did not differ significantly across race/ethnicity groups, except for durability of response where Black/African American participants rated this higher in importance relative to the other race/ethnicity groups. However, the sample sizes of Asian and "other" racial groups were smaller ($n \leq 20$) compared to the rest of the racial and ethnic groups. Likewise, FKSI-19 scores (high scores [>34.0] and low scores [≤34.0]) did not significantly impact preference weights. Among first-line treatment groups, the preference weights were consistent with the overall findings. However, those in the other first-line treatment group/treatment naïve showed relatively less importance for change in dosing regimen and instead favored improvement in QoL compared to IO-IO, IO-TKI, and TKI monotherapy treatment groups. It is important to note though that the other first-line treatment group/treatment naïve was smaller in size ($n = 33$) and had a longer time since diagnosis (mean: 62 months) than the overall sample (mean: 24 months). Subgroup results can be found within the Supplemental Table 1.

Discussion

This study utilized a DCE to assess patient preferences for treatment characteristics and trade-offs they were willing to make when choosing a treatment for aRCC. Patients prioritized improvements in survival time, QoL, and treatment regimen over other treatment attributes. DOR and reducing the risk of SAE were considered of lesser importance when choosing treatment; however, all attributes impacted treatment choices. Among the eight treatment attributes compared in the DCE, half focused on treatment efficacy (survival time progression-free time, DOR, ORR). An increase in survival time from 10% to 55% was the most important improvement relative to the other efficacy attributes (progression-free time, ORR, DOR). The importance of survival time was supported by a comparison of preferences for selected treatment profiles varying in survival time and regimen.

Past preference research in RCC found that efficacy attributes were most important to patients. Specifically, overall survival has been found to be most important in some studies, while progression-free survival and complete response were most important in others.[15,17,19,20,32,33] However, in a preference study of targeted therapies in metastatic RCC, Park et al reported that reducing the risk of AEs was more important than improving progression-free survival for patients.[18] This may be attributable to increased importance placed on maintaining QoL for as long as possible in the advanced RCC stage, as[34] was found in our study where aRCC patients placed substantial value on QOL improvement relative to the other attributes.

The value placed on improved QOL in this study is consistent with previous DCE reports in RCC[32] and breast cancer.[35] Additionally, in our study, patients equally valued reduced risk of SAEs and improvement in QoL from "worsens a lot" to "stays the same", which suggests the importance of QoL among patients with aRCC. QoL was also reported as a patient-reported outcome in landmark clinical trials in RCC as an adjunct to clinical benefits.[13,14] This inclusion suggests that our results hold significance, as QoL is increasingly being considered as one of the goals of care while deciding the value of treatment along with clinical benefit.[4,36]

With regard to dosing regimen, patients with aRCC preferred a combination of oral and IV infusion from every 2 weeks to every 6 weeks, which is in-line with earlier reports.[3,32] Notably, patients gave lower preference to once-a-day oral pills in comparison to three of the four regimens comprising IV treatment and depicted a bell-shaped curve representation. Although oral pills are more convenient,[37] Park et al also reported that patients with metastatic RCC showed a lower preference for oral drug administration. We hypothesize that patients may believe that IV options are

more convenient in comparison to daily pills, and patients likely get accustomed to hospital/infusion center visits and prefer the possibility of seeing their physicians more frequently during scheduled visits.[18] Further, adding pills to an infusion regimen does not appear to substantially impact preferences, as minimal differences in preferences were observed in the Q4W infusion regimen whether daily pills were included or not (preference weight = 0.18 vs 0.08, respectively). Nevertheless, patient preferences for the mode and frequency of administration may be dependent on multitude of factors including convenience, past experience, and patient characteristics such as employment status, distance from infusion center, cost or insurance coverage, or cultural or ethnic preferences.[37,38]

This study has limitations. The self-reported nature of this study is associated with potential biases such as inaccurate recall and potentially false reporting. As inherent with any research relying on convenience sampling methods, certain subgroups of patients may be over-represented or under-represented. Specifically, in this study, the sample population was younger (mean age: 55.7 years) compared to the mean age of RCC diagnosis in the US (64 years).[2] In addition, interpretation of the impacts of treatment experience was limited by the "other" category that could be endorsed for first-line treatment, which could include a mix of treatment-naïve, monotherapy, and other treatments not listed for RCC. Additionally, the DCE involved choosing between hypothetical treatment profiles that may be missing key factors that influence treatment choice. Finally, given that multiple efficacy attributes were included in the DCE, it is possible that preferences for efficacy overall may have been distributed across these attributes, effectively reducing the preference weights for each.

Conclusions

The results of this study indicate that on average, patients with aRCC preferred improvements in survival time and QoL. This study also highlights the importance of characteristics beyond efficacy that are influential when choosing treatment for aRCC. Therefore, discussions among patients and physicians may benefit from a holistic approach when discussing treatments, especially potential impacts on health-related QoL and specifics on treatment regimen, such as timing and administration.

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