Health state utilities in patients with advanced renal cell carcinoma receiving first-line pembrolizumab plus axitinib or sunitinib

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Background

- Few studies have measured preference-based utility weights as evaluation of health-related quality of life (HRQoL) under specific first-line treatments for advanced renal cell carcinoma (aRCC)
- Pembrolizumab plus axitinib was approved as first-line treatment for aRCC based on its significant survival advantage over sunitinib, as demonstrated in the phase 3 KEYNOTE-426 trial[1,2]
- KEYNOTE-426 administered various instruments, including EuroQol EQ-5D-3L, to measure HRQoL.[3] The EQ-5D-3L system measures generic health status, the results of which can be converted to preference-based health utility valuations using published algorithms[4]
- This study is to assess health state utilities and adverse event (AE)-related disutility among previously untreated patients with aRCC randomized to pembrolizumab + axitinib or sunitinib in KEYNOTE-426
- These health utility values can be applied while modeling the cost-effectiveness of treatments in the aRCC setting as well as in the adjuvant RCC setting, when considering the journey of patients crossing over from recurrence-free to having metastatic RCC and advancing in disease paradigm

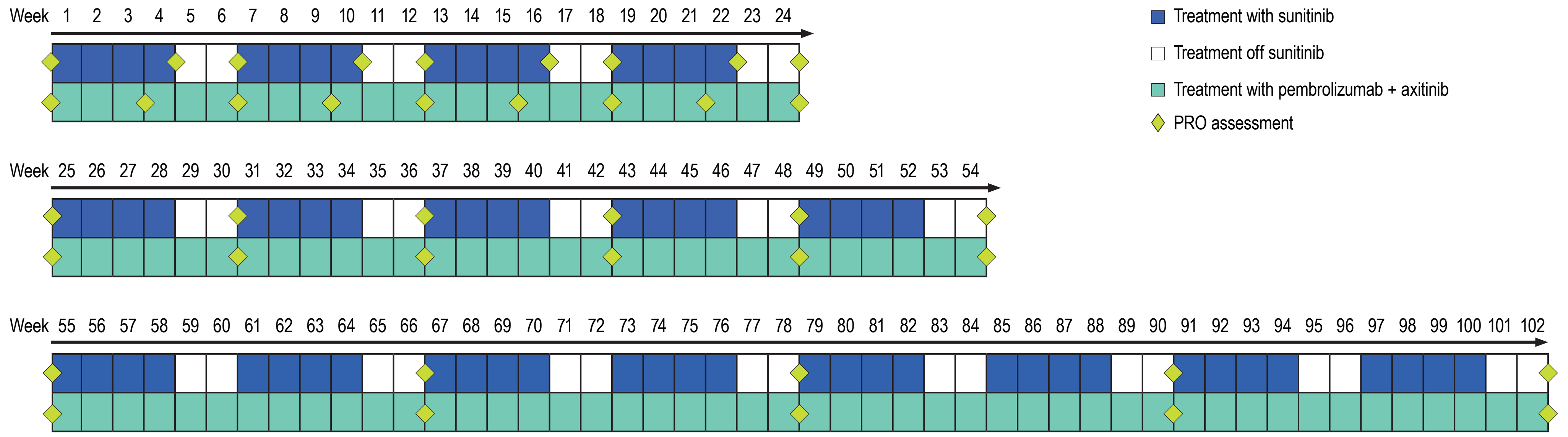
Objective

- To assess health state utilities and AE-related disutility among previously untreated patients with aRCC randomized to pembrolizumab + axitinib or sunitinib in KEYNOTE-426

Methods

- Study design and participants
  - In KEYNOTE-426, patients with previously untreated advanced renal cell carcinoma were randomly assigned in a 1:1 ratio to receive pembrolizumab + axitinib or sunitinib[1]
  - The analyses of EQ-5D-3L data were based on the full analysis set (FAS) population from KEYNOTE-426, made up of subjects who were randomized, received a study treatment, and completed at least one EQ-5D-3L questionnaire. Subjects were analyzed in the treatment group allocated at randomization
  - The EQ-5D-3L FAS population included a total of 850 subjects. The data cutoff date of KEYNOTE-426 for this study was August 24, 2018
- Measures
  - Utility outcome was measured using the EuroQol EQ-5D-3L. The questionnaire contains 5 attributes: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each attribute has 3 levels: no problem, some problems, and major problems
  - For patients receiving pembrolizumab + axitinib, EQ-5D-3L data were collected at Day 1 of every cycle from cycle 1 to 9 (1 cycle=21 days), every other cycle from cycle 9 to 19, and every 4th cycle from cycle 19 until treatment discontinuation, as well as at the discontinuation visit and the 30-day safety follow-up visit
  - For patients receiving sunitinib, EQ-5D-3L data were collected at Day 1 and Day 29 of every cycle from cycle 1 to 4 (1 cycle=42 days), Day 1 of each cycle from cycle 5 to 10, and every other cycle from cycle 10 until treatment discontinuation, as well as at the discontinuation visit and the 30-day safety follow-up visit
  - The schedule of EQ-5D-3L assessments is depicted in **Figure 1**

Figure 1. Schedule of treatment[a] and EQ-5D-3L assessments in KEYNOTE-426



[a]Pembrolizumab 200 mg was received intravenously once every 3 weeks for a maximum of 35 cycles plus axitinib 5 mg orally twice daily. Sunitinib 50 mg was received orally once daily for the first 4 weeks, followed by a 2-week off-drug period, during each 6-week cycle. Treatment was continued until disease progression, development of unacceptable toxic effects, or physician or patient decision to discontinue.

- Statistical analysis
  - A linear mixed-effects regression model was fitted using repeated measures data from patient visits in which both disease progression status (per Response Evaluation Criteria in Solid Tumors v1.1 criteria) and EQ-5D-3L were available (N=810 patients with 7,119 patient visits). The regression equations are noted in **Table 1**
  - The dependent variable of the equation was EQ-5D-3L utility scores, derived from United Kingdom valuation[4]
  - The independent variables included indicators for health state (progression-free vs progressive disease) and grade 3+ AE (presence vs absence) in regression Model 1
  - A treatment group indicator was added to the independent variables to derive treatment-specific utilities in regression Model 2
  - Patient-level random effects were included to account for within-subject correlation for both models
- Outcomes
  - Prediction of EQ-5D-3L utility scores based on patients' progression states, grade 3+ AE status, and treatment received

Table 1. Regression model and variable descriptions

A. Regression equations

Model	Specification[a]
Model 1	$Utility_{ij}=\beta_0+\beta_1\ Progression\ Status_{ij}+\beta_2\ AE_{ij}+e_i$
Model 2	$Utility_{ij}=\beta_0+\beta_1\ Progression\ Status_{ij}+\beta_2\ AE_{ij}+\beta_3\ Treatment_i+e_i$

[a]*i* denotes individual and *j* denotes time when the EQ-5D-3L measures were taken.

B. Variable definitions

Variable	Description
Utility	EQ-5D-3L utility based on UK algorithm and value set
Progression status	Progression-free vs progressive disease, according to RECIST, version 1.1, as determined by blinded independent central review (1=Progression)
AE	Indicator for whether an EQ-5D-3L score was measured during grade 3+ AEs (1=Yes)
Treatment	Pembrolizumab + axitinib vs sunitinib allocated at randomization (1=Sunitinib)

Results

- The estimates, standard errors, and *P* value of regression coefficients (defined in **Table 1**) are presented in **Table 2**
- Progression status and grade 3+ AEs were found to be statistically significant predictors for utilities under both regression models ($P<0.001$)
- No statistically significant dependence of specific treatment on utility was detected under Model 2 ($P=0.185$)

Table 2. Regression coefficients by progression and AE status

A. Model 1 (pooled treatments)

	Estimate	SE	*P* value
Progression-free state (β_0)	0.8033	0.0067	<0.001
Presence of progression (β_1)	-0.0309	0.0068	<0.001
Presence of grade 3+ AE (β_2)	-0.0405	0.0058	<0.001

B. Model 2 (including treatment as a covariate)

	Estimate	SE	*P* value
Progression-free state (β_0)	0.8115	0.0090	<0.001
Presence of progression (β_1)	-0.0310	0.0068	<0.001
Presence of grade 3+ AE (β_2)	-0.0404	0.0058	<0.001
Treatment of sunitinib (β_3)	-0.0169	0.0013	0.185

SE, standard error

- The utilities derived from the regressions are summarized in **Table 3** and **Figure 2**
- In Model 1, health state utilities pooled across treatment arms were estimated to be 0.8033 (SE=0.0067) for pre-progression vs 0.7724 (0.0090) for progressive disease ($P<0.001$) in the absence of grade 3+ AEs. Presence of any grade 3+ AE corresponded to an additive disutility of -0.0405 (0.0058) (P<0.001)
- In the sensitivity analysis, treatment-specific utilities for pre-progression vs progressive disease were 0.8115 (0.0091) vs 0.7805 (0.0109) for pembrolizumab + axitinib and 0.7946 (0.0094) vs 0.7637 (0.0112) for sunitinib; AE-related disutility from this model was -0.0404 (0.0058)

Table 3. EQ-5D-3L health utility scores by progression and AE status

A. Model 1 (pooled treatments)

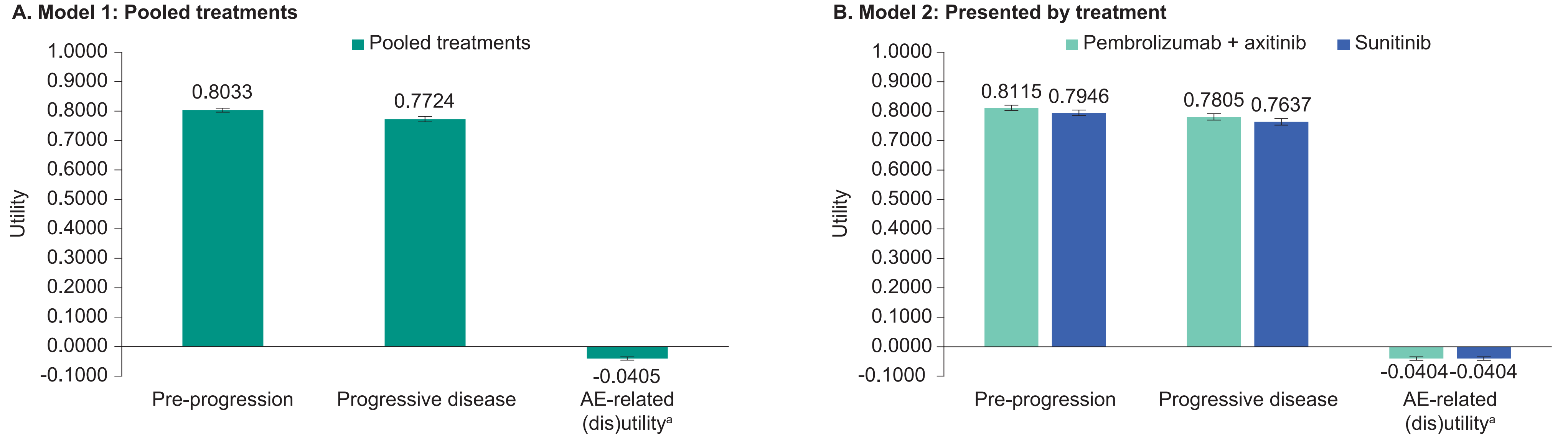
	Pooled (N=810), number of observations: 7,119		
	Estimate	SE	*P* value
Progression-free state	0.8033	0.0067	<0.001
Progressive disease state	0.7724	0.0090	<0.001
AE (dis)utility[a]	-0.0405	0.0058	<0.001

B. Model 2 (presented by treatment)

	Pembrolizumab + axitinib		Sunitinib	
	Estimate	SE	Estimate	SE
Progression-free state	0.8115	0.0091	0.7946	0.0094
Progressive disease state	0.7805	0.0109	0.7637	0.0112
AE (dis)utility[a]	-0.0404	0.0058	-0.0404	0.0058

[a]AE (dis)utility is expressed as a negative value, to represent the decrement in utility. That is, utility with grade 3+ AEs is derived by adding the AE (dis)utility to the utility in the absence of grade 3+ AEs.

Figure 2. Health utility scores by progression and AE status


A. Model 1: Pooled treatments

B. Model 2: Presented by treatment

[a]AE-related (dis)utility is expressed as a negative value, to represent the decrement in utility. That is, utility with grade 3+ AEs is derived by adding the AE (dis)utility to the utility in the absence of grade 3+ AEs.

Conclusions

- This study obtained utilities for aRCC health states both with and without differentiation by specific first-line treatment received
- Under both approaches, utility significantly worsened during grade 3+ AEs and after disease progression
- Patients treated with pembrolizumab + axitinib had utility values comparable to those receiving sunitinib monotherapy, regardless the progression status. This finding is consistent with the previously reported HRQoL analyses using various PRO scales[3]
- These utilities can be incorporated into cost-effectiveness analyses of approved and investigational treatments for RCC

References

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