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Quality-Adjusted Time Without Symptoms of Disease Progression or Toxicity (Q-TWiST) of Nivolumab Plus Ipilimumab Versus Sunitinib Among Untreated Advanced Renal Cell Carcinoma Patients With Intermediate or Poor Prognostic Risk

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Introduction

- Each year, 338,000 new cases of renal cell carcinoma (RCC) are diagnosed globally, including 30% with advanced disease[1,2]
- Sunitinib (SUN), a multikinase inhibitor, is recommended as a first-line therapy for patients with advanced RCC (aRCC)[3]
- The combination of nivolumab, a programmed death-1 inhibitor, and ipilimumab, a cytotoxic T lymphocyte antigen-4 inhibitor (NIVO+IPI), is approved in the United States and the European Union for the treatment of previously untreated aRCC in patients with intermediate or poor risk[4,5]
  - This combination is a category 1 preferred regimen for patients with previously untreated aRCC and at intermediate or poor risk in the National Comprehensive Cancer Network clinical practice guidelines for kidney cancer[6]
- CheckMate 214 is a phase 3 trial comparing NIVO+IPI versus SUN among previously untreated patients with aRCC[7]
  - Among patients with International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate or poor prognostic risk, the hazard ratios (HRs) for NIVO+IPI (n = 425) versus SUN (n = 422) for overall survival (OS) and progression-free survival (PFS) were 0.63 ($P < 0.001$) and 0.82 ($P = 0.03$; not significant per the prespecified threshold), respectively
  - The objective response rates were 42% with NIVO+IPI and 27% with SUN ($P < 0.001$)
  - In all treated patients, grade 3 or 4 treatment-related adverse events (AEs) occurred in 46% of patients in the NIVO+IPI arm (N = 547) versus 63% of patients in the SUN arm (N = 535)
- Understanding the clinical risk/benefit of various oncology therapies from the patient's perspective is of increasing interest to regulators and clinicians
- Quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST) is an analytical approach designed to provide an assessment of the net health benefits of a therapy in terms of quantity and quality of survival gains[8]
  - Q-TWiST accounts for the duration and quality-of-life impact of AEs (toxicities), length of time in relapse/progression (time with symptoms of disease), and duration of "good survival" (before relapse/progression and without toxicities)

Objective

- To compare the Q-TWiST of NIVO+IPI versus SUN among previously untreated aRCC patients with IMDC intermediate or poor prognostic risk enrolled in the CheckMate 214 trial at a maximum follow-up of 45 months

Methods

Data source

- Extended follow-up data from CheckMate 214 with minimum OS follow-up of 30 months and median OS follow-up of 32.4 months (data cutoff of August 6, 2018)

Study population

- IMDC intermediate/poor-risk patients enrolled in CheckMate 214 who were randomized to either NIVO+IPI or SUN

Statistical analyses

- Q-TWiST assesses the overall quantity and quality of patient survival based on the amount of time spent in the health states shown in **Figure 1**

Figure 1. Q-TWiST health states

Toxicity ("TOX" state)	Time without symptoms or toxicity ("TWiST" state)	Relapse ("REL" state)
Period of AEs grade ≥3 after randomization and before progression or censoring	Period without symptoms or toxicities before progression	Period after disease progression until death or censoring

- Mean Q-TWiST was calculated as the sum of the product of the time spent in each state by its respective utility (U), as follows:

$$\text{Q-TWiST} = U_{TWiST} \times \text{TWiST} + U_{TOX} \times \text{TOX} + U_{REL} \times \text{REL}$$

Where U_{TWiST} = utility of TWiST state
TWiST = restricted mean duration of TWiST state
U_{TOX} = utility of TOX state
TOX = restricted mean duration of TOX state
U_{REL} = utility of REL state
REL = restricted mean duration of REL state

- Using unadjusted Kaplan–Meier analysis, the restricted mean duration of time spent in each health state was calculated, up to 45 months of follow-up, as follows:
  - TOX = area under the TOX curve
  - TWiST = the difference in area under the PFS and TOX curves
  - REL = the difference in area under the OS and PFS curves
- 95% confidence intervals (CIs) were derived using a nonparametric bootstrap approach
- The following key assumptions were adopted:
  - In the base case, utilities were $U_{TWiST} = 1$, $U_{TOX} = 0.5$, and $U_{REL} = 0.5$
  - U_{TOX} was 0.5, irrespective of length and severity of the treatment-related AE
  - Treatment-related AE duration (to estimate TOX) was truncated at disease progression
  - All TOX time was grouped and modeled together at therapy start
- Sensitivity analyses were conducted as follows:
  - **Threshold utility analysis:** Q-TWiST was calculated for U_{TOX} and U_{REL} ranging from 0.00 (time not counted toward total Q-TWiST) to 1.00 (time fully counted toward total Q-TWiST)
  - **Q-TWiST gain function:** the difference in Q-TWiST between treatments was assessed using data truncated at various time points to assess how this difference in Q-TWiST changed under different analytic horizons
  - **Including grade ≥2 treatment-related AEs:** the TOX health state considered all grade ≥2 treatment-related AEs
- Relative gains in Q-TWiST were calculated as follows:

$$\frac{\textit{(Q-TWiST for NIVO+IPI)} - \textit{(Q-TWiST for SUN)}}{\textit{OS for SUN}}$$

- Relative gains of ≥10% and ≥15% were defined as clinically important and clearly clinically important, respectively[9]

Results

- NIVO+IPI had a significantly longer TWIST time, shorter TOX time, and numerically longer REL time versus SUN (**Table 1**)
- Patients receiving NIVO+IPI versus SUN had a statistically significant and clinically meaningful improvement in quality-adjusted OS of 3.5 months (**Table 1**)

Table 1. Restricted mean durations of health states at maximum follow-up of 45 months

Health state	NIVO+IPI	SUN	Difference	*P* value
TOX	0.5 (0.4–0.7)	1.1 (0.8–1.3)	–0.5 (–0.8 to –0.2)	0.001
TWiST	14.7 (13.3–16.0)	11.0 (10.0–12.2)	3.7 (1.8–5.4)	<0.001
PFS	15.2 (13.8–16.5)	12.1 (11.0–13.2)	3.1 (1.3–4.8)	0.001
REL	11.5 (10.4–12.9)	11.3 (10.1–12.4)	0.3 (–1.4 to 2.0)	0.729
OS	26.8 (25.5–27.9)	23.4 (22.1–24.6)	3.4 (1.6–5.1)	<0.001
Q-TWiST	20.7 (19.5–21.8)	17.2 (16.2–18.2)	3.5 (2.0–4.9)	<0.001

- In the base case (ie, $U_{TOX} = U_{REL} = 0.5$), patients receiving NIVO+IPI versus SUN had a clinically meaningful improvement in quality-adjusted OS with a 15.1% relative gain (**Table 2**)

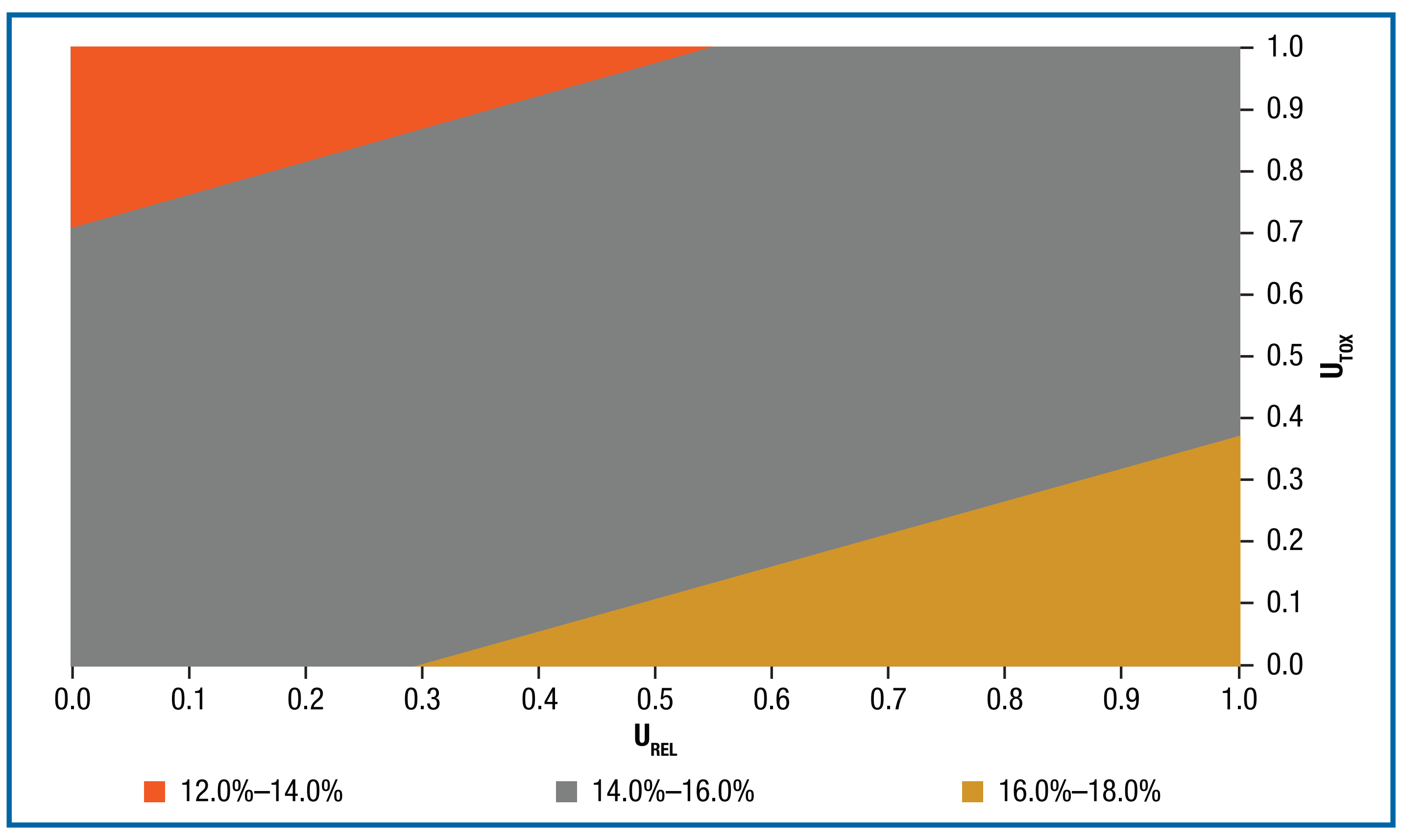
Table 2. Relative Q-TWiST gain and threshold utility analysis at maximum follow-up of 45 months

Utility (TOX–REL)	NIVO+IPI	SUN	Difference	Relative gain
(0.0–0.0)	14.7 (13.3–16.0)	11.0 (10.0–12.2)	3.7 (1.8–5.4)	15.6%
(0.0–0.5)	20.5 (19.3–21.5)	16.7 (15.7–17.7)	3.8 (2.3–5.2)	16.2%
(0.0–1.0)	26.2 (25.0–27.4)	22.3 (21.0–23.6)	3.9 (2.2–5.5)	16.9%
(0.5–0.0)	14.9 (13.6–16.2)	11.6 (10.5–12.7)	3.4 (1.6–5.1)	14.5%
(0.5–0.5)	20.7 (19.5–21.8)	17.2 (16.2–18.2)	3.5 (2.0–4.9)	15.1%
(0.5–1.0)	26.5 (25.2–27.6)	22.8 (21.5–24.1)	3.7 (1.9–5.3)	15.7%
(1.0–0.0)	15.2 (13.8–16.5)	12.1 (11.0–13.2)	3.1 (1.3–4.8)	13.3%
(1.0–0.5)	21.0 (19.8–22.1)	17.7 (16.7–18.8)	3.3 (1.7–4.7)	13.9%
(1.0–1.0)	26.8 (25.5–27.9)	23.4 (22.1–24.6)	3.4 (1.6–5.1)	14.5%

Shaded row represents the base case.

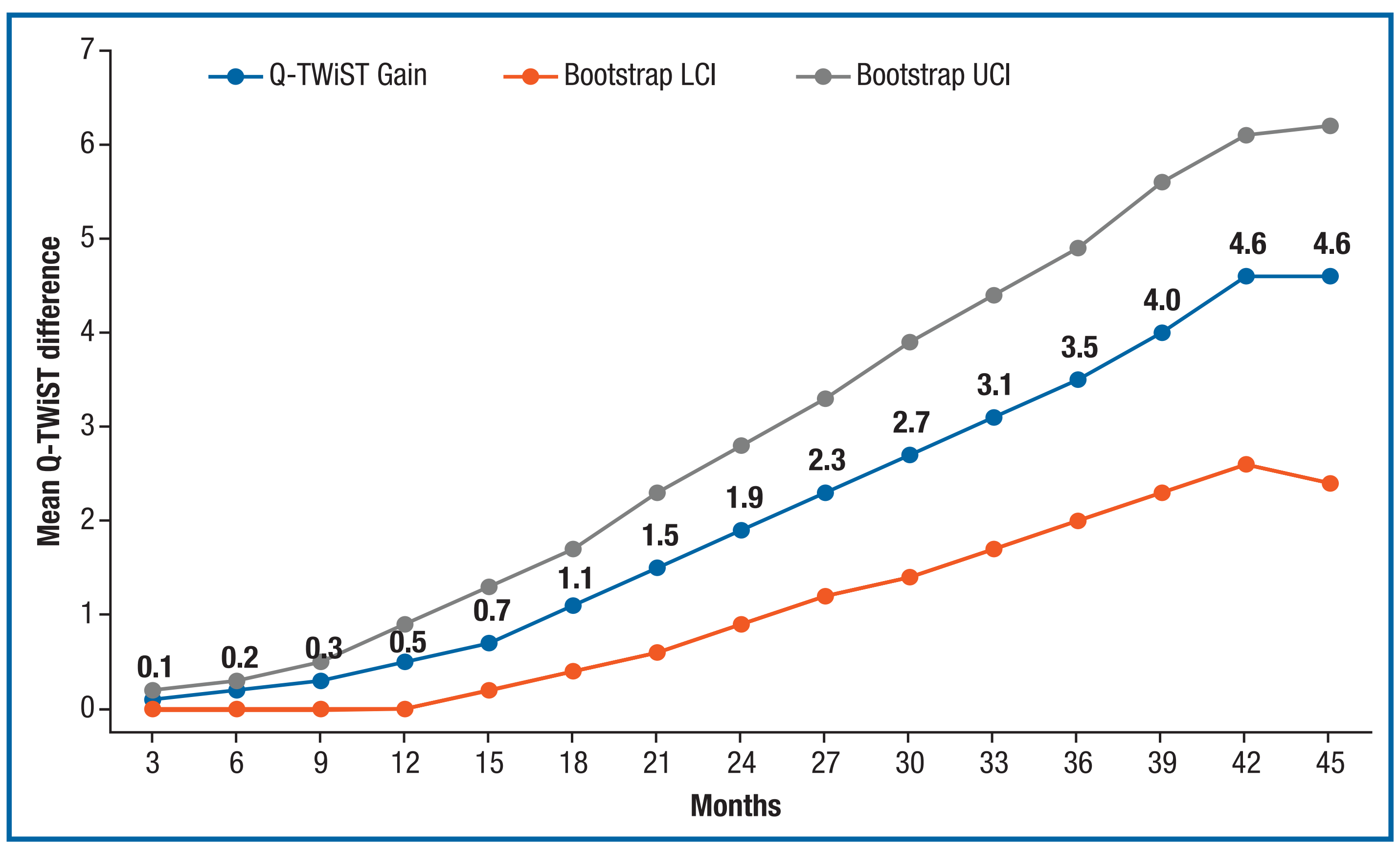
- In threshold analyses (**Table 2** and **Figure 2**), which varied utilities for TOX and REL across the full 0.00–1.00 range, Q-TWiST difference (and relative gain) varied from 3.1 months (13.3%) to 3.9 months (16.9%) in favor of NIVO+IPI versus SUN

Figure 2. Q-TWiST threshold utility analysis



- **Figure 3** shows the gain in Q-TWiST (in months) for NIVO+IPI versus SUN with increase in follow-up time in the trial:
  - The quality-adjusted OS gain for NIVO+IPI versus SUN increased from 0.1 months (at 3-month follow-up) to 4.6 months (at 45-month follow-up)
  - The relative gains reached the clinically meaningful gain threshold at 24 months (not shown in figure)
  - There was a plateau in the relative Q-TWiST gain from months 42–45 as all patients in the analytical data set had progressed and were in the REL health state after month 42. Therefore, minimal to no gains in quality-adjusted OS were seen for NIVO+IPI versus SUN after month 42

Figure 3. Q-TWiST gain function over follow-up time



- When grade ≥2 treatment-related AEs were included in the analysis, patients receiving NIVO+IPI had a statistically significant *and* clinically meaningful improvement in quality-adjusted OS of 3.7 months, with a 16.0% relative gain, versus patients receiving SUN (**Table 3**)
- The gains in quality-adjusted OS when grade ≥2 AEs were included in the analysis were only 0.2 months (corresponding relative gain increase, 0.9%) higher when compared with results from the base-case analysis. Thus, the results for the scenario including the grade ≥2 AEs were similar to the base case

Table 3. Quality-adjusted OS for NIVO+IPI vs SUN and relative Q-TWiST gain for sensitivity analysis including grade ≥2 treatment-related AEs at maximum follow-up of 45 months

Utility (TOX–REL)	NIVO+IPI	SUN	Difference	Relative gain
(0.0–0.0)	10.9 (9.7–12.1)	6.8 (6.0–7.7)	4.1 (2.4–5.6)	17.4%
(0.0–0.5)	16.6 (15.6–17.7)	12.4 (11.6–13.3)	4.2 (2.8–5.6)	18.1%
(0.0–1.0)	22.4 (21.2–23.6)	18.0 (16.9–19.2)	4.4 (2.6–6.0)	18.7%
(0.5–0.0)	13.0 (11.8–14.3)	9.4 (8.5–10.4)	3.6 (1.9–5.1)	15.4%
(0.5–0.5)	18.8 (17.7–19.9)	15.1 (14.2–16.0)	3.7 (2.3–5.1)	16.0%
(0.5–1.0)	24.6 (23.4–25.7)	20.7 (19.5–21.9)	3.9 (2.2–5.4)	16.6%
(1.0–0.0)	15.2 (13.8–16.5)	12.1 (11.0–13.2)	3.1 (1.3–4.8)	13.3%
(1.0–0.5)	21.0 (19.8–22.1)	17.7 (16.7–18.8)	3.3 (1.7–4.7)	13.9%
(1.0–1.0)	26.8 (25.5–27.9)	23.4 (22.1–24.6)	3.4 (1.6–5.1)	14.5%

- The gains in quality-adjusted OS when grade ≥2 treatment-related AEs were included in the analysis were 0.6 months (corresponding relative gain increase, 6.0%) higher when compared with results from the base-case analysis

Discussion

- NIVO+IPI resulted in a statistically significant and clinically important gain in quality-adjusted OS (3.5 months) versus SUN
- Relative gains in quality-adjusted survival (15.1% at base case) for NIVO+IPI versus SUN
  - Remained clinically important across all utilities for time in toxicity and relapse in threshold analyses, ranging from 13.3%–16.9%
  - Increased consistently from 3–42 months of follow-up, reaching a clinically meaningful threshold at 24 months
  - Improved when grade ≥2 treatment-related AEs were included in the analysis, ranging from 13.3%–18.7%
- In order to contextualize the results from the current study, the relative gains for NIVO+IPI versus SUN were compared with Q-TWiST gains from a systematic literature review of 81 published Q-TWiST studies across 13 different cancer types.[10] The relative gains demonstrated in the analysis are among the top 25% of published Q-TWiST studies included in the systematic review

Conclusions

- NIVO+IPI provides a significantly longer quality-adjusted survival benefit compared with SUN among previously untreated aRCC patients with IMDC intermediate or poor prognostic risk in first-line treatment
- In addition to the efficacy benefits from CheckMate 214, clinicians may also consider the quantity and quality of survival demonstrated here using the Q-TWiST approach in the shared patient–provider treatment decision-making process

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