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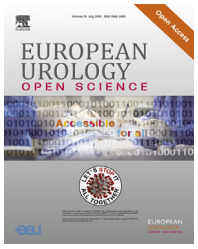

European Association of Urology

Kidney Cancer

Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) for Lenvatinib plus Everolimus Versus Everolimus Monotherapy in Patients with Advanced Renal Cell Carcinoma

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Abstract

Background: The lenvatinib (LEN) plus everolimus (EVE) combination demonstrated improved progression-free survival over everolimus alone in a phase 2 trial (Study-205).
Objective: To compare quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST) between LEN + EVE and EVE alone among patients with advanced renal cell carcinoma (RCC) following one prior antiangiogenic therapy.
Design, setting, and participants: This was a post hoc analysis of Study-205.
Outcome measurements and statistical analysis: Survival time was partitioned into three mutually exclusive health states: time with grade 3/4 toxicity (TOX); time before disease progression and without grade 3/4 toxicity (TWiST); and time after disease progression (REL). The mean time in each state was weighted by utility measures and summed to calculate Q-TWiST. Nonparametric bootstrapping generated 95% confidence intervals (CIs). In the base case, utility for TWiST, TOX, and REL was assigned as 1.0, 0.5, and 0.5, respectively. Sensitivity analyses applied alternative utility values for REL, TOX, and TWiST. A relative gain in Q-TWiST of $\geq$10% and $\geq$15% has been established as clinically important and clearly clinically important, respectively.
Results and limitations: Patients receiving LEN + EVE (n = 51) had a significant mean Q-TWiST gain of 3.7 mo (14.7 vs 11.0 mo; 95% CI for difference 1.3–6.3), with a relative gain of 24% compared to EVE alone. In a sensitivity analysis using alternative utility values for TWiST (varied from 0.55 to 0.9) with utility set to 0.5 for both TOX and REL, the relative Q-TWiST gain was maintained (ranging from 11.0% to 21.2%; all significant) across varying utility values. Limitations include the sample size, the absence of utility estimates, and the length of adverse events from the trial.
Conclusions: LEN + EVE showed a significant and clearly clinically important improvement in quality-adjusted survival time versus EVE alone.

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Patient summary: Patients with advanced kidney cancer who had received other previous treatments experienced a clearly clinically important improvement in quality survival time when treated with lenvatinib plus everolimus compared to everolimus alone.

1. Introduction

Renal cell cancer (RCC) accounts for 2–3% of all adult malignancies, representing the seventh most common cancer among men and the ninth most common among women [1]. Globally, RCC accounts for approximately 2.4% of all cancer-related deaths [2]. Among patients diagnosed with RCC, approximately one-third present with metastatic disease and approximately one-quarter progress to the metastatic stage even after complete surgical removal of the primary tumor [3].

There has been significant research on the development of targeted therapies that include VEGF pathway inhibitors (eg, axitinib, bevacizumab, pazopanib), mTOR inhibitors (eg, everolimus), and immunotherapies (pembrolizumab, nivolumab, ipilimumab, avelumab) [4–7]. According to the National Comprehensive Cancer Network guidelines, lenvatinib plus everolimus combination therapy, and nivolumab, cabozantinib, and axitinib as monotherapies are listed as category 1 subsequent treatment options for RCC patients with clear cell histology [5].

The combination of lenvatinib and everolimus received regulatory approval from the US Food and Drug Administration for the treatment of patients with advanced RCC following one prior antiangiogenic therapy [8]. This approval was based on the findings from a randomized, phase 2, open-label, multicenter, three-arm trial (Study-205) in patients with advanced or metastatic RCC who progressed on a VEGF inhibitor. The results of Study-205 showed that lenvatinib plus everolimus significantly prolonged progression-free survival (PFS) compared with everolimus alone (hazard ratio [HR] 0.40, 95% confidence interval [CI] 0.24–0.68; $p = 0.0005$). In the study, the safety profile for lenvatinib plus everolimus was consistent with the known safety profile of each individual agent [9]. However, no quality-of-life (QoL) outcome measures were included in the phase 2 trial.

Assessing the tradeoff between efficacy and toxicity is important for a comprehensive assessment of the risk-benefit profile of competing interventions. Quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST) is a method that allows integration of the benefits in quantity and quality of survival time into a single measure and assessment of the clinical risk-benefit of the available therapies [10,11]. The Q-TWiST method has been used since the mid-1980s, and in the past decade has been increasingly used to assess the net benefits of oncology treatments across various cancers, including RCC, by integrating the trade-off between clinical benefit and the risk of oncology treatments. In the present study, we assess the quality-adjusted survival time of lenvatinib plus everolimus versus everolimus alone using a Q-TWiST methodology applied to the Study-205 data.

2. Patients and methods

2.1. Data source and study population

A post hoc analysis of individual patient-level data from Study-205 (ClinicalTrials.gov NCT01136733) was conducted. The trial included adult patients with advanced or metastatic, clear-cell RCC with Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and with radiographic evidence of disease progression on a VEGF-targeted therapy within 9 mo of stopping the treatment. Of the 153 patients randomized, 51 received lenvatinib plus everolimus (18 mg/d and 5 mg/d, respectively), 50 received everolimus alone (10 mg/d), and 52 patients received lenvatinib alone (24 mg/d). The primary outcome measure in the clinical trial was investigator-assessed PFS, defined as the time from randomization to first documentation of disease progression (according to Response Evaluation Criteria in Solid Tumors v1.1) or death. Secondary outcome measures included overall survival (OS), the objective response rate, safety, tolerability, and pharmacokinetic profiles of lenvatinib (alone and in combination with everolimus). The primary efficacy analysis was based on the intent-to-treat population. Details on study design and methodology have been described previously [9].

2.2. Statistical analyses

The primary objective of the current post hoc analyses was to compare the absolute and relative Q-TWiST gain with lenvatinib plus everolimus over everolimus alone. Additional comparisons of interest were: (1) lenvatinib plus everolimus versus lenvatinib alone; and (2) lenvatinib alone versus everolimus alone.

2.2.1. Q-TWiST methodology

Patient survival time was partitioned into three mutually exclusive health states, TOX, TWiST, and REL, defined as follows:

- TOX: time spent with grade 3/4 toxicity, with any day with multiple adverse events counted once;
- TWiST: time before disease progression (as defined in the trial) and without grade 3/4 toxicity; and
- REL: time from disease progression until death or loss to follow-up.

The restricted mean time (referred to as "mean time" hereafter) spent in each state through 24-mo follow-up was obtained by calculating the area under the Kaplan-Meier curve for each state and was then weighted by a health-state utility associated with that state [12]. If the grade $\geq$3 adverse events were ongoing at the time of disease progression or end of follow up, the toxicity duration was capped at disease progression or end

of follow up as a proxy for the TOX time [13]. A health-state utility is considered a proxy for a patient's generic QoL and is used to describe the value (ie, patient's preferences) of a defined health state on a scale from 0 to 1, where 1 represents perfect health and 0 represents a health state close to death [14].

The following steps were followed to obtain the TOX, TWiST, and REL health-state values:

1 Kaplan-Meier curves were built for TOX, PFS, and OS, separately.
2 The mean duration for each Kaplan-Meier curve (TOX, PFS, and OS) was obtained by calculating the area under each curve.
3 Then the mean time in TOX, TWiST, and REL was calculated as:

- Mean TOX time = area under the TOX curve.
- Mean TWiST time = area under the PFS curve – area under the TOX curve.
- Mean REL time = area under the OS curve – area under the PFS curve.

Q-TWiST was then calculated using the following equation [10]:

$$\text{Q-TWiST} = \textbf{Utility}(\textbf{TWiST}) \times \textbf{TWiST} + \textbf{Utility}(\textbf{TOX}) \times \textbf{TOX} + \textbf{Utility}(\textbf{REL}) \times \textbf{REL},$$

where TWiST = mean TWiST time; TOX = mean TOX time; REL = mean REL time; Utility(TWiST) = utility weight assigned for TWiST; Utility(TOX) = utility weight assigned for TOX; and Utility(REL) = utility weight assigned for REL.

In the base case, Utility(TWiST), Utility(TOX), and Utility(REL) were assigned as 1.0, 0.5, and 0.5, respectively. These utilities are commonly used in the Q-TWiST literature [11]. Nonparametric bootstrapping was used to generate a 95% CI for the difference in Q-TWiST between the treatment groups. A relative gain in Q-TWiST was calculated as the Q-TWiST difference divided by the mean OS for the control arm (ie, everolimus alone). A relative gain in Q-TWiST of ≥10% and ≥15% has been established in previous studies as clinically important and clearly clinically important, respectively [14].

2.3. Sensitivity analyses

Sensitivity analyses were performed to examine the robustness of the results by applying alternative utility values (ie, threshold analyses). In the first scenario, Utility(TOX) and Utility(REL) were set to 0.5 and Utility(TWiST) was varied from 0.55 to 0.9. In the second scenario, Utility(TWiST) was set to 0.78 (obtained from EQ-5D index data from a RCC clinical trial published in the literature and applied to all treatment arms in the current analyses [15]) and Utility(TOX) and Utility(REL) were varied from 0.0 to 0.78.

2.4. Subgroup analyses

Additional subgroup analyses were conducted for prespecified subgroups including age, sex, region, baseline hypertension status, ECOG status, baseline hemoglobin level, serum calcium level, and prognostic risk groups (Memorial Sloan Kettering Cancer Center and International Metastatic RCC Database Consortium). In addition, subgroup analysis by lenvatinib/everolimus five-factor composite biomarker score (CBS) was also performed. The five-factor CBS is a baseline serum biomarker score that could identify patients who might have an enhanced response to lenvatinib/everolimus [16]. CBS-low was defined as CBS of 0–2 and CBS-high as CBS of 3–5 [16].

3. Results

3.1. Primary comparison: base-case analyses

In Study-205, lenvatinib plus everolimus significantly prolonged PFS in comparison to everolimus alone (median 14.6 vs 5.5 mo; HR 0.40, 95% CI 0.24–0.68; $p = 0.0005$; primary data cutoff June 13, 2014). Patients in the lenvatinib plus everolimus arm had median OS of 25·5 mo (95% CI 20.8–25.5) compared to 17.5 mo (11.8–not estimable) in the everolimus arm (HR 0.55, 95% CI 0.30–1.01; $p = 0.062$). In Study-205, the grade 3/4 adverse event (AE) rate was 50% in the everolimus arm and 71% in the lenvatinib plus everolimus arm. The most common grade 3 treatment-emergent AEs (TEAEs) in the lenvatinib plus everolimus arm were diarrhea, fatigue or asthenia, and hypertension. The most common grade 3 TEAEs in the everolimus arm were anemia, dyspnea, hypertriglyceridemia, and hyperglycemia [9]. A total of 24% patients in the lenvatinib plus everolimus arm and 12% in the everolimus arm had TEAEs leading to study treatment discontinuation. In addition, 71% of patients in the combination arm and 26% in the everolimus arm had a dose reduction. Most patients had their first dose reduction within the first three cycles of treatment for both treatment arms. Figure 1A,B shows partitioned survival plots with distinct TOX, TWiST, and REL states for the two treatment arms. The area under TOX curve, the area between the PFS and TOX curves, and the area between the OS and PFS curves show the partitioning of survival time into TOX, TWiST, and REL, respectively. For the primary comparison, lenvatinib plus everolimus had a significantly longer mean restricted TWiST time (difference 4.5 mo, 95% CI 1.4–7.8), numerically longer mean restricted TOX time (difference 1.2 mo, 95% CI–0.3 to 3.1), and numerically shorter mean restricted REL time (difference −2.8 mo, 95% CI–6.2 to 0.6) versus everolimus alone (Table 1).

In the base case with Utility(TOX) = Utility(REL) = 0.5 and Utility(TWiST) = 1.0, patients treated with lenvatinib plus everolimus experienced a positive Q-TWiST gain compared to patients receiving everolimus alone, with a mean Q-TWiST difference of 3.7 mo (95% CI 1.3–6.3), representing a 24.1% relative Q-TWiST gain that was statistically significant (Table 1).

3.2. Primary comparison: sensitivity analyses

In the sensitivity analysis for scenario 1, in which TWiST time was assigned utilities ranging from 0.55 to 0.9 while holding the utility for TOX and REL at 0.5, the absolute gain in mean Q-TWiST ranged from 1.7 to 3.3 mo, with the relative improvement ranging from 11.0% to 21.2%, both of which were statistically significant (Table 2).

In the sensitivity analyses for scenario 2, in which TOX and REL times were assigned different utilities ranging from 0.0 to 0.78 while holding the utility for TWiST at 0.78, the absolute gain in mean Q-TWiST ranged from 1.4 to 4.5 mo, with the relative improvement ranging from 8.7% to 28.8%. The majority of the scenarios showed statistically significant and clinically important Q-TWiST gains for the combination treatment (Table 3).

3.3. Primary comparison: gain in Q-TWiST at various time points during follow-up

Figure 2 shows the gain in mean Q-TWiST for lenvatinib plus everolimus versus everolimus at different time points during the 24-mo follow-up. Patients receiving lenvatinib plus everolimus had a positive Q-TWiST gain ranging from

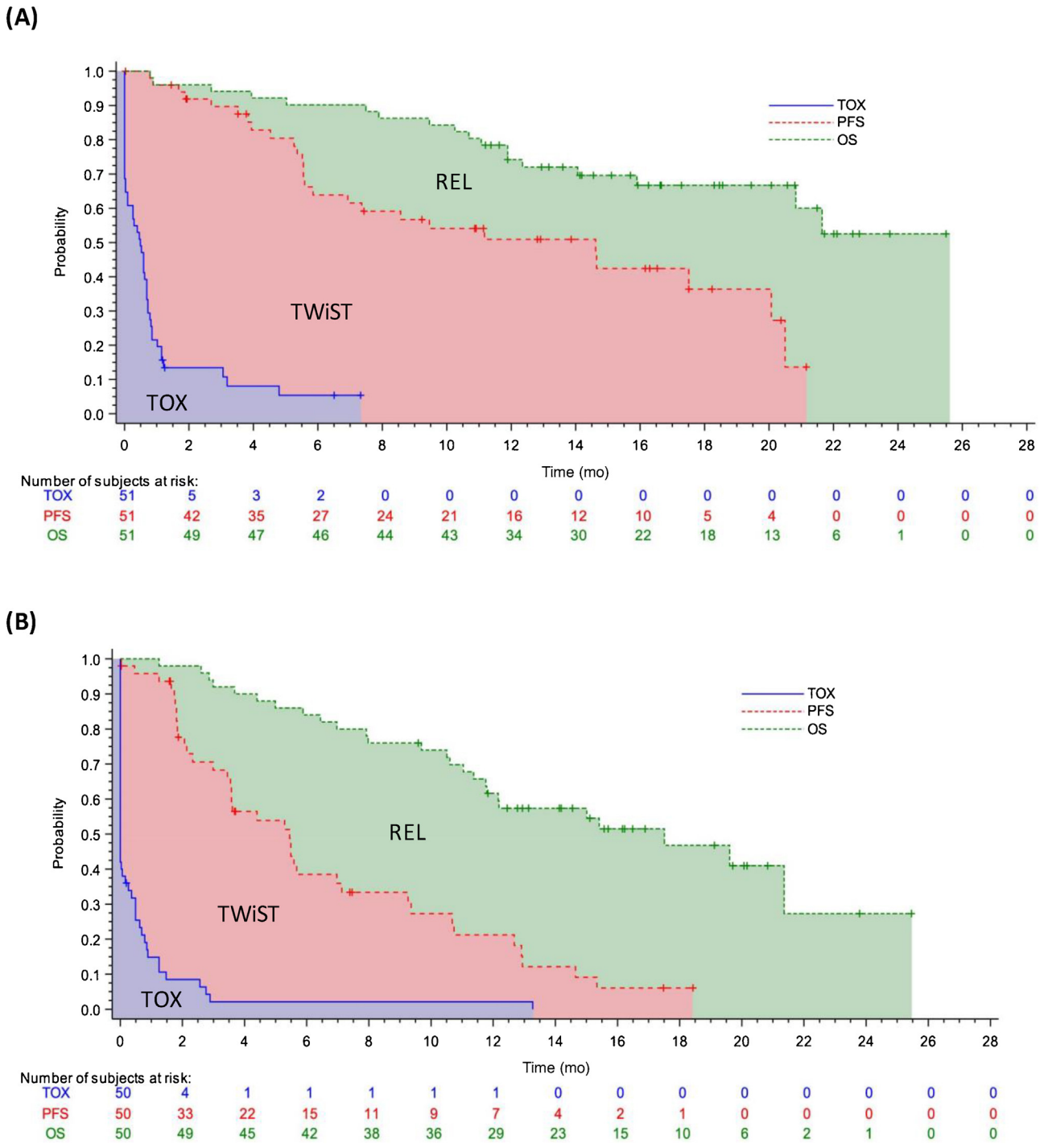

Fig. 1 – Partitioned survival plot for (A) patients who received lenvatinib plus everolimus and (B) patients who received everolimus alone. OS = overall survival; PFS = progression-free survival; Q-TWiST = quality-adjusted time without symptoms of disease progression or toxicity; REL = time from disease progression until death or lost to follow-up; TOX = time spent with grade 3/4 toxicity; TWiST = time prior to disease progression and without grade 3/4 toxicity.

0.3 mo at 6-mo follow-up to 3.7 mo at 24-mo follow-up versus everolimus alone.

3.4. *Primary comparison: subgroup analyses*

The subgroup analyses consistently favored the lenvatinib plus everolimus combination, although not all comparisons were statistically significant, which could be attributed to the small sample size for the subgroups. The results should be interpreted with caution owing to the relatively small number of patients in each subgroup (Fig. 3).

3.5. *Secondary comparisons*

There were no significant differences in Q-TWiST values between lenvatinib plus everolimus and lenvatinib alone

Table 1 – Restricted mean duration for the health states

Health state	Restricted mean duration (mo)		
	LEN + EVE (n = 51)	EVE (n = 50)	Difference (95% CI)
Overall survival	18.6	15.6	3.0 (−0.04 to 6.0)
Progression-free survival	12.8	7.0	5.8 (2.8–8.8)
TOX	1.9	0.7	1.2 (−0.3 to 3.1)
REL	5.8	8.5	−2.8 (−6.2 to 0.6)
TWiST	10.9	6.4	4.5 (1.4–7.8)
Q-TWiST (base case)	14.7	11.0	3.7 (1.3–6.3)

CI = confidence interval; EVE = everolimus; LEN = lenvatinib; Q-TWiST = quality-adjusted time without symptoms of disease progression or toxicity; REL = time from disease progression until death or loss to follow-up; TOX = time spent with grade 3/4 toxicity; TWiST = time prior to disease progression and without grade 3/4 toxicity.

Table 2 – Sensitivity analyses for Q-TWiST (TOX/REL utility set to 0.5, TWiST utility varies) [a]

Utility			Mean Q-TWiST (mo)			Relative improvement in Q-TWiST (%)
TWiST	TOX	REL	LEN + EVE (n = 51)	EVE (n = 50)	Difference (95% CI)	
0.9	0.5	0.5	13.6	10.3	3.3 (1.1–5.6)	21.2
0.8	0.5	0.5	12.5	9.7	2.8 (0.8–5.0)	18.3
0.78	0.5	0.5	12.3	9.6	2.8 (0.8–4.8)	17.7
0.7	0.5	0.5	11.5	9.1	2.4 (0.6–4.3)	15.4
0.6	0.5	0.5	10.4	8.4	1.9 (0.3–3.6)	12.5
0.55	0.5	0.5	9.8	8.1	1.7 (0.1–3.3)	11.0

CI = confidence interval; EVE = everolimus; LEN = lenvatinib; Q-TWiST = quality-adjusted time without symptoms of disease progression or toxicity; REL = time from disease progression until death or loss to follow-up; TOX = time spent with grade 3/4 toxicity; TWiST = time before disease progression and without grade 3/4 toxicity.

[a] The mean Q-TWiST values were rounded. The relative improvement in Q-TWiST was calculated using the numbers before rounding for accuracy purposes.

Table 3 – Sensitivity analyses for Q-TWiST (TWIST utility set to 0.78, TOX/REL utility varies)

Utility			Mean Q-TWiST (mo)			Relative improvement in Q-TWiST (%)
TWiST	TOX	REL	LEN + EVE (n = 51)	EVE (n = 50)	Difference (95% CI)	
0.78	0	0	8.5	5.0	3.5 (1.1– 6.1)	22.6
0.78	0	0.4	10.8	8.4	2.4 (0.3–4.6)	15.5
0.78	0	0.78	13.0	11.6	1.4 (−1.5 to 4.2)	8.7
0.78	0.4	0	9.3	5.2	4.0 (1.9–6.4)	25.8
0.78	0.4	0.4	11.6	8.7	2.9 (1.0–4.9)	18.7
0.78	0.4	0.78	13.8	11.9	1.9 (−0.7 to 4.4)	11.9
0.78	0.78	0	10.0	5.5	4.5 (2.2–6.9)	28.8
0.78	0.78	0.4	12.3	8.9	3.4 (1.3–5.3)	21.7
0.78	0.78	0.78	14.5	12.2	2.3 (−0.03 to 4.7)	14.9

CI = confidence interval; EVE = everolimus; LEN = lenvatinib; Q-TWiST = quality-adjusted time without symptoms of disease progression or toxicity; REL = time from disease progression until death or loss to follow-up; TOX = time spent with grade 3/4 toxicity; TWiST = time before disease progression and without grade 3/4 toxicity.

(difference 2.6 mo, 95% CI–0.02 to 5.3) or between lenvatinib and everolimus (difference 1.2 mo, 95% CI–1.2 to 3.6) in the base-case analyses Supplementary Tables 1 and 2). Results for the sensitivity analyses (ie, threshold analyses) for the additional comparisons also showed nonsignificant differences in Q-TWiST (data available on request).

4. Discussion

Q-TWiST is a well-established and generally accepted method for estimating integrated outcomes of survival, toxicity, and clinical endpoints for different treatments in oncology. It is a useful tool for patients and physicians to assess the trade-offs between the clinical benefits and

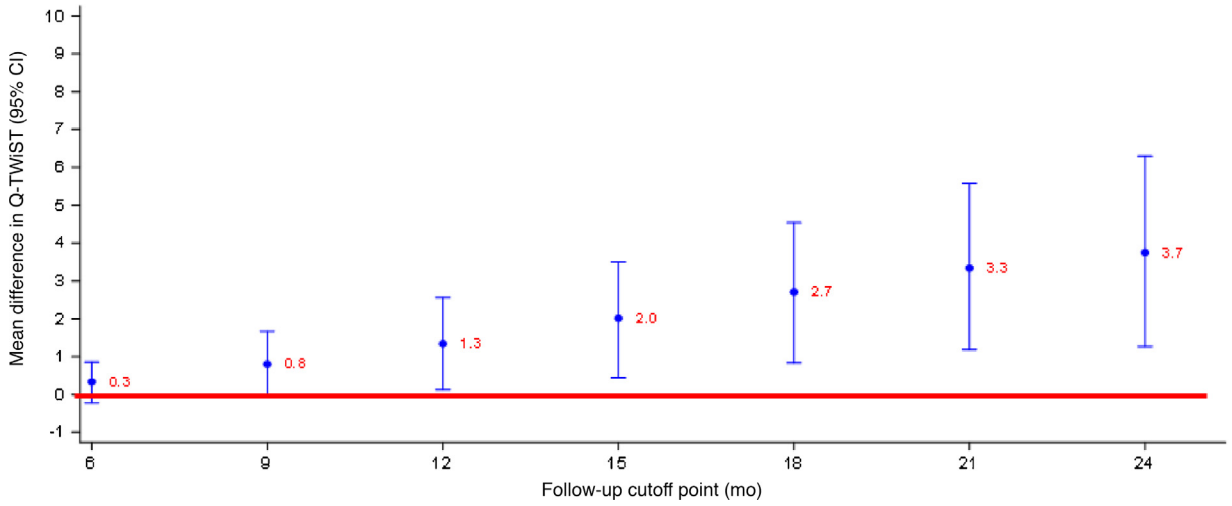

Fig. 2 – Difference in Q-TWiST between lenvatinib + everolimus and everolimus at various follow-up durations. CI = confidence interval; Q-TWiST = quality-adjusted time without symptoms of disease progression or toxicity.

toxicities of competing treatments. Our analyses demonstrated that the lenvatinib plus everolimus combination is associated with a significant positive gain in Q-TWiST (relative Q-TWiST gain of 24.1%) compared to everolimus alone in patients with advanced or metastatic RCC who had progressed on an initial VEGF-based therapy. Revicki et al [14] previously established thresholds demonstrating clinically important and clearly clinically important relative Q-TWiST gains of $\geq$10% and $\geq$15%, respectively. Using these criteria, the relative Q-TWiST gain of 24.1% with lenvatinib plus everolimus versus everolimus alone was clearly clinically important. Furthermore, when the utilities of different health states were varied in the sensitivity/threshold analyses, the Q-TWiST gains mostly remained statistically significant and clinically important in favor of lenvatinib plus everolimus versus everolimus alone, underscoring the robustness of the results. The subgroup analyses consistently showed a trend in favor of the lenvatinib plus everolimus combination; however, the differences were not always statistically significant, which could be attributed to the relatively small number of subjects in each subgroup. However, the subgroup analyses are exploratory in nature and there is a small sample size. In order to generate robust conclusions regarding the subgroup analysis results, larger clinical trials are warranted.

The majority of previously published Q-TWiST analyses in advanced RCC focused on first-line treatments [17–20]. Shah et al [21] compared quality-adjusted survival time (measured using the Q-TWiST method) between nivolumab and everolimus in the second or third line in advanced RCC using CheckMate 025 data. They found that treatment with nivolumab was associated with a significant Q-TWiST gain of 3.3 mo (relative gain 14%) versus everolimus [21]. In the phase 3 METEOR trial, cabozantinib was compared with everolimus in patients with advanced RCC who progressed after previous tyrosine-kinase inhibitor treatment [22]. However, no Q-TWiST data based on the METEOR trial were found.

This is the first analysis to explore the quality-adjusted survival time for lenvatinib plus everolimus using clinical trial data from Study-205, as no QoL data were prospectively collected in this clinical trial. The Q-TWiST methodology has been used to evaluate other regimens in advanced RCC in both the first and subsequent lines of therapy [17,20,21].

An important goal in the management of RCC is tumor control while delaying a deterioration in QoL [11,14,23]. The Q-TWiST method incorporates clinical efficacy (OS and PFS) and toxicity into a single measure of quality-adjusted survival time. This information is vital to clinicians and patients in making informed decisions on treatment choices.

While the Q-TWiST approach is a well-established method and widely used in oncology research across multiple indications, it has certain limitations. Particularly important is the choice of utilities, as the validity may vary depending on the source. While patient-based utility estimates from clinical trials are the most valid, in the absence of utility estimates from these direct sources, sensitivity and threshold analyses can be useful in testing the validity of the base-case results and assist clinicians in balancing the efficacy, survival, and toxicities associated with different therapies [11,14]. In our post hoc analysis of the Study-205 clinical trial, given that no utility or QoL data were collected, we used assumptions for the utility values and conducted sensitivity analyses to test the robustness of the base-case results. The Q-TWiST gains with lenvatinib plus everolimus were maintained across different scenarios with varying utilities for TOX/ REL or TWiST time.

Another limitation is related to the small sample size in Study-205, which could limit the generalizability of the results. Finally, the current analysis was not designed to parse the length of grade 3/4 AEs owing to limited data availability. This could lead to overestimation of time spent in TOX [20].

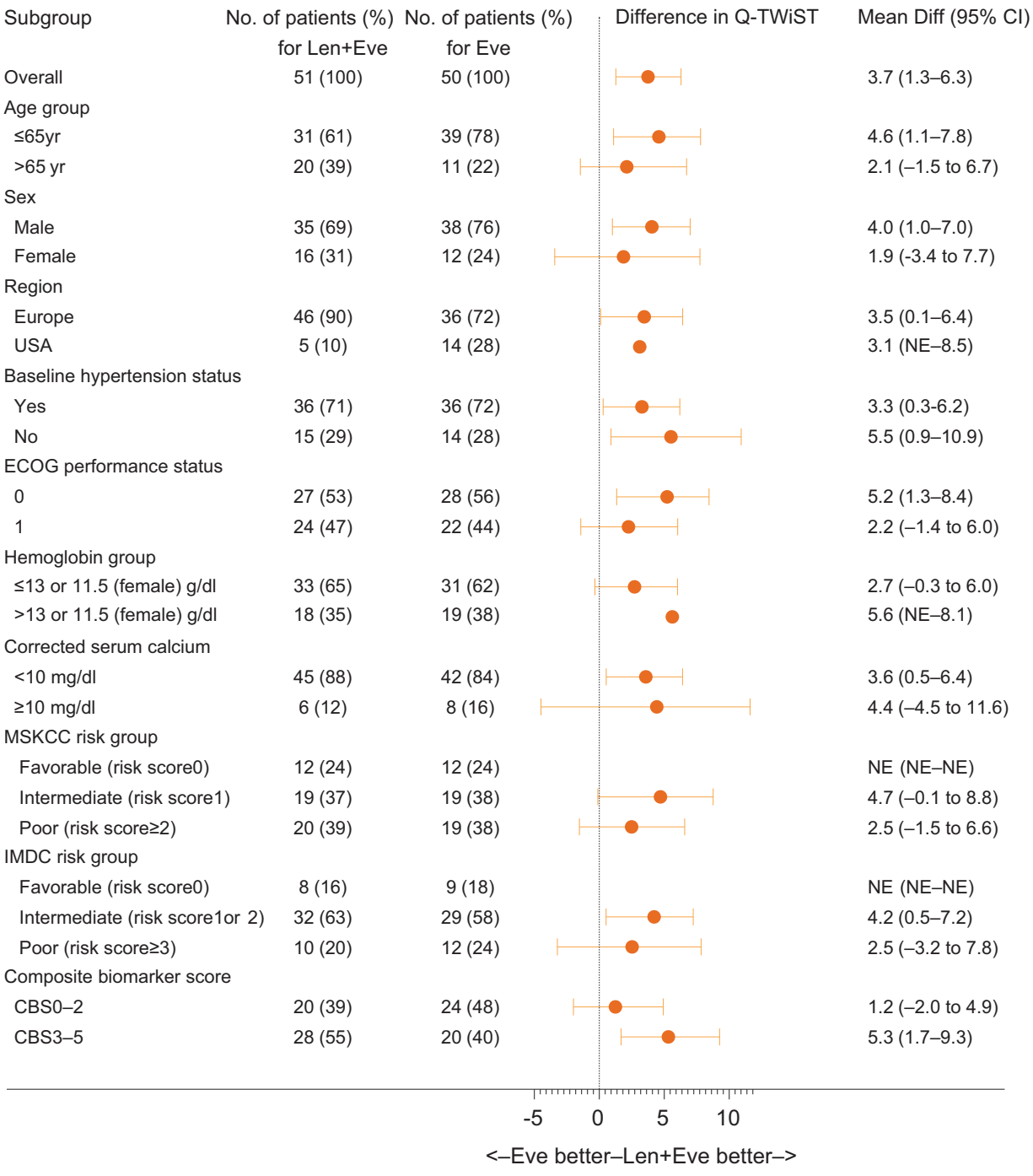

Fig. 3 – Differences in Q-TWiST (base case) among prespecified subgroups and CBS biomarker subgroups through 24 mo. CI = confidence interval; Q-TWiST = quality-adjusted time without symptoms of disease progression or toxicity; MSKCC = Memorial Sloan Kettering Cancer Center; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ECOG = Eastern Cooperative Oncology Group; CBS = composite biomarker score; LEN + EVE, lenvatinib + everolimus. Note: for subgroups with no or a small number of events, the CIs for the mean differences in Q-TWiST are not estimable (NE).

5. Conclusions

Combination therapy with lenvatinib plus everolimus showed a significant and clearly clinically important improvement in quality-adjusted survival time versus everolimus alone among patients with advanced RCC and treated with one prior antiangiogenic therapy. The results of the Q-TWiST analysis could be of value to clinicians and patients as it integrates clinical information (toxicity, progression, and OS) and quality of life for each of the health states into a single meaningful index.

Author contributions: Chung-Han Lee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wan, Motzer, Lee.
Acquisition of data: Motzer.
Analysis and interpretation of data: Xie, Wan, Motzer.
Drafting of the manuscript: Wan, Xie.
Critical revision of the manuscript for important intellectual content: Wan, Smith, Xie, Motzer, Lee.
Statistical analysis: Xie.
Obtaining funding: Lee, Motzer, Wan.
Administrative, technical, or material support: Wan.
Supervision: Motzer, Lee.
Other: None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euros.2021.06.008.

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