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ORIGINAL ARTICLE

Adjuvant sunitinib in patients with high-risk renal cell carcinoma: safety, therapy management, and patient-reported outcomes in the S-TRAC trial

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Background: Adjuvant sunitinib has significantly improved disease-free survival versus placebo in patients with renal cell carcinoma at high risk of recurrence post-nephrectomy (hazard ratio 0.76; 95% confidence interval, 0.59–0.98; two-sided $P = 0.03$). We report safety, therapy management, and patient-reported outcomes for patients receiving sunitinib and placebo in the S-TRAC trial.

Patients and methods: Patients were stratified by the University of California, Los Angeles Integrated Staging System and Eastern Cooperative Oncology Group performance status score, and randomized (1 : 1) to receive sunitinib (50 mg/day) or placebo. Single dose reductions to 37.5 mg, dose delays, and dose interruptions were used to manage adverse events (AEs). Patients' health-related quality of life, including key symptoms typically associated with sunitinib, were evaluated with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

Results: Patients maintained treatment for 9.5 (mean, SD 4.4) and 10.3 (mean, SD 3.7) months in the sunitinib and placebo arms, respectively. In the sunitinib arm, key AEs occurred ∼1 month (median) after start of treatment and resolved within ∼3.5 weeks (median). Many (40.6%) AEs leading to permanent discontinuation were grade 1/2, and most (87.2%) resolved or were resolving by 28 days after last treatment. Patients taking sunitinib showed a significantly lower EORTC QLQ-C30 overall health status score versus placebo, although this reduction was not clinically meaningful. Patients reported symptoms typically related to sunitinib treatment with diarrhea and loss of appetite showing clinically meaningful increases.

Conclusions: In S-TRAC, AEs were predictable, manageable, and reversible via dose interruptions, dose reductions, and/or standard supportive medical therapy. Patients on sunitinib did report increased symptoms and reduced HRQoL, but these changes were generally not clinically meaningful, apart from appetite loss and diarrhea, and were expected in the context of known sunitinib effects.

Clinical trial registration: ClinicalTrials.gov, NCT00375674.

Key words: renal cell carcinoma, adjuvant sunitinib, cancer, patient-reported outcomes

Introduction

The global burden of renal cell carcinoma (RCC) is approximately 300 000 new cases and 129 000 deaths per year, with an annual rate of increase of approximately 0.7% [1]. Until recently, surgical resection followed by observation was the only treatment for non-metastatic RCC. Patients at high risk of recurrence based on the University of California, Los Angles Integrated Staging System (UISS) [2] represent about 15% of all non-metastatic RCC cases, and around 60% of these patients will experience recurrence and metastatic disease within 5 years [3]. There was therefore a clear need for adjuvant therapies, especially for patients with loco-regional disease.

Sunitinib malate (Sutent®) has been recently approved by the US Food and Drug Administration for adjuvant treatment of patients at high risk [defined as tumor grade ≥3 (≥T3), any Fuhrman grade, and/or nodal involvement (N+)] for recurrent RCC post-nephrectomy based on the Sunitinib as Adjuvant Treatment for High-risk Renal Cell Carcinoma Following Nephrectomy (S-TRAC) trial that evaluated the efficacy and safety of sunitinib in patients with loco-regional RCC at high risk (≥T3 and/or N+) of relapse post-nephrectomy [4]. S-TRAC results demonstrated a statistically significant and clinically meaningful 24% reduction in the risk of occurrence of a disease-free survival (DFS) event versus placebo [hazard ratio 0.76; 95% confidence interval (CI), 0.59–0.98; two-sided $P = 0.03$; median DFS, 6.8 versus 5.6 years, respectively] [4].

Managing adverse events (AEs) and monitoring how patients are feeling and functioning while on treatment are especially important in the adjuvant setting, to optimize accumulative dosing for efficacy while maintaining tolerability for patients. Here we report safety and therapy management data for the S-TRAC trial. We also present the patient's experience as measured by a patient-reported outcome (PRO) instrument, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). This provided a direct assessment of the patient experience at baseline, while on treatment, and at end of treatment, and provided insight into how patients are feeling and functioning. In an adjuvant treatment setting, the goal was to determine whether there were clinically meaningful impacts on health-related quality of life (QoL) measures of functioning and treatment-related symptoms.

Methods

Patients

Complete eligibility criteria have been previously reported [4]. Briefly, the study population in S-TRAC consisted of patients with a diagnosis of loco-regional RCC at high risk for recurrence based on the modified UISS criteria (≥T3 and/or N+) [2, 4]. Inclusion criteria included having histologically confirmed clear-cell RCC; a pre-nephrectomy Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2; and the absence of macroscopic residual or metastatic disease post-nephrectomy as confirmed by blinded independent review, no prior systemic treatment, and beginning treatment within 3–12 weeks of nephrectomy [4]. This study was approved by the institutional review board or ethics committee at participating centers and conducted in accordance with provisions of the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided informed consent.

Study design

S-TRAC was a prospective, international, multicenter, randomized, double-blind phase III trial comparing sunitinib with placebo. Patients were stratified by UISS high-risk groups, ECOG PS (<2 versus 2), and assigned (1 : 1) to receive sunitinib (oral, 50 mg/day; $n = 304$) or placebo ($n = 306$). Both arms were planned to be treated on a 4-weeks-on/2-weeks-off schedule for nine cycles (~1 year). Treatment continued until disease relapse, occurrence of secondary malignancy, significant toxicity, death, or withdrawal of consent.

Investigators were required to record in the clinical report form (CRF), all reported or observed patient AEs from the first dose of study drug until ≥28 days after the last on-study treatment administration. AEs were classified by type, incidence, timing, severity (graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0), seriousness, and relationship to study drug (investigator's judgement). Outcomes of all serious or study drug-related toxicities were recorded on the CRF until they had resolved, or were determined to be stable.

Dose interruption or dose reduction by one dose level, to 37.5 mg/day only, were allowed, in accordance with the type/severity of toxicity encountered. The investigators were provided with the rules for dose reductions for sunitinib associated AEs (supplementary Table S1, available at *Annals of Oncology* online). During treatment, delay of the start of any treatment cycle was defined as dose delay, while interruption during the cycle was defined as dose interruption. Patients requiring >6 weeks of dosing interruption or dose reductions to <37.5 mg were considered for discontinuation from the study.

The EORTC QLQ-C30 was used to directly evaluate the patient's experience during treatment [5]. The PRO instrument was completed on day 1 and approximately every 6 weeks thereafter (day 1 of each cycle) until end of study treatment. More study design details have been previously described [4]. The EORTC QLQ-C30 consists of 30 items grouped into 15 scales: global health status/QoL, functional scales (physical, role, cognitive, emotional, and social) and symptom scales (fatigue, nausea/vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact of cancer). All 15 scales were normalized to 0–100 with higher scores corresponding to better QoL, better functioning for functional scales and, conversely, more extreme symptom for symptom scales. The published clinically important difference (CID), reflecting meaningful change, for the EORTC scales is 10 points [6, 7] as specified by study protocol. In the literature, 10–20 points represents moderate change and >20 points large change; changes <10 points are not considered clinically meaningful [6, 7].

Analyses

The mean duration of treatment was determined. Data on dose reduction, dose interruption, treatment discontinuation due to AEs by cycle, and reasons for sunitinib treatment discontinuation were summarized. Time to onset of five most common AEs occurring in the sunitinib arm was determined. Median time to sunitinib treatment discontinuation, reduction, and interruption were calculated. Length of time of reduced doses, dose interruptions, and dose delays were also calculated. Mean and median time to onset and time to resolution for key AEs in both arms was determined. For patients who discontinued treatment, maximum severity of AE and reversibility were determined.

A repeated-measures mixed-effects model based on change from baseline was used to compare means on sunitinib and placebo groups across all of the 15 EORTC QLQ-C30 scores. *Post hoc* exploratory analyses were carried out to assess the impact of the highest incidence AEs (diarrhea, fatigue, PPE, appetite loss and hypertension, all grades) reported in the previous cycle on all 15 PRO scores of the EORTC. This assessment was conducted across each of the nine cycles. The Global Health status measure of the QLQ C-30 is considered representative of the patient's overall experience and the impact of these AEs on this score were assessed.

Table 1. Time to dose interruption, dose reduction, and dose delay: sunitinib arm

Sunitinib treatment arm	*n*	Length of time (days)	
		Mean (SD)	Median (range)
Time to first dose interruption	116	115.8 (91.2)	92.0 (3–336)
Time to first dose reduction	139	120.7 (83.1)	88.0 (15–344)
Length of time of dose interruptions[a]	116	15.7 (20.1)	9.5 (1–163)
Length of time of reduced doses	139	117.3 (69.0)	113.0 (7–235)
Length of time of dose delays	98	10.6 (11.4)	8.0 (1–68)

[a]Noncumulative.
SD, standard deviation.

Table 2. Time to onset and resolution for common adverse events

	Sunitinib-treated patients (*n* = 306)	
	Time to onset	Time to resolution
Diarrhea		
n (% resolved)	174	154 (89)
Mean (SD)	9.3 (11.6), weeks	6.5 (11.2)
Median (min, max)	3.9 (0.1, 54.3), weeks	2.6 (0.1, 58.4)
Fatigue		
n (% resolved)	112	80 (71)
Mean (SD)	9.7 (11.7), weeks	9.5 (21.0)
Median (min, max)	4.1 (0.1, 43.4), weeks	3.6 (0.3, 270.9)
Hypertension		
n (% resolved)	113	78 (69)
Mean (SD)	7.1 (9.1), weeks	9.3 (14.0)
Median (min, max)	3.4 (0.1, 44.9), weeks	3.1 (0.1, 62.9)
PPE		
n (% resolved)	154	118 (77)
Mean (SD)	10.3 (11.7), weeks	7.8 (11.0)
Median (min, max)	5.5 (0.1, 51.4), weeks	3.6 (0.1, 78.9)

AE, adverse event; max, maximum; min, minimum; PPE, palmar-plantar erythrodysesthesia; SD, standard deviation.

Results

Extent of sunitinib exposure

Mean duration of treatment (SD) was 9.5 (4.4) and 10.3 (3.7) months for the sunitinib and placebo arms, respectively. Of the 306 patients allocated to sunitinib treatment, 71% maintained treatment for ≥8 months (cycle 6) with 56% completing the full 1-year treatment. The median daily dose of sunitinib was 45.9 (8.9–52.6) mg.

Therapy management: dose reduction and dose interruption

The most common (>35%) treatment-emergent AEs reported in the sunitinib versus placebo arm were diarrhea (56.9% versus 21.4%), palmar-plantar erythrodysesthesia (PPE) (50.3% versus 10.2%) and hypertension (36.9% versus 11.8%) [4]. As previously reported, AEs were the most frequent reason for dose reduction or dose interruption in the sunitinib arm: 106 (34.6%) and 142 (46.4%) patients, respectively [4]. Median time to first dose reduction and first dose interruption in the sunitinib arm was 2.9 and 3.0 months, respectively. Time to first dose interruption and first dose reduction, and duration of dose interruptions, reduced doses, and dose delays for sunitinib are presented in Table 1. Frequency of serious AEs was similar between sunitinib [67 (21.9%)] and placebo [52 (17.1%)] arms [4], with no individual serious AEs reported at ≥3% frequency in either arm.

Treatment discontinuations and AE resolution

The leading reason for treatment discontinuation was AEs (28.1%) in the sunitinib arm with PPE the most common AE leading to permanent discontinuation [4]. The percentages of discontinuations due to treatment-emergent AEs in the sunitinib arm in cycles 1, 3, 6, and 9 were 7.8%, 3.3%, 2.6%, and 1.6%, respectively, in the sunitinib arm and 0.3%, 1.3%, 0.3%, and 0.0%, respectively, in the placebo arm. In the sunitinib arm, the median time to treatment discontinuation ($n = 86$) was 4.5 months.

The percentage of common AEs that resolved in the sunitinib arm and mean time of resolution are presented in Table 2. Key AEs (any grade) occurred ∼1 month (median) after start of sunitinib treatment and resolved within ∼3.5 weeks (median). Many (40.6%) AEs leading to permanent discontinuation were grade 1 or 2, and most (87.2%) resolved or were resolving at the end of treatment. Maximum severity and reversibility of AEs leading to permanent discontinuation are shown in Figure 1.

Deaths

Fewer deaths were reported over the treatment and follow-up periods in the sunitinib arm [66 (21.6%)] than the placebo arm [74 (24.3%)]. No deaths were attributed to study treatment. The most common cause of death in both arms was disease under study [49 (16.0%) patients in the sunitinib arm and 50 (16.4%) patients in the placebo arm]. Two patients in the sunitinib arm died on study treatment, in both cases cause of death was reported as disease under study.

Patient-reported outcomes

Top-line PRO findings were reported previously [4]. The PRO completion rate was high in both arms (>89% of available patients) at every cycle [4]. In the prespecified repeated-measures mixed-effects model analyses, the global health status/QoL score showed a mean (95% CI) difference in the overall means of –4.76 (95% CI: –6.82, –2.71; $P \geq 0.0001$) favoring placebo. While statistically significant, the point estimate of the difference was below the published and commonly accepted CID (10 points), indicating no clinically meaningful deterioration in patient-reported global health status/QoL with sunitinib treatment. The mean scores from baseline in the global

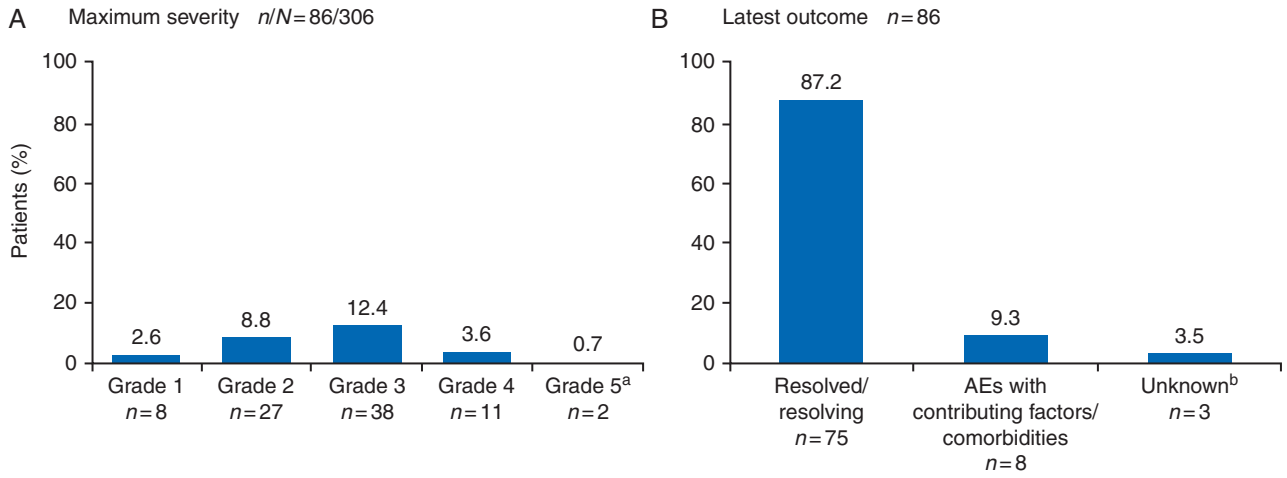

Figure 1. Maximum severity (A) and reversibility (B) of treatment-emergent adverse events (AEs) leading to permanent discontinuation. [a]Two grade 5 events with fatal outcome unrelated to study treatment reported during active treatment period. [b]Grades 2 and 3 palmar-plantar erythrodysesthesia grade 2 unexpected therapeutic effect (increased thyroid function); AEs known to be manageable/reversible.

health status/QoL score over time for both arms are shown in Figure 2. Despite differences in the curves, both remain in the top one-third of the graph showing a minimal deterioration for the sunitinib arm.

The results observed for global health status/QoL were consistent with the pattern of changes in the other EORTC scales, including physical, social, and emotional functioning scales; symptoms such as fatigue and pain all indicated a statistically significant difference without reaching the threshold of clinical significance (as previously reported) [6]. The two exceptions were the PRO scores for diarrhea and loss of appetite, which reached a clinically meaningful difference (Figure 3). However, only one patient permanently discontinued due to an AE of diarrhea, and no patients permanently discontinued due to the AE of loss of appetite with sunitinib treatment.

Based on the *post hoc* exploratory analyses, patients in any cycle with any grade AEs of diarrhea, PPE, decreased appetite, and fatigue reported a consistent negative impact on many of the symptom and functioning scales in the following cycle, compared with patients who did not experience these AEs. By contrast, patients with the AE hypertension (all grades) did not report any impact on PROs, and their rating on the PROs was similar to those who did not experience the AE. These impacts are represented in the Global Health Status measure and in the social functioning scale (supplementary Figures S1 and S2, available at *Annals of Oncology* online). Relatively smaller impacts were seen in other functioning scales, with no significant impact on cognitive and physical functioning.

Discussion

In S-TRAC, a statistically significant and clinically meaningful DFS improvement was seen in patients treated with sunitinib in the adjuvant setting as compared with placebo [4]. Therapy management (dose interruption, dose delay, or dose reduction) was proactively employed by clinicians as necessary. This clinical strategy, informed by over 12 years of clinical experience managing sunitinib treatment in the metastatic disease setting, likely helped to keep many patients on sunitinib treatment during the trial. AEs reported in the sunitinib arm were consistent with the known safety profile of sunitinib [8].

Most of the serious AEs were known risks of sunitinib treatment (e.g. hypertension, thrombocytopenia, and pulmonary embolism) [8]. Overall, the rate of AEs was similar to rates reported for sunitinib treatment in metastatic RCC, except for grade 3/4 PPE, which was reported at higher rates than previously [4, 8]. Higher PPE was reported in ASSURE trial with sorafenib or sunitinib and in PROTECT trial with pazopanib [9, 10]. Higher PPE was significantly associated with improved outcomes in sunitinib-treated patients with metastatic RCC [11]. The most common (>35%) AEs overall in the sunitinib arm were diarrhea, PPE, hypertension, and fatigue [4].

In addition to S-TRAC, the ASSURE trial also evaluated efficacy and safety of adjuvant sunitinib versus sorafenib versus placebo in patients with RCC, but reported no progression-free survival benefit for patients treated with sunitinib or sorafenib versus placebo [9]. Furthermore, the ASSURE trial discontinued early because of toxicity leading to high rates of discontinuation. The difference in outcome with sunitinib in S-TRAC and ASSURE is likely due to differences in patient population and study design, including AE management, which in S-TRAC helped to keep patients on treatment for longer, giving them a greater mean cumulative dose of sunitinib compared with ASSURE. A lower percentage of patients completed sunitinib treatment in ASSURE compared with S-TRAC (40% versus 56%), and a greater percentage of patients who started at the 50 mg/day dose permanently discontinued due to AE or patient refusal (44% versus 32%) [4, 9]. These differences in maintaining patients on treatment and subsequent differences in exposure underscore the impact of AE management on outcome.

Patient health-related QoL measures can contribute to a more complete picture of the patient experience of adjuvant therapy and can aid patients and clinicians in making informed risk/

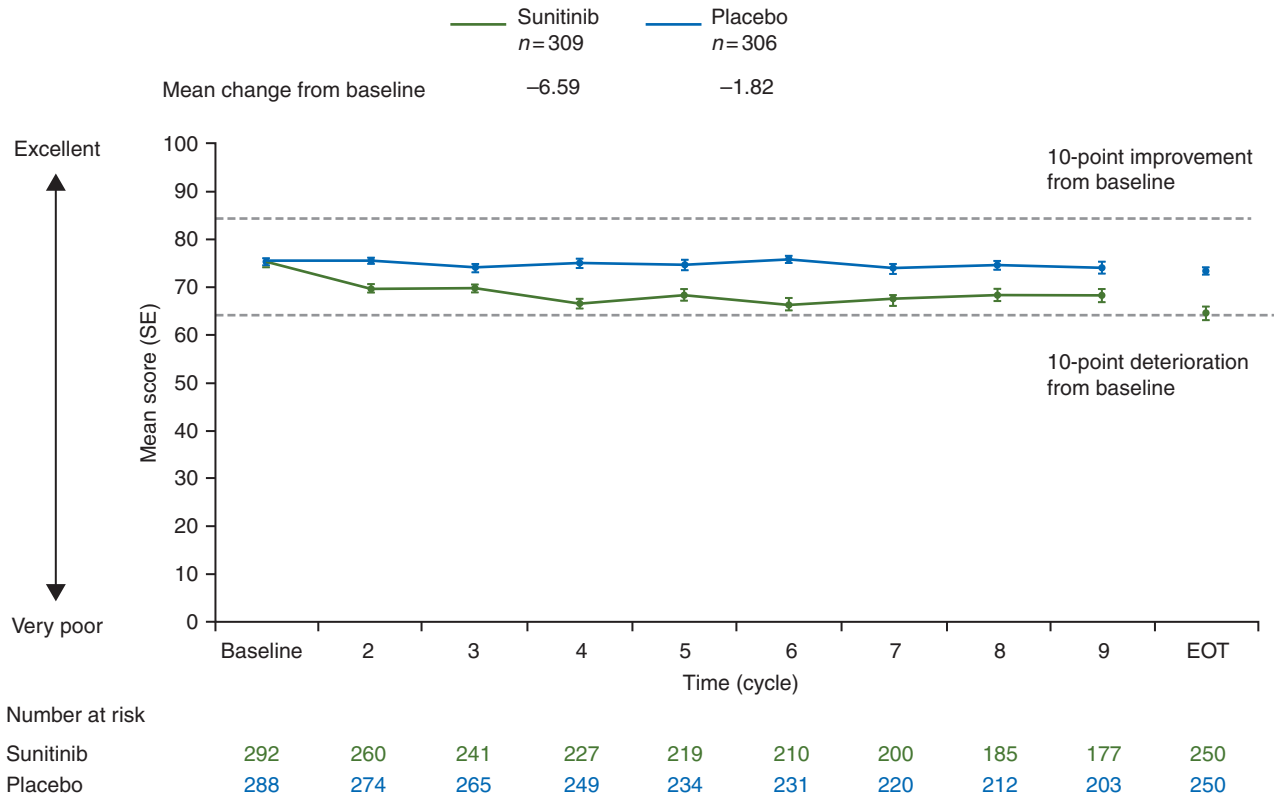

Figure 2. EORTC QLQ-C30 mean scores over time: Global Health Status/Quality of Life domain (S-TRAC)—intent-to-treat population. QLQ-C30 was measured on day 1 of each cycle. Patients were responding using the recall period of 1 week. Mean change from baseline based on repeated measures longitudinal analysis. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT, end of treatment; SE, standard error.

benefit judgements [12]. The analysis of the EORTC QLQ-C30 in S-TRAC indicated that patients in both groups maintained a relatively high level of functioning and global health status with little clinically meaningful deterioration in their global health status/QoL and functional scales. While patients who received sunitinib treatment experienced symptoms consistent with the drug's known safety profile, these were reported at low levels, and remained in a range between 'not at all' and 'a little'. Unlike S-TRAC, the PRO analysis in ASSURE trial focused on fatigue using PROMIS Fatigue SF1 and FACIT fatigue scale that were applied only at baseline and on weeks 10 and 22 [13]. Therefore, the PRO data from ASSURE and S-TRAC may not be comparable.

The clinically meaningful changes observed in the PROs domains of diarrhea and loss of appetite were associated with known AEs of sunitinib. Finally, the EORTC QLQ-C30 showed changes associated with symptomatic AEs (diarrhea, fatigue, PPE, and appetite loss), but not to asymptomatic AEs (i.e. hypertension) that would not be expected to impact how a patient feels or functions (global health status/QoL and functioning scales); this suggests the PRO instrument and the AEs were aligned in reflecting and detecting the patient's experience on sunitinib, validating the prespecified analyses for PROs. It is likely proactive management contributed to preservation of global health status/QoL, and alleviation of treatment-related symptoms, thereby enabling patients to remain on effective adjuvant therapy.

A limitation of this analysis is that PROs were only obtained during and at the end of the study treatment period (some patients also ended treatment before 1 year) to capture the potential burden posed by treatment on patients. No conclusions can be drawn about the timing or extent of resolution of any PRO declines following the end of treatment.

Conclusions

The safety profile of sunitinib was generally acceptable in the adjuvant RCC treatment setting without any new safety signals in this study. AEs reported in the sunitinib arm were consistent with the established safety profile of sunitinib. There were no treatment-related deaths. AEs were predictable, manageable, and reversible, via dose interruption, dose reduction, dose delay, and/or standard supportive medical therapy. A proactive and effective therapy management strategy enabled many patients to remain on therapy. The analysis of PROs while on treatment in S-TRAC indicated that adjuvant sunitinib therapy was not associated with clinically meaningful deterioration in most quality of life measures.

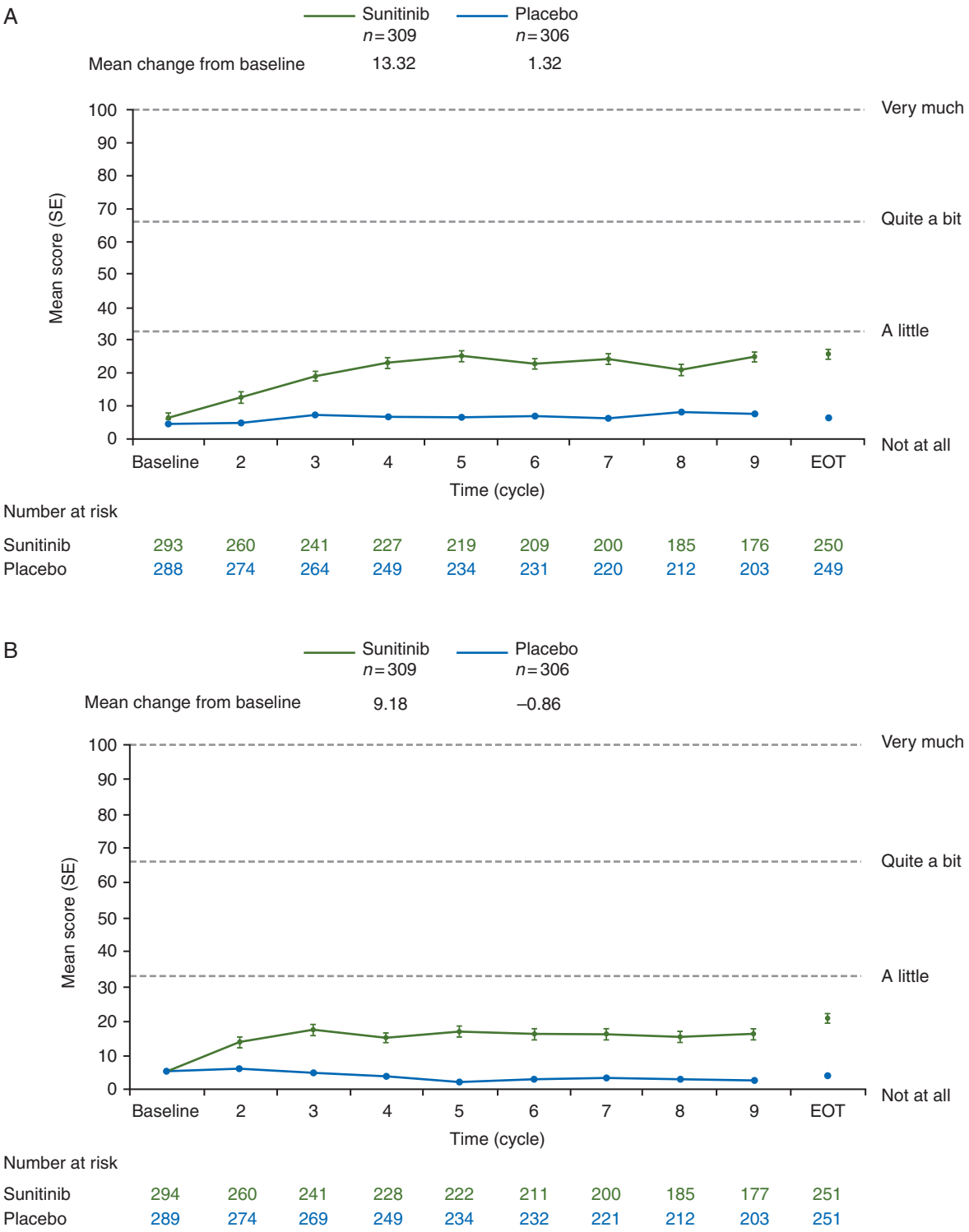

Figure 3. Change from baseline over time for diarrhea and loss of appetite (S-TRAC)—intent-to-treat population. (A) Diarrhea. (B) Loss of appetite. The labels (1) not at all, (2) a little, (3) quite a bit, and (4) very much are the response options directly chosen by the patients. The *Y*-axis represents the standardized transformation applied to these choices by the EORTC calculation guidelines. Intent-to-treat population. QLQ-C30 was measured on day 1 of each cycle. Patients were responding using the recall period of 1 week. Mean change from baseline based on repeated measures longitudinal analysis. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EOT, end of treatment; SE, standard error.

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Disclosure

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Data sharing statement

Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (i) for indications that have been approved in the US and/or EU or (ii) in programs that have been terminated (i.e. development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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