C.P. PHARMACEUTICALS INTERNATIONAL C.V., A SUBSIDIARY OF PFIZER INC.

SUTENT® (sunitinib)

as adjuvant treatment for adult patients at high risk of recurrent renal cell carcinoma following nephrectomy

FDA ONCOLOGIC DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

1.1. Introduction

A supplemental New Drug Application (sNDA) was submitted to the United States (US) Food and Drug Administration (FDA) in March 2017 seeking the approval of sunitinib malate for use after surgery (adjuvant treatment) in adult patients with loco-regional renal cell carcinoma (RCC) at high risk of recurrence based on the results of the Sunitinib Treatment of Renal Adjuvant Cancer (S-TRAC) Study A6181109.

Sunitinib is an oral multi-targeted tyrosine kinase inhibitor (TKI) that targets various receptors, including vascular endothelial growth factor receptors (VEGFRs), which are important in the regulation of tumor cell growth, angiogenesis, and metastasis, processes involved in the pathogenesis of clear cell RCC. It was originally approved for the treatment of patients with metastatic RCC (mRCC) in January 2006. The efficacy of sunitinib 50 mg daily on Schedule 4/2 (4 weeks on treatment followed by 2 weeks off treatment) in patients with mRCC was further confirmed in a large Phase 3 study (A6181034), which demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) for sunitinib compared to interferon-alpha (IFN-α), together with an acceptable safety profile. Overall survival (OS) was also longer in the sunitinib arm than in the IFN-α arm.[1]

During the last decade, numerous therapies were approved for mRCC. However, currently, there are no approved therapies for the adjuvant treatment of patients with non-metastatic RCC at high risk of recurrence following nephrectomy. Patients with high-risk non-metastatic RCC typically harbor occult or micrometastatic disease as demonstrated by the higher incidence of distant metastasis at the time of disease recurrence.[2] Metastatic RCC is associated with considerable morbidity due to metastases to bone, lung, and other locations and mortality, with a median OS of 2-3 years.[3] Therefore, Pfizer is seeking approval for extending the use of sunitinib, a standard-of-care treatment in mRCC, to the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy based on the positive results from the S-TRAC study.

This briefing document presents a summary of the clinical data included in the sNDA and provides the evidence to establish that sunitinib has a favorable benefit/risk relationship for the adjuvant treatment of patients with high-risk non-metastatic RCC, a disease for which there is a high unmet medical need without any approved therapies.

1.2. Loco-Regional Renal Cell Carcinoma

RCC continues to have the highest mortality rate of the genitourinary cancers. In the US, it is estimated that there will be approximately 64,000 newly diagnosed cases of RCC and 14,000 deaths from RCC in 2017.[4]

Currently, surgical resection followed by observation is the only treatment option for non-metastatic RCC. For patients with disease localized to the kidney, surgery alone may be sufficient, as the expected recurrence rate post-nephrectomy is less than 25%,[5] but for patients where the tumor has spread outside of the kidney (loco-regional disease), the risk of recurrence is greater than 40% over a 5-year period.[6] Furthermore, in a subset of these patients comprising approximately 15% of all patients with non-metastatic RCC, classified as

high risk of recurrence based on the University of California, Los Angeles (UCLA) Integrated Staging System (UISS) risk classification (based on factors including tumor, nodes, metastasis [TNM] stage, Fuhrman's grade, and Eastern Cooperative Oncology Group [ECOG] performance status [PS] pre-nephrectomy), the risk is even greater with an approximate 60% rate of recurrence at 5 years.[6]

Although the prognosis for patients with mRCC has improved over the past decade with the availability of a number of molecularly targeted and immunotherapeutic agents, mRCC remains a largely incurable disease with a 5-year survival rate of 12%.[4] Given this high systemic failure rate, there is a clear need for the adjuvant treatment of patients with resected loco-regional disease who are at high risk of recurrence that can prevent or delay disease relapse and shift the natural progression of the disease.

1.3. Adjuvant Treatment of Patients with Renal Cell Carcinoma

Over the past few decades, many attempts have been made without success to identify treatment options for patients with resected loco-regional RCC at high risk of recurrence.

The S-TRAC study was designed to demonstrate that adjuvant treatment with sunitinib was superior to placebo in prolonging disease-free survival (DFS) in patients with RCC at high risk of disease recurrence (i.e., clear cell histology, ≥T3 and/or lymph node positive [N+]) following nephrectomy. The primary endpoint was DFS, defined as the time from the date of randomization to the first date of recurrence or the occurrence of any secondary primary cancer or death from any cause, which is consistent with that used in other solid tumor adjuvant trials.[7,8,9] Deaths from all causes and second primary cancers were included as DFS events to account for any long-term effects of treatment.[9] DFS was assessed by blinded independent central review (BICR) to reduce bias relative to investigator assessment and to mitigate against adverse events (AEs) leading to functional unblinding of the study.

The choice of DFS as the primary endpoint was based on a number of considerations. Firstly, DFS represents a biologically relevant measure of the impact of treatment on the disease process, as the goal of adjuvant therapy is to prevent or delay recurrence and alter the natural progression of the disease.[10] Secondly, DFS is a consistent and accepted primary endpoint in studies supporting the approval of cancer drugs in the adjuvant solid tumor treatment setting,[11,12,13] including those in the adjuvant breast cancer and colorectal cancer treatment settings.[7, 8, 9] Thirdly, DFS enables evaluation of potential adjuvant therapies in a timely manner, without being affected by crossover or subsequent therapy, since an endpoint such as OS in RCC would require extended follow-up (e.g., approximately 18.5 years to detect a 25% improvement in this treatment setting) making OS impractical as a primary efficacy endpoint. Finally, notwithstanding the advancements in the treatment of mRCC over the past decade, RCC still remains an incurable disease, and many patients would consider additional treatment options following surgical resection to delay or prevent recurrence, and therefore morbidity and mortality of mRCC, rather than adopt a watchful-waiting approach. For these reasons, DFS was considered to be a clinically meaningful endpoint to establish the efficacy of sunitinib in the adjuvant RCC treatment setting.

In addition to S-TRAC, there have been 5 Phase 3 clinical trials evaluating the potential of various targeted therapies as adjuvant treatment in RCC (Section 6.1); 2 have been

completed, and 3 are ongoing. The 2 completed trials are the Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE) study (ECOG 2805)[14], which evaluated 1 year of adjuvant sorafenib or sunitinib versus placebo, and the Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma (PROTECT) study[15], which evaluated 1 year of adjuvant pazopanib versus placebo. Neither study met its primary endpoint of demonstrating improved DFS for the drugs evaluated versus placebo. Review of the ASSURE study clinical trial data (Section 4.1.1) showed important differences from the S-TRAC study, such as the enrollment of low-/intermediate-risk patients with RCC (by UISS categorization) and with non-clear cell histologies, and lower sunitinib dose intensity that likely contributed to the negative primary outcome in the ASSURE study. A comparison of baseline characteristics and dosing criteria showed that only 30% of the patients in the ASSURE study matched the protocol criteria for the S-TRAC study. In addition, subgroup analyses of the ASSURE study indicated that the more closely the patients were aligned with those enrolled and treated in the S-TRAC study based on patient population and dosing, the more favorable the DFS hazard ratios (HRs) were for sunitinib compared to placebo (Section 4.1.1).

Patients in the PROTECT study were largely similar to those in the S-TRAC study, with 86% of the patients having RCC with ≥T3 or N+ and clear cell histology. However, a reduced starting pazopanib dose of 600 mg daily compared to the approved dose of 800 mg daily in mRCC was administered in more than 70% of the patients. Although the primary analysis of DFS comparing pazopanib 600 mg daily versus placebo was negative, the secondary analysis of pazopanib at the original full starting dose (800 mg daily) showed a statistically significant DFS improvement compared to placebo (Section 4.2). These data provide external corroboration of the importance of patient population and dose to achieve clinical benefit in the adjuvant treatment setting.[15]

1.4. Benefit/Risk Assessment

The sNDA is based on efficacy and safety results from the S-TRAC study and an overall assessment of the long-term safety profile of sunitinib in patients with mRCC. S-TRAC demonstrated that in adult patients at high risk of recurrent RCC following nephrectomy, 1 year of treatment with sunitinib provided a statistically significant and clinically meaningful 24% reduction in the risk of a DFS event occurrence (as assessed by BICR) compared with placebo (Section 3.6.1), a treatment effect that is consistent with those from adjuvant treatment studies of patients with resected breast cancer or colorectal cancer (Section 6.9). This reduction in the risk of a DFS event as assessed by BICR was maintained over time with an absolute improvement of 8.0% in favor of sunitinib maintained at 5 years. A number of sensitivity analyses were performed on the intent-to-treat (ITT) population (Section 3.6.3), and the results of these analyses demonstrated the robustness of the primary DFS analysis, with consistent HRs (0.76-0.81) favoring sunitinib.

The OS data are immature in the S-TRAC study, as the median OS was not reached in either treatment arm (Section 3.6.5). Available data indicates that sunitinib did not have a detrimental effect on OS compared to placebo.

Sunitinib has been an available mRCC treatment for over 11 years in the US and has a well-characterized safety profile. It is estimated that more than 350,000 patients have been exposed to sunitinib globally since it was first approved in 2006.[16] As expected, AEs reported in the sunitinib arm of S-TRAC were more frequent compared with the placebo arm (Section 3.7.1). The AEs in the sunitinib arm were consistent with the known safety profile, and no new safety signals were observed. The most common AEs in the sunitinib arm were Diarrhoea, Palmar-plantar erythrodysaesthesia (PPE) syndrome, Hypertension, and Fatigue. Management of these events by dosing interruption, dose reduction, and/or standard supportive medical therapy enabled resolution of these events and continuation of effective adjuvant therapy, with <5% of patients permanently discontinuing treatment due to any of these events (Section 3.7.4). The overall rate of permanent discontinuations due to AEs in the sunitinib arm (28%) is comparable to that observed in the metastatic disease setting.[17] Most (87%) of the AEs leading to permanent treatment discontinuation recovered or were recovering at the time of last patient contact. For the remaining 13% (11 patients), potential contributing factors/co-morbidities were identified in 8 patients, while no additional information was available at the time of last contact for 3 patients with AEs known to be manageable (Section 3.7.4). There were no treatment-related deaths as well as no differences in cardiovascular events between the 2 treatment arms. Hepatic events in the sunitinib arm were primarily Grade 1 or 2 elevations in liver transaminases. No Hy's Law cases were observed in either treatment arm. Overall, the AEs in the sunitinib arm were as expected based on the known safety profile, generally manageable and reversible, enabling patients to remain on effective adjuvant therapy and achieve a meaningful clinical benefit.

Patient-reported outcomes (PROs) were evaluated using 2 quality of life (QoL) instruments. Sunitinib treatment was associated with statistically significant differences favoring placebo that were not considered clinically meaningful in the majority of QoL measures, including global health status/QoL. Two (2) exceptions to this were the PROs of diarrhea and loss of appetite, which exceeded the published threshold for clinical relevance. Diarrhea and loss of appetite are known AEs of sunitinib and were clinically manageable. Overall, patients maintained a relatively high level of quality of life and functioning and low level of symptoms throughout the treatment period.

The data demonstrate that sunitinib has a favorable benefit/risk relationship to support the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy. Therefore, sunitinib should be approved as a treatment option for this additional indication, enabling treating physicians to make individual benefit/risk assessments for their patients.

2. BACKGROUND AND DEVELOPMENT RATIONALE

2.1. Disease Background

RCC is the most common type of kidney cancer representing 90% of all renal cancers.[18] It is diagnosed in approximately 304,000 people worldwide,[19] resulting in approximately 129,000 deaths each year.[18,20] In the US, it is estimated that there will be approximately 64,000 newly diagnosed cases of RCC and 14,000 deaths in 2017.[4] Although RCC only represents 2%–3% of all cancers,[20] its incidence has been increasing.

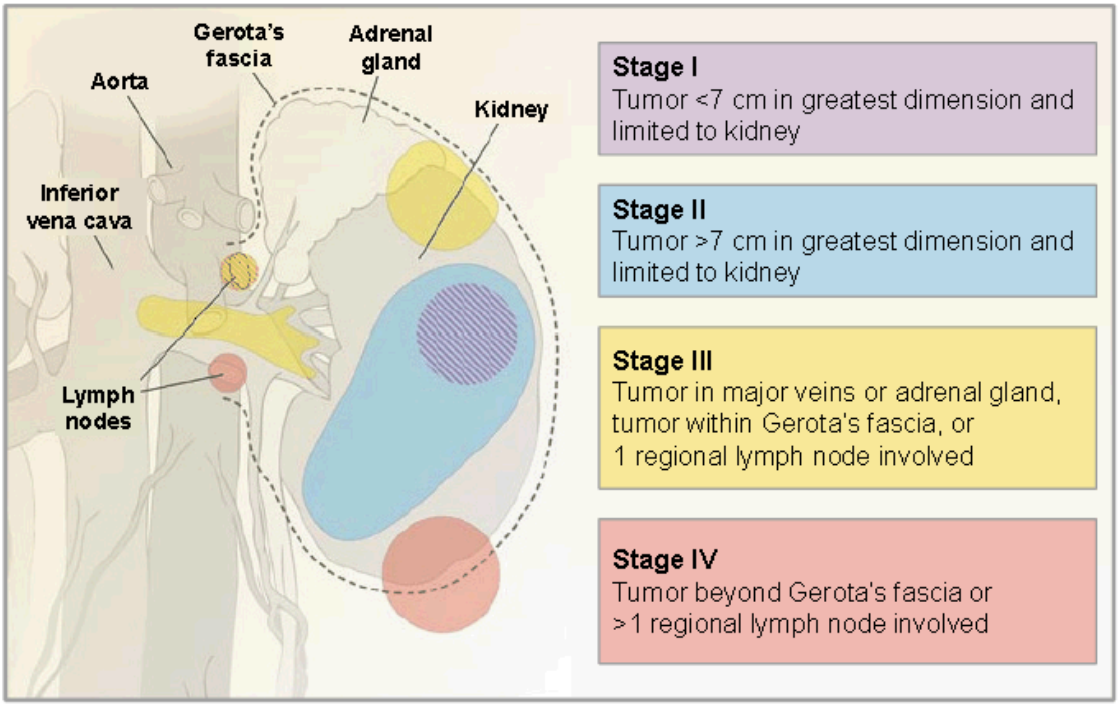
Historically, approximately 25%-30% of patients diagnosed with RCC had metastasis at diagnosis.[21] However, due to increased use of radiologic and ultrasound imaging techniques, incidental detection is more frequent, and more patients are being diagnosed with Stage I–III (localized or loco-regional) disease.[22]

Surgical resection is the standard of care for non-metastatic disease, including radical or partial nephrectomy, followed by observation.

2.2. Risk Stratification

The prognosis of patients with RCC depends on disease stage and risk stratification at diagnosis. Figure 1 represents the TNM staging for non-metastatic RCC (2002) when the S-TRAC study started. Stages I and II are limited to kidney parenchyma. Stages III and IV represent locally advanced disease, beyond the kidney parenchyma, tumors of which may expand to vessels and lymph nodes.

Figure 1. Staging for Renal Cell Carcinoma



Source: Adapted from Figure 1, Cohen and McGovern[23] and AJCC/UICC TNM classification, 6th edition, 2002[24]

The risk of recurrence following nephrectomy is, however, multifactorial, as it includes tumor size, histology, stage, Fuhrman's grade, presence of symptoms, and ECOG PS.[25]

The UISS was designed in 2001 to account for this complex interaction between TNM stage (I to IV), ECOG PS prior to nephrectomy, and Fuhrman's grade with the ultimate goal of producing a simple and accurate prognostic system.[2] Descriptions of UISS criteria when the S-TRAC study started are provided in Table 1.

Table 1. UISS Criteria Descriptions

UISS Criteria	Description
T (tumor size)[a]	T1-2: organ confined T3: Tumor extends into major veins or invades the adrenal gland or perinephric tissues but not beyond Gerota's fascia T4: Tumor invades beyond Gerota's fascia
N (nodal involvement)[a]	N0: No nodal involvement N1: Tumor has spread to one nearby lymph node N2: Tumor has spread to more than one nearby lymph node NX: Nearby lymph nodes cannot be assessed
M (metastases)[a]	M0: No metastases M1: Distant metastases present
ECOG PS (functional performance status) prior to nephrectomy [b]	ECOG PS0: Fully active, able to carry on all pre-disease performance without restriction ECOG PS1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work ECOG PS2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Fuhrman's Nuclear Grade[c]	Pathologic assessment of nuclear size, shape, and nucleoli of primary RCC tumor

a. AJCC/UICC TNM classification, 6th edition, 2002[24]
b. National Palliative Care Research Center: ECOG Performance Status
c. Stanford Medicine Surgical Pathology Criteria: Clear Cell Renal Cell Carcinoma

Based on the parameters noted above, the UISS stratification system categorizes patients with RCC into 3 groups: patients with low risk, intermediate risk, or high risk of disease recurrence (further discussed in the context of the S-TRAC study in Section 3.2).

A summary of RCC distribution and 5-year recurrence-free rates by UISS risk group is provided in Table 2.

Table 2. Renal Cell Carcinoma Distribution and 5-Year Recurrence-Free Rates by UISS Risk Group

UISS Risk Group	Proportion of Patients	5-Year Recurrence-Free Rate
Low	37.8%	90.4%
Intermediate	48.4%	61.8%
High	13.9%	41.9%

Source: Lam et al[6]
RCC = renal cell carcinoma; UISS = University of California, Los Angeles Integrated Staging System

2.3. Unmet Medical Need

As discussed, prognosis of RCC depends on risk stratification at diagnosis. Risk stratification methods such as the UISS combine disease stage as well as clinical and pathological features to categorize patients by risk of disease recurrence. As shown in Table 2, for low- and intermediate-risk RCC patients, the 5-year recurrence rates post-nephrectomy range from 10% (low) to 40% (intermediate). On the other hand, high-risk

RCC patients represent approximately 15% of all patients with primary resected RCC, and approximately 60% of these patients will have recurrence and develop metastatic disease within 5 years,[6] suggesting high risk of occult metastases at diagnosis (not visible to imaging techniques).

The current standard of care for primary resected RCC is observation, as there are no approved adjuvant therapies. After surgery, many patients will be cancer free and resume their normal lives. However, a sizable subset will relapse after surgery, and once their disease becomes metastatic, their long-term prognosis is poor. While observation may be acceptable for low- and intermediate-risk RCC patients, there is an urgent need for adjuvant therapies that can reduce the risk of or delay disease relapse and shift the natural progression of the disease, especially for patients at high risk of RCC recurrence. Despite new treatments in mRCC, the long-term prognosis is poor, and mRCC today remains a largely incurable disease, with a 5-year survival rate of 12%.[4] Consistent with these observations, the S-TRAC study included patients with ≥T3 and/or lymph node-positive tumors, as these are the patients where surgery is unlikely to be curative and who are at risk of harboring micrometastatic disease, with the potential to develop clinically evident metastatic disease over time.

Intense research to evaluate the activity of the standard treatments for metastatic RCC in the adjuvant setting has been conducted in the last decade. However, the outcome of adjuvant trials with immunotherapeutic agents (e.g., interleukin-2 [IL-2][26,27,28] and interferon-α [IFN-α][1,28,]), hormone therapy, and chemotherapy were negative.[29]

The improved understanding of the molecular pathophysiology of RCC and the discovery and approval of effective targeted therapies in mRCC aroused high interest in exploring their potential in the adjuvant setting. Over the past 10 years, several randomized multicenter Phase 3 trials were initiated evaluating these targeted therapies in the adjuvant setting.[30]

2.4. Rationale for Adjuvant Treatment with Sunitinib and Dose Selection

Sunitinib 50 mg daily on Schedule 4/2 was first approved in 2006 in the US for the treatment of patients with advanced RCC and for the treatment of patients with gastrointestinal stromal tumor (GIST) after disease progression on or with intolerance to imatinib mesylate. Subsequently, sunitinib was approved for the treatment of patients with unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumor (pNET). Sunitinib has been approved in 119 countries, and more than 350,000 patients have been exposed to sunitinib worldwide since the product was first approved.

Sunitinib is an orally active small molecule with anti-tumor properties that are mediated through the inhibition of multiple receptor tyrosine kinases (RTKs). These RTKs are important in the regulation of tumor cell growth, angiogenesis, and metastasis. Specifically, sunitinib is a potent adenosine triphosphate (ATP)-competitive inhibitor of the catalytic activity of a group of closely related RTKs consisting of VEGF receptors -1, -2, and -3, platelet-derived growth factor receptors (PDGFR)–α and –β, stem cell factor receptor (kinase insert domain for tyrosine; KIT), colony stimulating factor-1 receptor (CSF-1R), Fms-like tyrosine kinase-3 receptor (FLT-3), and glial cell line-derived neurotrophic factor

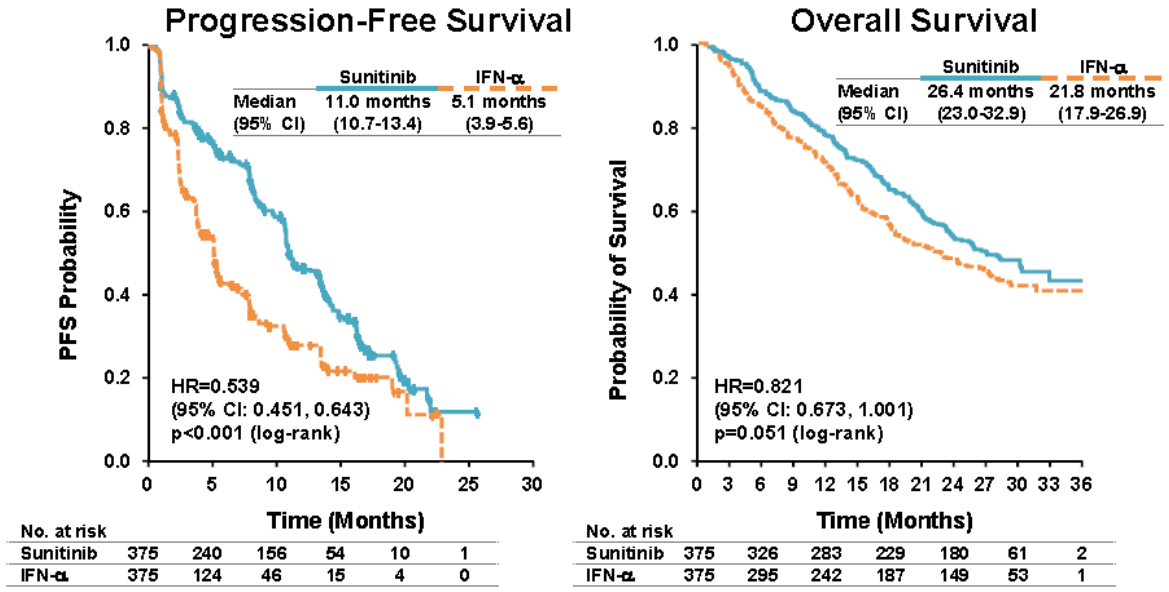
receptor (rearranged during transfection, RET). Due to its multi-targeted profile, the activity of sunitinib is likely mediated by multiple distinct anti-tumor mechanisms.

Von Hippel-Lindau (VHL) inactivation is an important event in the pathogenesis of clear-cell RCC, but it is not sufficient to cause the disease.[31] Several other molecular aberrations have been reported, which further promote the development of neoplasm, including mutations occurring in a set of chromatin-modifying enzymes.[32] The combination of the inactivation of VHL and other aberrations leads to increased HIF activity. As a result, RCC cells secrete increased levels of VEGF and platelet-derived growth factor (PDGF), which activate VEGF and PDGF receptors to promote angiogenesis; in addition, a series of other growth factors and cytokines are upregulated (e.g., insulin-like growth factor 2 (IGF2)[33]; IL6[34]). Those factors promote changes to the tumor microenvironment including immune evasion,[35,36] inflammation, and tumor-associated macrophage (TAM) polarization switch.[37]

Originally, the main mechanistic basis to evaluate sunitinib in patients at high risk of recurrent RCC following nephrectomy was focused on its antiangiogenic activity and inhibition of the VEGF pathway. In addition, it has been shown preclinically that bone marrow-derived hematopoietic progenitor cells that express VEGFR-1 homed to tumor-specific pre-metastatic sites and formed cellular clusters before the arrival of tumor cells. Preventing VEGFR-1 function using antibodies or by the removal of VEGFR-1+ cells from the bone marrow of wild-type mice abrogated the formation of these pre-metastatic clusters and prevented tumor metastasis.[38] Hence, it was thought that antiangiogenics such as sunitinib by inhibiting VEGFR-1 function and disrupting tumor neovascularization might interfere with nascent micrometastasis, which is important in the development of recurrence after surgical resection of a primary tumor.[39] In addition, in the past 5 years, it has been established that sunitinib activity goes beyond the regulation of the VEGF/VEGFR signaling pathway and angiogenesis by modulating TAM polarization, immune suppression, and influencing the tumor microenvironment.[40] Therefore, sunitinib's multipronged activity appears well suited to deliver an aggressive and sustained angiopreventive effect aimed at preventing disease recurrence following curative tumor resection.[41]

The wide use of sunitinib in the first-line treatment of patients with mRCC today is supported by the high degree of efficacy in that treatment setting. In the Phase 3 Study A6181034 conducted in patients with mRCC, sunitinib 50 mg daily on Schedule 4/2 demonstrated statistically significant and clinically meaningful improvements in PFS and prolongation of OS versus interferon-α (Figure 2).

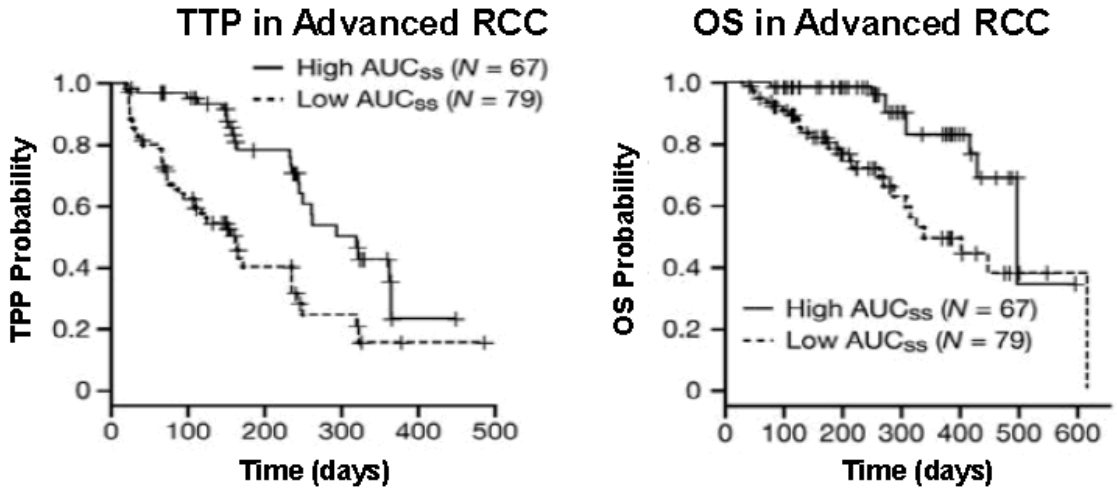
Figure 2. Efficacy of Sunitinib in Metastatic RCC (Study A6181034)



Source: Motzer RJ et al, ASCO 2007[42] and Motzer et al, J Clin Oncol 2009[1] * Independent central review for progression-free survival. CI = confidence interval; HR = hazard ratio.

In patients with mRCC and GIST, exposure-response analyses have been performed with respect to efficacy endpoints showing that patients with higher average daily plasma sunitinib exposures (expressed using area under the concentration-time curve [AUC]) have higher objective response rate, stable disease rate, time to tumor progression, and overall survival.[43] In the metastatic setting, there is an optimal dose and treatment exposure of sunitinib required to maintain dose intensity, with the time to progression (TTP) as well as the OS being significantly influenced when dose is maintained as illustrated by the Kaplan-Meier curves for patients with higher mean AUC when compared to those with a lower mean AUC (Figure 3).

Figure 3. Effect of Dose Intensity on Sunitinib Efficacy in Metastatic RCC



Source: Houk et al.[43] Abbreviations: AUC_{ss}= area under the curve at steady state; OS = overall survival; RCC = renal cell carcinoma; TTP=time to progression.

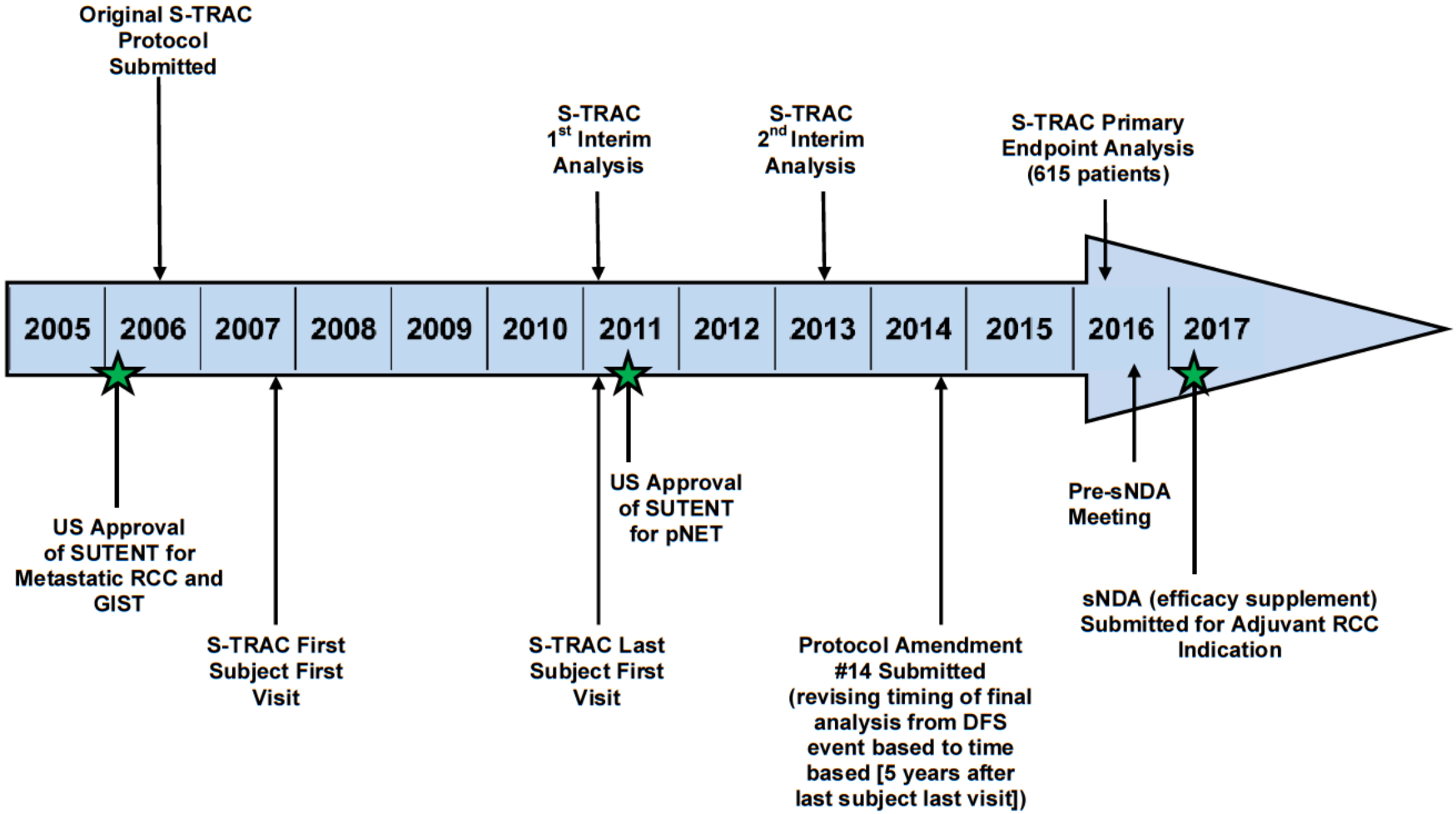
Pharmacokinetic-pharmacodynamic (PK-PD) analyses in patients with mRCC and GIST with respect to target lesion sums of longest diameter (SLD) have also shown that higher plasma exposures are associated with higher percent decrease in the target lesion SLD.[43,44] Both the exposure-response analyses and PK-PD modelling indicated that patients on higher average daily doses will have higher average daily drug plasma exposures and, hence, are more likely to experience better antitumor activity in mRCC and GIST. Recently, similar findings have also been observed in pNET in which patients with higher plasma exposures had higher objective response rate and PFS.[45] Considering that one of the key objectives of sunitinib therapy in the high-risk adjuvant RCC treatment setting is the eradication/regression of the cancer cells which remain present but undetectable/undetected after surgery, it is likely that the exposure-response findings in the metastatic RCC and other tumor type (GIST and pNET) settings are also applicable to the high-risk adjuvant RCC setting, since the primary tumors have extracapsular disease extension. Consequently, patients with higher average daily plasma exposures are more likely to remain disease free and relapse free as compared to patients with lower average daily plasma exposures. Therefore, in the adjuvant RCC setting, it is of importance to ensure that the daily sunitinib dose is maintained as high as possible/tolerated to provide the optimal plasma concentrations needed for more effective eradication/regression of the residual undetectable cancer cells and prevent blood vessel formation.[41]

Based on sunitinib's proven efficacy in patients with mRCC, and its potential to inhibit the development of neovasculature in nascent metastases through inhibition of the VEGFR function, the potential for sunitinib as an adjuvant therapy was evaluated in the S-TRAC study. S-TRAC was specifically designed to evaluate the efficacy and safety of adjuvant treatment with sunitinib, at a dose consistent with the approved mRCC dose, in patients with RCC at high risk of recurrence following nephrectomy and who most likely harbor micrometastatic disease.

2.5. S-TRAC Timeline and Regulatory History

The key milestones in the S-TRAC study timeline and regulatory history are provided in Figure 4. S-TRAC was initiated in 2007, a year after the approval for metastatic RCC. An external Data Monitoring Committee (DMC) was instituted to monitor the efficacy and safety of patients in the study. Over the 10-year period, 2 interim analyses were conducted, and the final analysis of the primary DFS endpoint occurred in 2016, 5 years after the last patient was randomized. The change in timing of final DFS analysis is discussed in Section 3.1 Study Design, and important amendments to the S-TRAC protocol are summarized in Section 6.2.

Figure 4. Key Milestones in the S-TRAC Study Timeline and Regulatory History



3. S-TRAC STUDY A6181109

S-TRAC (Study A6181109) was a Pfizer-sponsored, international, multicenter, randomized, double-blind, parallel-arm Phase 3 study of adjuvant therapy with sunitinib versus placebo in patients at high risk of recurrent RCC following nephrectomy.

3.1. Study Design

An overview of the S-TRAC study design is provided in Figure 5.

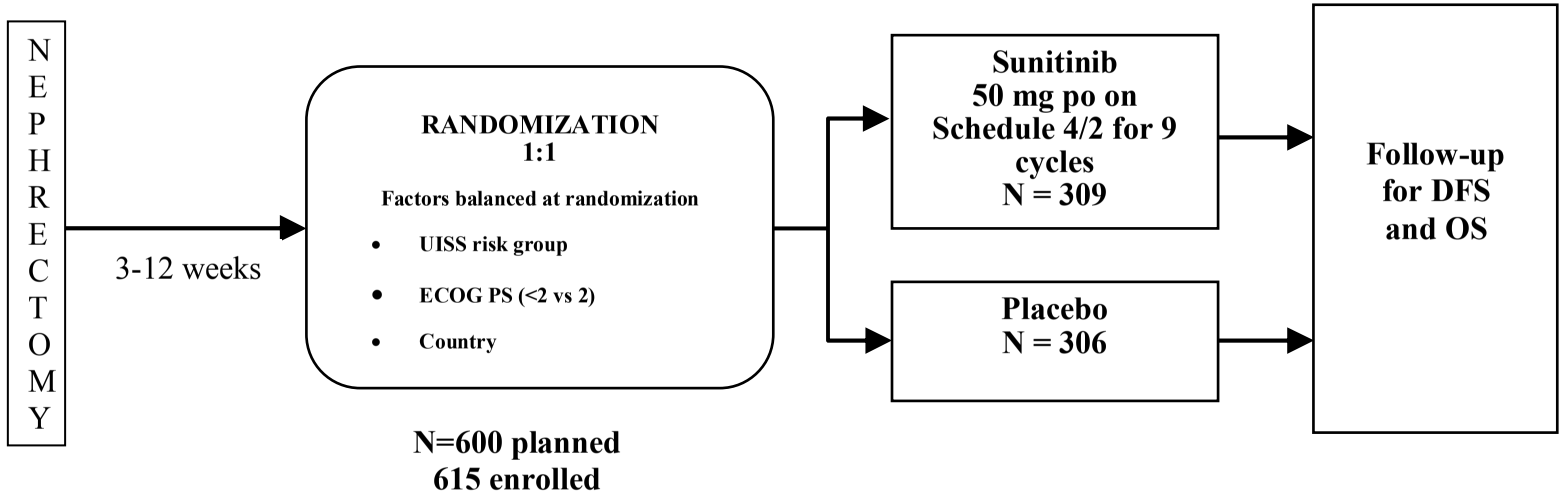
The primary objective of this study was to demonstrate that adjuvant treatment with sunitinib was superior to placebo in prolonging DFS in patients with RCC at high risk of disease recurrence following nephrectomy. The primary endpoint was DFS assessed by BICR, defined as the time from the date of randomization to the first date of recurrence or the occurrence of any secondary primary cancer or death from any cause. Secondary objectives included OS, safety, and PROs. Exploratory biomarker analyses were also evaluated and correlated with DFS.

Patients were randomized 1:1 to receive sunitinib (50 mg) or placebo and stratified by UISS-defined high-risk groups, ECOG PS (<2 vs 2), and country of origin. Sunitinib (50 mg) or placebo was administered orally once daily on Schedule 4/2 for 9 cycles (approximately 1 year). The starting dose in S-TRAC was the same as the approved mRCC indication for sunitinib. A single dose reduction to 37.5 mg was allowed.

Patients continued on study treatment until disease recurrence, occurrence of a second primary cancer, significant toxicity, withdrawal of consent, or for a maximum of 9 cycles.

Tumor assessments were performed at baseline and every 12 weeks during the first 3 years, then every 6 months thereafter until the time of final analysis, disease recurrence, second primary cancer, or withdrawal of consent, whichever came first. Computed tomography (CT) or magnetic resonance imaging (MRI) scans included the chest, abdomen, and pelvis. Additional imaging of potential disease sites, including brain or bone, was performed if clinically indicated.

Figure 5. S-TRAC Study A6181109 Design



Enrollment Criteria

- Clear cell RCC
- ≥T3 and/or N+
- ECOG PS 0-2
- Lack of residual disease by BICR

External Data Monitoring Committee performed regular data reviews.

BICR = Blinded Independent Central Review; DFS = Disease-Free Survival; ECOG = Eastern Cooperative Oncology Group; OS = Overall Survival; PO = per os (oral); PS = Performance Status; RCC = Renal Cell Carcinoma; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer; UISS = University of California Los Angeles Integrated Staging System; vs = versus.

The initial target sample size (320 DFS events) was determined based on 90% power at a 2-sided significance level of 0.05 to detect an HR of 0.69. However, during the course of the study, the event rate observed was lower than expected. A semi-parametric statistical model was fitted to the observed DFS data for the combined treatment arms which predicted that the time for the final readout with 320 events would require an additional 5 years of follow-up; this was confirmed by 3 consecutive annual projections (2011-2013). Therefore, with FDA feedback, the protocol was amended in July 2014 to change the time of the final DFS analysis from an event-based (320 DFS events) to a calendar date-based (April 2016, 5 years after last subject first visit [LSFV]) analysis. According to these revised projections, the estimated number of DFS events at the time of the final analysis would be approximately 258 providing 84% power to detect an HR of 0.69 with a 2-sided significance level of 0.05. Important amendments to the S-TRAC protocol are summarized in Section 6.2.

The primary analysis of DFS as assessed by BICR was the comparison between treatment arms with a 2-sided log-rank test stratified by UISS-based high-risk groups. ECOG PS (<2 vs 2) and country were not utilized in the stratified log-rank test due to the limited number of patients with ECOG PS 2 and the limited number of patients enrolled in some countries. For the same reason, the risk groups "T4 N0 or NX, M0, any Fuhrman's grade and any ECOG PS" and "Any T, N1-2, M0, any Fuhrman's grade, and any ECOG PS" were combined; these 2 risk groups were subsequently referred to as "Other" in the efficacy analyses.

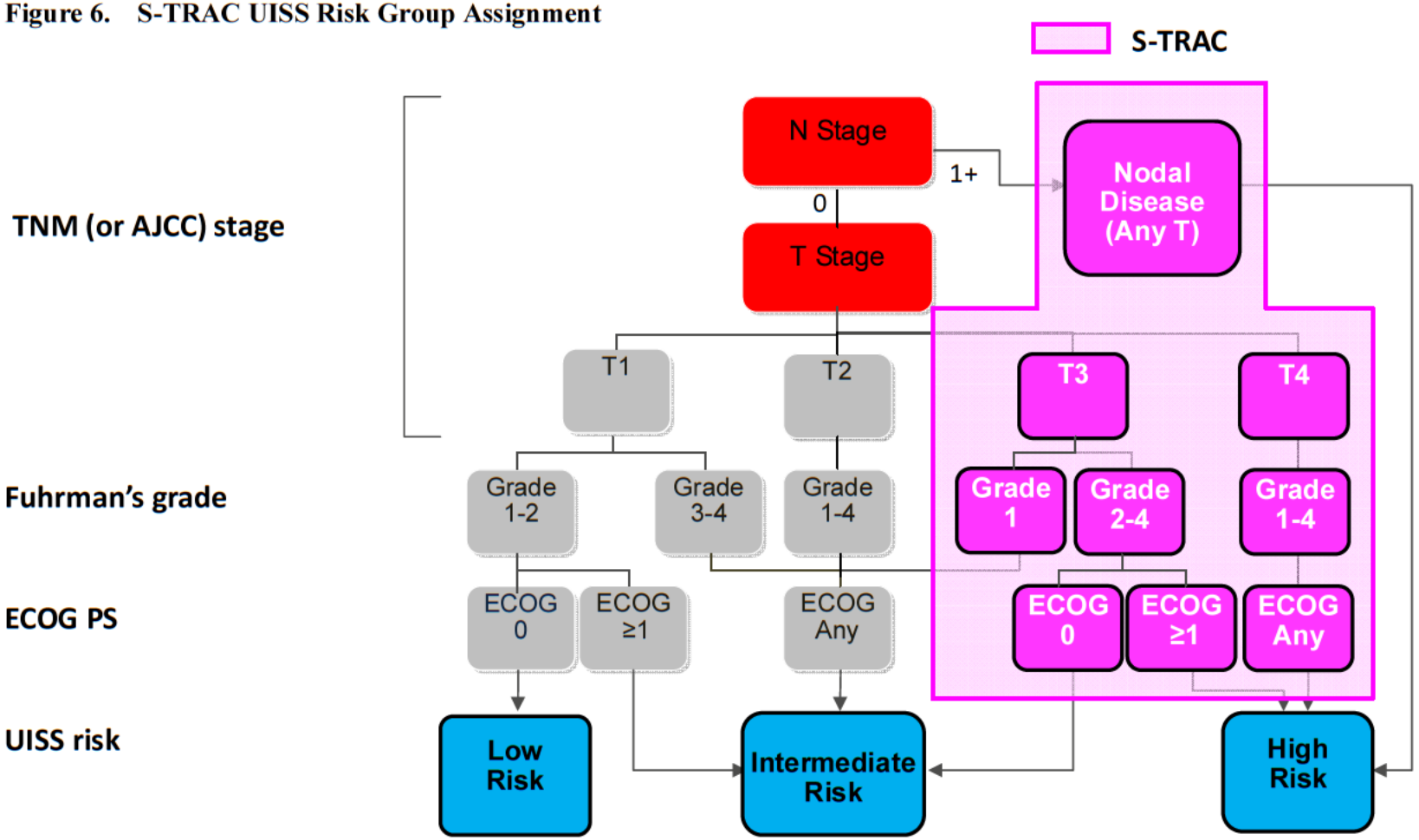
Secondary endpoints included OS, safety, and PROs. OS was defined as the time from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive. OS was compared between treatment arms with a 2-sided stratified log-rank test as described in the primary analysis of DFS and is discussed in Section 3.6.5 of this document. Safety data and PROs are discussed in Section 3.7 and Section 3.8 of this document, respectively.

3.2. Patient Population

Eligible patients were 18 years of age or older with histologically confirmed preponderant (defined as >50%) clear cell RCC; ECOG PS 0-2 prior to nephrectomy; no evidence of macroscopic residual or metastatic disease as confirmed by BICR; no previous anti-angiogenic treatments; adequate cardiac, renal, and hepatic function; and T3 or higher and/or lymph node positive regardless of stage according to UISS criteria.

Figure 6 highlights the population (within the box in the figure) included in S-TRAC based on UISS criteria.

Figure 6. S-TRAC UISS Risk Group Assignment



AJCC = American Joint Committee on Cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; TNM = tumor, node, metastasis; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer; UISS = UCLA integrated staging system. Adapted from Zisman et al[2] and Lam JS, et al.[6]

Key exclusion criteria included:

- Histologically undifferentiated carcinoma, sarcoma, or patients with any metastatic renal sites.
- National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 hemorrhage within the 4 weeks prior to the date of randomization.
- Diagnosis of any second malignancy within the 5 years prior to the date of randomization, except basal cell carcinoma, squamous cell skin cancer, or in situ carcinoma of the cervix uteri that was adequately treated with no evidence of recurrent disease for 12 months.

3.3. Baseline Demographics and Disease Characteristics

The baseline demographic and disease characteristics of patients enrolled in S-TRAC were balanced between the 2 treatment arms. A summary of selected baseline demographic and disease characteristics is provided in Table 3.

Table 3. Summary of Selected Baseline Demographic and Disease Characteristics from S-TRAC – Intent-to-Treat Population

	Sunitinib (N = 309)	Placebo (N = 306)
Age, mean (range) years	56.8 (25-83)	57.9 (21-82)
<65, n (%)	233 (75.4)	224 (73.2)
≥65, n (%)	76 (24.6)	82 (26.8)
Gender, n (%)		
Male	222 (71.8)	229 (74.8)
Female	87 (28.2)	77 (25.2)
Race, n (%)		
White	254 (82.2)	263 (85.9)
Black	3 (1.0)	1 (0.3)
Asian	43 (13.9)	33 (10.8)
Other	9 (2.9)	9 (2.9)
ECOG Performance Status at Randomization, n (%)		
0	228 (73.8)	220 (71.9)
1	79 (25.6)	84 (27.5)
2	1 (0.3)	0
3	0	0
4	0	0
Not Reported	1 (0.3)	2 (0.7)
Fuhrman's Grade		
1	11 (3.6)	8 (2.6)
2	104 (33.7)	104 (34.0)
3	139 (45.0)	141 (46.1)
4	54 (17.5)	52 (17.0)
Not reported	1 (0.3)	1 (0.3)
Histological Classification at Screening, n (%)		
Clear Cell Carcinoma	306 (99.0)	306 (100.0)
Non-Clear Cell Carcinoma	3 (1.0)	0
UISS High-Risk Group, n (%)		
T3 Low[a]	115 (37.2)	112 (36.6)
T3 High[b]	165 (53.4)	166 (54.2)
T4 N0 or NX[c]	4 (1.3)	4 (1.3)
Any T, N1-2[c]	25 (8.1)	24 (7.8)
Region		
US	24 (7.8)	24 (7.8)
Europe[d]	236 (76.4)	237 (77.5)
Asia[e]	41 (13.3)	32 (10.5)
Rest of World[f]	8 (2.6)	13 (4.2)

a. T3 N0 or NX, M0, any Fuhrman's grade and ECOG PS 0 or T3 N0 or NX, M0, Fuhrman's Grade = 1 and ECOG PS ≥1.
b. T3 N0 or NX, M0, Fuhrman's Grade ≥2, ECOG PS ≥1.
c. M0, any Fuhrman's grade, and any ECOG PS.
d. Czech Republic, Denmark, France, Germany, Greece, Ireland, Italy, Poland, Slovakia, Spain, Sweden, Switzerland, and United Kingdom.
e. China, Republic of Korea, Malaysia, and Taiwan, Province of China.
f. Australia, Colombia, and Israel

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; N = number of patients in arm; n = number of patients with observations; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer; UISS = University of California, Los Angeles Integrated Staging System.

3.4. Patient Disposition

Between 19 September 2007 and 07 April 2011, a total of 615 patients were randomized (1:1) to receive sunitinib (50 mg) or placebo (ITT population). The ITT population was the primary population for efficacy analyses, patient characteristics, and PROs. Three hundred six (306) patients were treated in the sunitinib arm, and 304 patients were treated in the placebo arm (as-treated [AT] population). The AT population was the primary population for evaluating safety.

More patients permanently discontinued treatment in the sunitinib arm (136 [44.4%]) than in the placebo arm (93 [30.6%]). The most common single reason for permanently discontinuing treatment was AEs[a] in the sunitinib arm (84 [27.5%] vs 16 [5.3%] patients in the placebo arm) and objective progression or relapse in the placebo arm (59 [19.4%] vs 22 [7.2%] patients in the sunitinib arm).

A total of 123 (39.8%) patients in the sunitinib arm and 115 (37.6%) patients in the placebo arm permanently discontinued from the study. The most common reason for discontinuation from the study was death in both treatment arms (61 [19.7%] in the sunitinib arm vs 64 [20.9%] in the placebo arm). No deaths in either treatment arm were attributed to study treatment toxicity (Section 3.7.2).

3.5. Drug Exposure

Patients were allowed to receive a maximum of 9 cycles (approximately 1 year) of study treatment. A summary of drug exposure in S-TRAC is provided in Table 4. The mean durations of study treatment in the sunitinib and placebo arms were 9.5 months and 10.3 months, respectively. Dosing interruptions and dose reductions were more frequent in the sunitinib arm; however, the median relative dose intensity[b] remained high in the sunitinib arm at 88.4% suggesting that most patients were able to tolerate either full-dose or close to full-dose sunitinib during their treatment.

The maximum 9 cycles (1 year) of study treatment was completed by 55.6% patients in the sunitinib arm and by 69.4% patients in the placebo arm; 70.9% of patients in the sunitinib arm and 78.6% of patients in the placebo arm were on treatment during Cycle 6 (8 months). Thus, the use of dosing interruption and dose reduction to manage AEs in the sunitinib arm enabled patients to remain on therapy.

[a] Data taken from end of treatment page and not AE page of the case report form.

[b] Defined as the actual number of milligrams administered in relation to the protocol-specified dose of 50 mg daily for 4 weeks of each 6-week cycle and is calculated relative to the actual time of treatment (including dosing interruptions, cycle delays, and the scheduled 2-week off-treatment period).

Table 4. Summary of Exposure in S-TRAC[a] – As-Treated Population

	Sunitinib (N=306)	Placebo (N=304)
Treatment duration (months)[b],		
Median	12.4	12.4
Mean	9.5	10.3
Range	0.13 – 14.9	0.03 – 13.7
Treatment completion, %	55.6	69.4
Relative dose intensity, median (range)[c]	88.4 (15-106.2)	99.7 (10-105.7)
Patients with dose reductions, n (%)	140 (45.8)	15 (4.9)
Patients with dosing interruptions, n (%)	166 (54.2)	84 (27.6)

a. Starting dose was 50 mg and patients were allowed to reduce their dose to 37.5 mg per protocol.
b. Duration of treatment was defined as the period between first and last doses of the drug and included dosing interruptions, cycle delays, and the scheduled 2-week off-treatment period.
c. Relative dose intensity (%) >100 is due to >28 days of dosing within a cycle, <14 days off between cycles, and/or the cycle end date for the last cycle not accounting the 14 days off-treatment period
Abbreviations: S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

3.6. S-TRAC Efficacy Results

S-TRAC met its primary objective of demonstrating that adjuvant treatment with sunitinib significantly reduced the risk of a DFS event compared to placebo, as assessed by BICR.

3.6.1. Primary Endpoint – Disease-Free Survival by BICR Assessment

The results of the primary DFS (assessed by BICR) analysis are summarized in Table 5.

A total of 257 patients had a DFS event in the ITT population, 113 (36.6%) from the sunitinib arm and 144 (47.1%) from the placebo arm. DFS events in the sunitinib arm (101/113) and placebo arm (129/144) were predominantly recurrence within the kidney, local or distant. The remaining events were deaths (8/113 and 4/144, respectively) or secondary malignancies (4/113 and 11/144 respectively).

The HR comparing sunitinib with placebo was 0.761 (95% CI: 0.594, 0.975) with a 2-sided p-value of 0.030 in favor of sunitinib, representing a statistically significant and clinically meaningful 24% relative reduction in the risk of a DFS event. The median DFS was 6.8 years (95% CI: 5.8, not reached [NR]) in the sunitinib arm and 5.6 years (95% CI: 3.8, 6.6) in the placebo arm.

The Kaplan-Meier plot of DFS by treatment arm is shown in Figure 7, where the DFS curves for each treatment arm separated early and remained separated throughout the observation period. The median follow-up time was 5.4 years (95% CI: 5.2, 5.6) for the sunitinib arm and 5.4 years (95% CI: 5.3, 5.6) for the placebo arm based on the reverse Kaplan-Meier method. The cumulative probabilities of being event-free at 1, 2, 3, and 5 years are provided in Table 6. The absolute improvement in favor of sunitinib in the cumulative probability of being event-free at 5 years was 8.0%.

Table 5. Disease-Free Survival by BICR Assessment in S-TRAC – Intent-to-Treat Population

	Sunitinib (N = 309)	Placebo (N = 306)
Number (%) with Event	113 (36.6)	144 (47.1)
Type of Event, n (%)		
Disease Recurrence or Occurrence of a Secondary Malignancy	105 (34.0)	140 (45.8)
Death	8 (2.6)	4 (1.3)
Number Censored, n (%)	196 (63.4)	162 (52.9)
Reason for Censorship, n (%)		
No Post-Baseline Cancer Event Assessments	14 (4.5)	6 (2.0)
No Event at Time of Data Cutoff	182 (58.9)	156 (51.0)
Withdrew Consent for Follow-Up	16 (8.8)	15 (9.6)
Lost to Follow-Up	9 (4.9)	6 (3.8)
Receiving Further Anti-Cancer Therapy Prior to an Event	12 (6.6)	13 (8.3)
Still in Disease Follow-up	124 (68.1)	112 (71.8)
Other	10 (5.5)	4 (2.6)
Disease Relapse or Death Occurred After ≥2 Consecutive Missed Assessments	11 (6.0)	6 (3.8)
Kaplan-Meier estimates of DFS (Year)		
50% Quartile (95% CI)[a]	6.8 (5.8, NR)	5.6 (3.8, 6.6)
Versus Placebo		
Hazard Ratio[b] (95% CI)	0.761 (0.594, 0.975)	
p-value[c]	0.030	

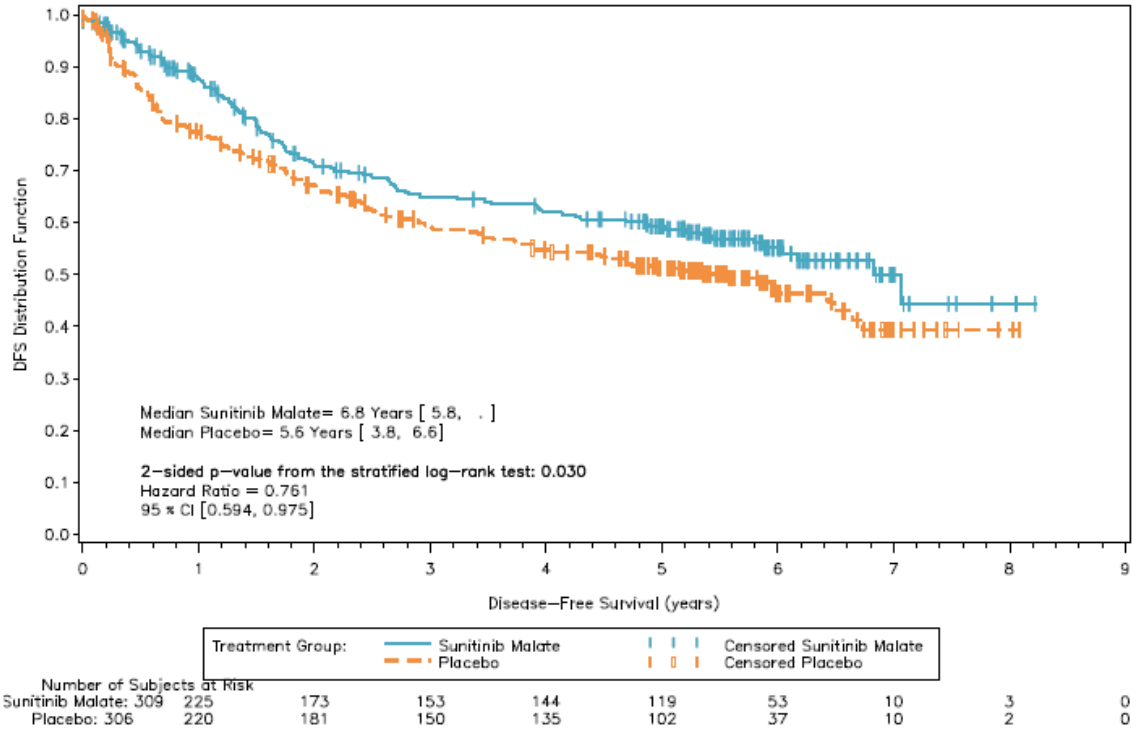
a. Based on the Brookmeyer and Crowley method.
b. Based on the Cox Proportional Hazards model stratified by UISS High-Risk Group.
c. 2-sided p-value from the log-rank test stratified by UISS High-Risk Group.
Abbreviations: BICR = Blinded Independent Central Review; CI = confidence interval; DFS = disease-free survival; N = number of patients in arm; n = number of patients with observations; NR = not reached; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer; UISS = University of California, Los Angeles Integrated Staging System.

Table 6. Cumulative Probabilities of Being Disease-Free by BICR Assessment in S-TRAC – Intent-to-Treat Population

	Probability of Being Event Free		
	Sunitinib (N=309) %	Placebo (N=306) %	Absolute Difference Between Sunitinib and Placebo Arms[a] %
Year 1[b]	87.7	77.6	10.1
Year 2[b]	71.3	67.2	4.1
Year 3[b]	64.9	59.5	5.4
Year 5[b]	59.3	51.3	8.0

a. Sunitinib minus placebo.
b. Estimated from the Kaplan-Meier curve.
Abbreviations: CI = confidence interval; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

Figure 7. Kaplan-Meier Plot of Disease-Free Survival by BICR Assessment in S-TRAC – Intent-to-Treat Population (Primary Analysis)

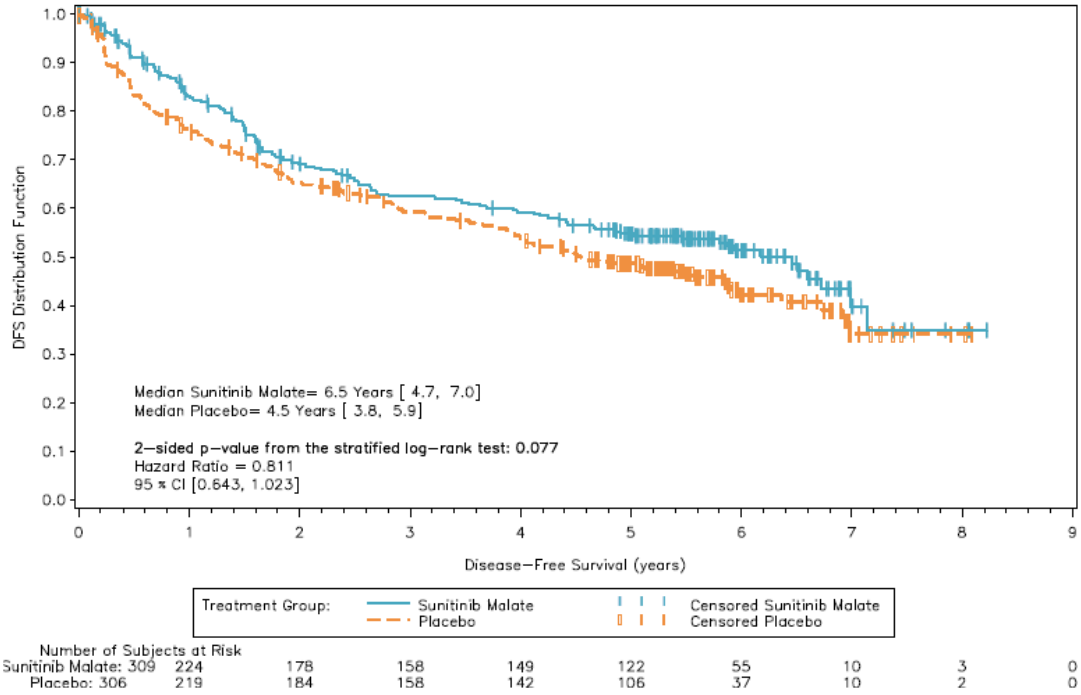


Note: Patients with disease at baseline were included in the events and their disease–free survival (DFS) time was Day 1. Abbreviations: BICR = Blinded Independent Central Review; CI = confidence interval; DFS = disease-free survival; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

3.6.2. Disease-Free Survival by Investigator Assessment

The benefit of adjuvant treatment with sunitinib in S-TRAC was also observed in the DFS analysis based on investigator assessment with a 19% reduction in the risk of recurrence or death, although this did not reach statistical significance (HR 0.811 [95% CI: 0.643, 1.023], 2-sided p-value=0.077; median DFS 6.5 years [95% CI: 4.7, 7.0] for sunitinib vs 4.5 years [95% CI: 3.8, 5.9] for placebo). Two hundred ninety (290) DFS events were observed based on the investigator assessment. The Kaplan-Meier plot of DFS based on investigator assessment by treatment arm is shown in Figure 8.

Figure 8. Kaplan-Meier Plot of Disease-Free Survival by Investigator Assessment in S-TRAC – Intent-to-Treat Population



Note: Patients with disease at baseline were included in the events and their disease–free survival (DFS) time was Day 1.
Abbreviations: CI = confidence interval; DFS = disease-free survival; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

Per protocol, patients were to be followed until BICR-confirmed relapse. The majority of patients (96.4%) either had event or censoring times at the same or earlier time points by the BICR compared to the investigator, or had at least 1 additional assessment following censoring by the investigator or following disease relapse by the investigator that was not confirmed by the BICR.

Discordance between BICR and investigator assessments at the individual patient level is common and can be reflective of the inherent variability in the disease assessment process and not necessarily systematic bias. Differential discordance, defined as the difference between treatment arms in discordance rates, provides a framework for evaluating bias.[46] Table 7 provides the rates of overall, early, late, and total discordance in each treatment arm as well as the differential rates. Overall discordance provides an evaluation of the difference in event status and/or timing, while the total disagreement rate considers only differences in the event status. Early disagreement rate evaluated the proportion of cases where the investigator assessed relapse earlier than the BICR, while late disagreement rate evaluated the proportion of cases where the investigator assessed relapse later than the BICR. Differential rates in early and late disagreement are indicative of potential bias.

Table 7. Discordance of BICR and Investigator Assessments of Disease-Free Survival in S-TRAC – Intent-to-Treat Population

Parameter and Disagreement Type	Sunitinib (N = 309)	Placebo (N = 306)	Difference (%)
Overall Disagreement Rate	27.8%	27.8%	0
Total Event Disagreement Rate	11.3%	8.5%	2.8
Early Disagreement Rate	36.4%	24.7%	11.7
Late Disagreement Rate	44.2%	54.1%	−9.9

Abbreviations: BICR = blinded independent central review; N = the number of patients in arm.
Source: Supplementary Table S3, Ravaud A et al.[47]

The overall discordance rate between the BICR and investigator assessment was 27.8% in both treatment arms (i.e., differential rate of 0), a rate that was lower than rates as high as 50% reported in the metastatic setting.[46] However, there was a difference between the treatment arms in terms of early and late discordance with the early discrepancy rate defined as when the investigator called relapse earlier than BICR and late discrepancy rate defined as when the investigator called relapse later than BICR. The differential discordance was positive (11.7%) for early discrepancy rate, which indicated that the investigators called relapse earlier than the BICR more frequently in the sunitinib arm than in the placebo arm. The differential discordance was negative (-9.9%) for the late discrepancy rate, which indicated that the investigators called relapse later than the BICR more frequently in the placebo arm than in the sunitinib arm. The early and late differential discordance rates demonstrated no evidence of bias in favor of sunitinib, but rather a potential bias in favor of placebo by investigator assessment.

3.6.3. Sensitivity Analyses of Disease-Free Survival

Sensitivity analyses were performed to evaluate the robustness of study results by investigating the extent to which the overall results and conclusions may be affected by various limitations of the data, assumptions, and analytic approaches to data analysis. For endpoints such as DFS, differences in assessment schedule between treatment arms and treatment decisions such as initiating new anticancer therapy prior to a confirmed relapse by the BICR could impact results.

Sensitivity analyses of DFS presented in Figure 9 were performed to test the robustness of the primary DFS analysis. The primary endpoint by BICR is shown at the top followed by the assessment of DFS by investigator assessment.

The next 2 analyses consider the same event and censoring rules as the primary analysis but consider earlier dates of relapse for equivocal new lesions later determined to be unequivocal as well as some alternative dates for secondary malignancies where there were differences noted between the investigator assessment and the BICR assessment.

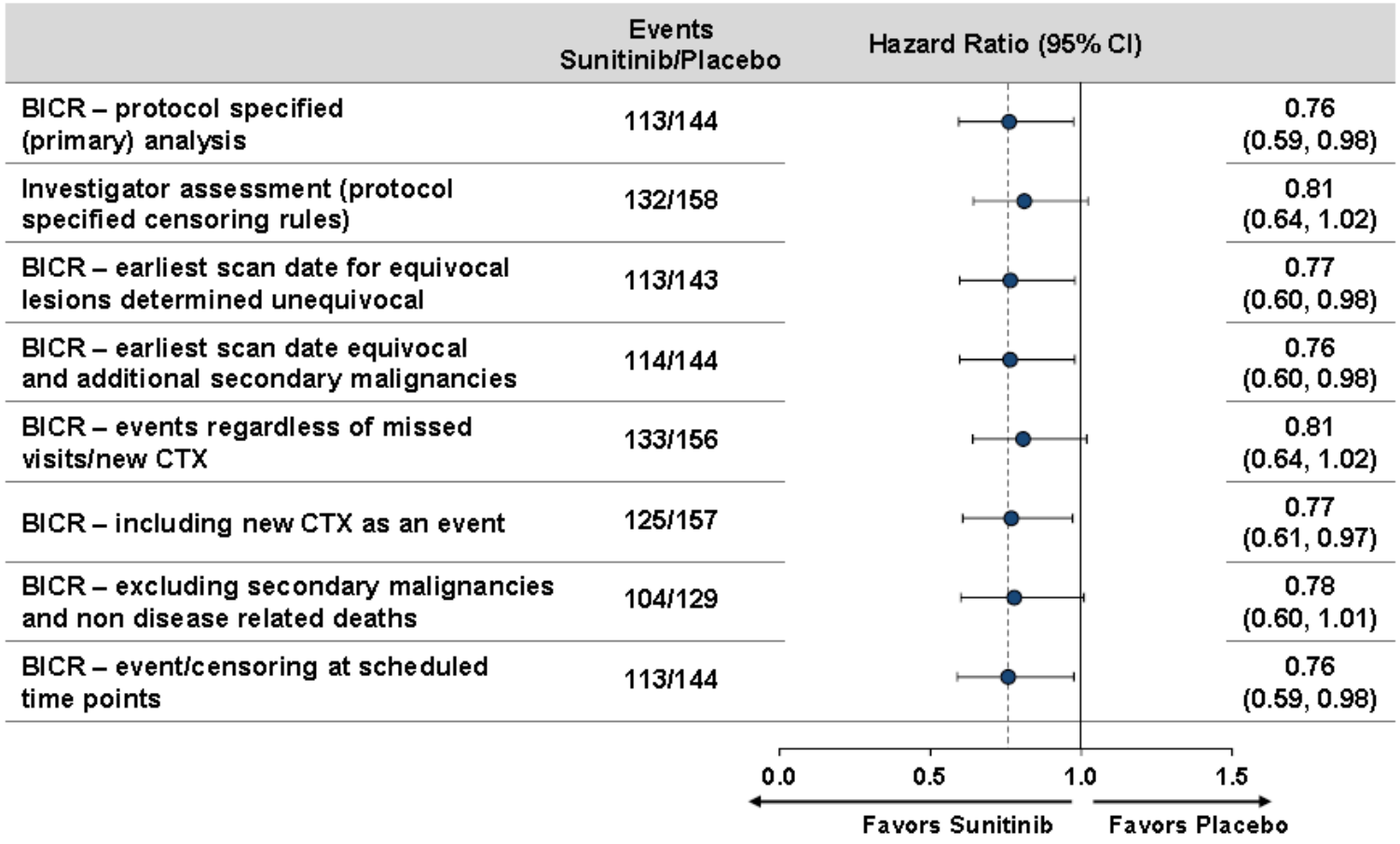
The next 3 analyses consider alternative event and censoring rules including considering events which occurred after extended lost to follow-up or new anticancer therapy, considering start of new anticancer therapy as an event, and considering a time to recurrence

(TTR) analysis where secondary malignancies and deaths due to cause other than disease understudy were excluded.

The final analysis presented adjusts for any potential bias associated with a difference in assessment between the 2 treatment arms which could have resulted from patients coming in for unscheduled visits more often on one arm compared to the other.

Results of these analyses demonstrated the robustness of the primary DFS analysis, with consistent HRs (0.76-0.81) favoring sunitinib.

Figure 9. Forest Plot of Sensitivity Analyses in S-TRAC – Intent-to-Treat Population



Dotted line represents the hazard ratio (0.76) for the protocol-specified analysis of the primary BICR-assessed DFS endpoint in S-TRAC. Abbreviations: BICR = blinded independent central review; CI = confidence interval; CTX = anti-cancer therapy; DFS = disease-free survival; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

In addition to the sensitivity analyses outlined above, the imbalance in censoring in the first year in the primary analysis of DFS by BICR assessment was examined.

- A higher number of patients were censored in the first year in the sunitinib arm compared to the placebo arm (50 [16.2%] patients vs 21 [6.9%] patients, respectively).

- Fourteen (14) of the 50 patients (28%) censored within the first year in the sunitinib arm were censored due to either initiation of new anticancer therapy (7 patients) or 2 or more consecutive missed assessments prior to an event (7 patients) compared with 7 of the 21 patients (33.3%) in the placebo arm, all of whom were censored due to the start of new anticancer therapy.

- Of the patients over both treatment arms combined who were censored due to the start of new anticancer therapy, all but 1 patient in the sunitinib arm had a DFS event based on investigator assessment prior to initiating the new anticancer therapy.

- Ten percent (10%) of the patients censored in the first year in both treatment arms (5/50 on sunitinib and 2/21 on placebo) were still in overall survival follow-up but did not have any additional DFS assessments and were also censored based on the investigator assessment.

- The remaining patients censored in the first year in both treatment arms either withdrew consent or were otherwise lost to follow-up, 3 of whom had investigator-assessed DFS events (sunitinib arm).

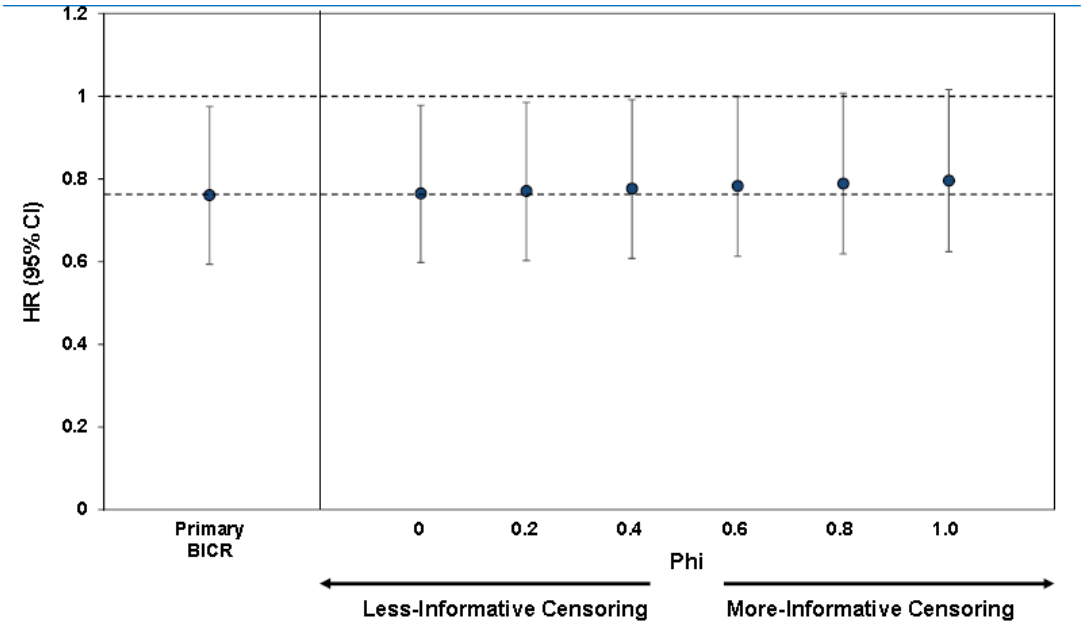
It should be noted that censoring in the first year was not primarily due to DFS events assessed by the investigator which were not confirmed by the BICR. As noted in Section 3.6.2, the majority of patients either had a DFS event or censoring times at the same or earlier time points by the BICR compared to the investigator, or had at least 1 additional assessment following disease relapse by the investigator that was not confirmed by the BICR.

An analysis of early censoring during Year 2 (>1 year and ≤2 years) based on BICR assessment showed that the number of patients censored was smaller and balanced between the treatment arms (11 [3.6%] patients in the sunitinib arm vs 10 [3.3%] patients in the placebo arm).

The sensitivity analyses presented in Figure 9 address some of the reasons for censoring during the first year (e.g., considering new anticancer therapy as an event) demonstrating the robustness of the primary DFS analysis. An additional imputation-based censoring analysis was performed given the imbalance in censoring in the first year and to examine the potential for this to be informative censoring (i.e., related to the study or study treatment). A reference-based imputation method as outlined by Lu, Li, and Koch[48] was implemented to assess the impact of censoring in the first year. This method assumes that the hazard for the sunitinib arm patients who are censored in the first year lies between the hazard for the sunitinib arm patients who continued and the hazard for the placebo arm patients. The method considers DFS events if imputed values lie between the time of censoring and 6 years of follow-up, or it censors for imputed values beyond 6 years.

Figure 10 provides the results of a simulation for various values of phi, where phi is a sensitivity parameter that ranges from 0 to 1, with 0 representing non-informative independent censoring (missing at random), and 1 representing informative censoring (missing not at random), where the imputations for the sunitinib arm were performed in accordance with the observed DFS in the placebo arm. Phi was 0 for the placebo arm in all cases. The stability of the point estimates of the HRs as well as the 95% confidence intervals (CIs) indicate that the primary analysis was not impacted by the potential informative censoring in the first year in the sunitinib arm.

Figure 10. Sensitivity Analysis of Disease-Free Survival by Blinded Independent Central Review to Evaluate the Potential Informative Censoring During the First Year

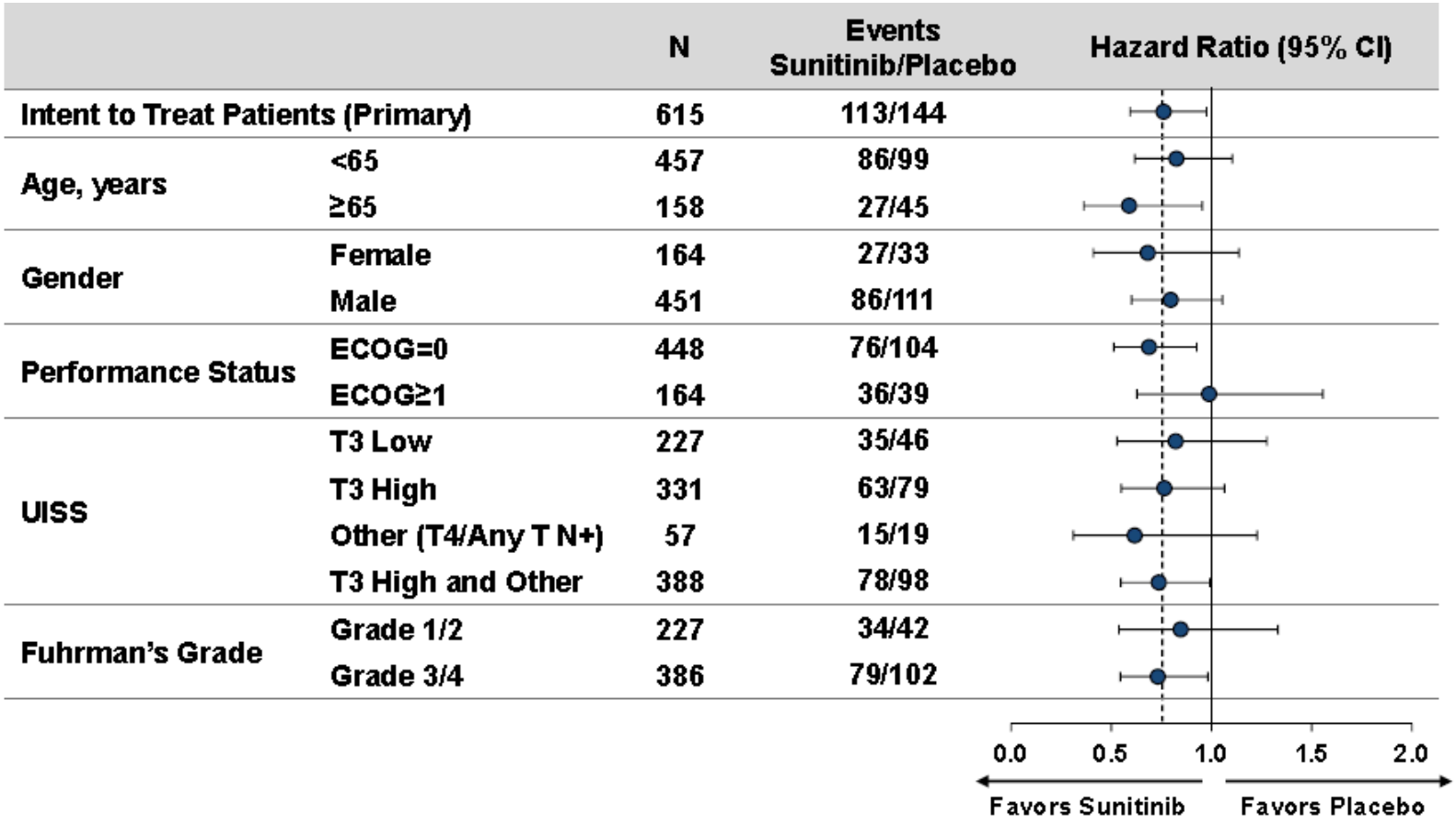


Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio.

3.6.4. Efficacy in Subpopulations

The potential influence of baseline characteristics on the observed outcomes with sunitinib was evaluated for DFS in the S-TRAC study. Pre-specified subgroup analyses included those by UISS-based risk group, age, gender, and ECOG PS. A post-hoc analysis by Fuhrman's grade was also performed. All subgroup analyses were considered exploratory. Interactions between the treatment effect and the baseline factors mentioned above were analyzed and none of the interaction terms were statistically significant. The CIs for the HRs were wide for many of the subgroups due to limitations in sample size; however, in the majority of subgroups, the result of the analysis demonstrated longer DFS on sunitinib treatment compared to placebo and all of the confidence intervals contain the point estimate of the hazard ratio observed in the primary analysis (Figure 11), and thereby consistent with the findings of DFS improvement in the overall study population.

Figure 11. Forest Plot of Disease-Free Survival by Additional Baseline Characteristics by BICR Assessment in S-TRAC – Intent-to-Treat Population



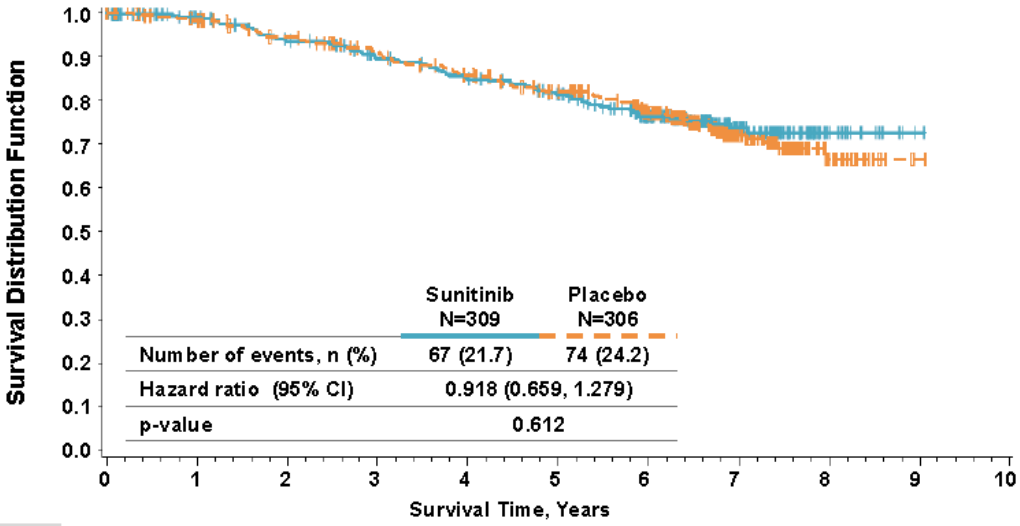
Dotted line represents the hazard ratio for the protocol-specified analysis of the primary BICR-assessed DFS endpoint in S-TRAC. Abbreviations: BICR = blinded independent central review; CI = confidence interval; DFS = disease-free survival; ECOG = Eastern Cooperative Oncology Group; N = number; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer; UISS = University of California Los Angeles, Integrated Staging System.

3.6.5. Secondary Endpoints – Overall Survival

In S-TRAC, after disease recurrence, occurrence of a secondary malignancy, or discontinuation of DFS follow-up for other reasons (e.g., patient withdrew consent), all patients were followed for survival status (regardless of the duration of study treatment). OS was defined as the time interval (in years) from the date of randomization to the date of death due to any cause. In the absence of confirmed death, survival time was censored at the last date the patient was known to be alive. Patients lacking data beyond randomization had their survival times censored at Day 1.

At the time of data cutoff (31 January 2017), a total of 67 (21.7%) deaths in the sunitinib arm and 74 (24.2%) deaths in the placebo arm were reported. Furthermore, 55 (17.8%) and 48 (15.7%) patients, respectively, had withdrawn consent or were otherwise lost to follow-up. The observed stratified HR comparing sunitinib with placebo was 0.918 (95% CI: 0.659, 1.279; 2-sided p-value = 0.612) indicating that sunitinib did not have a detrimental effect on OS based on a median follow-up of approximately 6.5 years. The median OS was not reached for either treatment arm. Based on the current event rate, it is estimated that an additional 10 years of follow-up would be needed to reach the median OS in this patient population. A Kaplan-Meier plot of OS is provided in Figure 12.

Figure 12. Kaplan-Meier Plot of Overall Survival in S-TRAC – Intent-to-Treat Population



Number at Risk											
Sunitinib	309	278	258	236	222	205	160	82	16	1	0
Placebo	306	289	269	250	231	210	172	82	23	1	0

Date of data cutoff: 31 January 2017.

Abbreviations: CI = confidence interval; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

3.7. S-TRAC Safety Results

Sunitinib has a well-known and well-established safety profile based on more than 11 years of post-marketing and clinical trial experience. The most common AEs reported in more than 7,000 patients participating in single agent clinical studies in the approved indications are Diarrhoea, PPE syndrome, Hypertension, Fatigue/Asthenia, Nausea, Vomiting, Decreased appetite, Stomatitis, and Abdominal pain.

An overall summary of all-causality treatment-emergent AEs (TEAEs) in S-TRAC is provided in Table 8. Most patients in both treatment arms experienced TEAEs, while approximately one-fifth of patients in both treatment arms experienced serious adverse events (SAEs) (21.9% in the sunitinib arm vs 17.1% in the placebo arm). As expected, Grade 3 or 4 TEAEs and permanent discontinuations due to TEAEs were higher in the sunitinib arm than in the placebo arm. The overall frequencies of Grade 5 AEs was low (1.6%) in both treatment arms without any treatment-related deaths. Most deaths in either treatment arm were not reported as Grade 5 AEs and were attributed to disease under study (Section 3.7.2).

Table 8. Overall Summary of All-Causality Adverse Events[a,b] in S-TRAC

	Sunitinib N=306 n (%)	Placebo N=304 n (%)
Patients with AEs	305 (99.7)	269 (88.5)
Patients with SAEs	67 (21.9)	52 (17.1)
Patients with Grade 3 or 4 AEs	189 (61.8)	61 (20.1)
Patients with Grade 5 AEs[c]	5 (1.6)	5 (1.6)
Patients temporarily discontinued due to AEs	142 (46.4)	40 (13.2)
Patients dose reduced due to AEs	105 (34.3)	6 (2.0)
Patients permanently discontinued due to AEs	86 (28.1)	17 (5.6)

a. Includes data from the active treatment and follow-up periods.
b. Information from Adverse Events CRF pages.
c. Per protocol, deaths due to disease progression in the follow-up period were not required to be reported as Grade 5 AEs.
Abbreviations: AE = adverse event; N = number of patients in arm; n = number of patients with observations; SAE = serious adverse event; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

When reviewing the TEAEs from the active treatment period (within 28 days after the last dose of study drug), no new patterns and safety concerns were identified. A review of the TEAEs in the follow-up period (beyond 28 days after the last dose of study drug) also did not identify any new safety concerns.

Overall, no new safety signals were observed for the adjuvant treatment of RCC patients with sunitinib. AEs were predictable, as they were consistent with those observed in mRCC patients treated with sunitinib, and manageable by dosing interruptions, dose reductions, and/or standard supportive medical therapy in order to enable patients to remain on study treatment. Overall, AEs leading to permanent discontinuation were reversible, as most of them (87%) were reported as recovered or recovering at the last patient contact. In the

remaining patients, potential contributing factors were identified for 8 events, and no additional information was available at the last patient contact for 3 events (Grade 2 and Grade 3 PPE syndrome and Grade 2 Unexpected therapeutic effect [increased thyroid function]), which are events that are generally manageable.

3.7.1. Treatment-Emergent Adverse Events

All-Causality Treatment-Emergent Adverse Events

The pattern of all-causality TEAEs was consistent with the known safety profile of sunitinib (Table 15 in Section 6.3). A total of 305 (99.7%) and 269 (88.5%) patients experienced at least 1 all-causality TEAE in the sunitinib and placebo arms, respectively. The most common all-causality TEAEs in the sunitinib arm were Diarrhoea (56.9% vs 21.4% in the placebo arm), PPE syndrome (50.3% vs 10.2% in the placebo arm), Hypertension (36.9% vs 11.8% in the placebo arm), and Fatigue (36.6% vs 24.3% in the placebo arm). However, permanent treatment discontinuations in response to these AEs were low (0.3% – 4.2%). PPE syndrome was the only TEAE reported at a higher frequency than that in patients with mRCC treated with sunitinib in Phase 3 Study A6181034[17] (50.3% in S-TRAC vs 28.8% in Study A6181034). The median time to resolution of key events (Diarrhoea, PPE syndrome, Hypertension, Fatigue, and cardiovascular events) was 2.3 – 3.6 weeks.

All-Causality Grade 3 and Grade 4 Treatment-Emergent Adverse Events

In the sunitinib arm, 148 (48.4%) and 37 (12.1%) patients experienced a Grade 3 or Grade 4 TEAE compared to 48 (15.8%) and 11 (3.6%) patients in the placebo arm, respectively. There were no Grade 4 events that were reported in more than 1.3% of patients in the sunitinib arm. A summary of all-causality TEAEs (all grades and Grade 3 and Grade 4 events) by decreasing frequency within each system organ class (SOC) reported in ≥10% of patients is provided in Table 9. TEAEs (Grade ≥3) observed in >5% of patients in the sunitinib arm were PPE syndrome (16.0% vs 0.3% in the placebo arm), Neutropenia (8.5% vs 0% in the placebo arm), Hypertension (7.8% vs 1.3% in the placebo arm), and Thrombocytopenia (6.2% vs 0.3% in the placebo arm). However, most events were reported as resolved at the last patient contact.

Table 9. Summary of All-Causality, Treatment-Emergent Adverse Events (All Grades and Grade 3 and Grade 4) Experienced by ≥10% of Patients in S-TRAC[a] – As-Treated Population

System Organ Class MedDRA Preferred Term	Sunitinib (N=306) n (%)			Placebo (N=304) n (%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any Adverse Events	305 (99.7)	148 (48.4)	37 (12.1)	269 (88.5)	48 (15.8)	11 (3.6)
Blood and lymphatic system disorders						
Neutropenia	72 (23.5)	23 (7.5)	3 (1.0)	2 (0.7)	0	0
Thrombocytopenia	64 (20.9)	15 (4.9)	4 (1.3)	5 (1.6)	1 (0.3)	0
Leukopenia	45 (14.7)	3 (1.0)	1 (0.3)	2 (0.7)	0	0
Anaemia	33 (10.8)	4 (1.3)	1 (0.3)	7 (2.3)	0	0
Endocrine disorders						
Hypothyroidism	56 (18.3)	0	0	4 (1.3)	0	0
Gastrointestinal disorders						
Diarrhoea	174 (56.9)	12 (3.9)	0	65 (21.4)	1 (0.3)	0
Nausea	105 (34.3)	6 (2.0)	0	42 (13.8)	0	0
Dyspepsia	82 (26.8)	4 (1.3)	0	19 (6.3)	0	0
Stomatitis	81 (26.5)	5 (1.6)	2 (0.7)	13 (4.3)	0	0
Vomiting	58 (19.0)	7 (2.3)	0	20 (6.6)	0	0
Abdominal pain	42 (13.7)	4 (1.3)	1 (0.3)	16 (5.3)	1 (0.3)	0
Abdominal pain upper	39 (12.7)	0	0	13 (4.3)	0	0
Constipation	36 (11.8)	0	0	32 (10.5)	0	0
General disorders and administration site conditions						
Fatigue	112 (36.6)	13 (4.2)	2 (0.7)	74 (24.3)	4 (1.3)	0
Mucosal inflammation	103 (33.7)	14 (4.6)	0	25 (8.2)	0	0
Asthenia	69 (22.5)	11 (3.6)	0	37 (12.2)	2 (0.7)	1 (0.3)
Pyrexia	36 (11.8)	0	1 (0.3)	17 (5.6)	0	0
Metabolism and nutrition disorders						
Decreased appetite	59 (19.3)	2 (0.7)	0	16 (5.3)	0	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	45 (14.7)	1 (0.3)	0	20 (6.6)	0	0
Arthralgia	35 (11.4)	1 (0.3)	0	29 (9.5)	0	0
Nervous system disorders						
Dysgeusia	103 (33.7)	0	0	18 (5.9)	0	0
Headache	57 (18.6)	2 (0.7)	0	36 (11.8)	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	55 (18.0)	0	0	9 (3.0)	0	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysaesthesia syndrome	154 (50.3)	46 (15.0)	3 (1.0)	31 (10.2)	1 (0.3)	0
Hair colour changes	68 (22.2)	0	0	7 (2.3)	0	0
Rash	59 (19.3)	2 (0.7)	0	29 (9.5)	0	0
Dry skin	43 (14.1)	0	0	17 (5.6)	0	0
Yellow skin	32 (10.5)	0	0	2 (0.7)	0	0
Vascular disorders						
Hypertension	113 (36.9)	24 (7.8)	0	36 (11.8)	3 (1.0)	1 (0.3)

a. Includes data from the active treatment and follow-up periods in S-TRAC.
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in arm; n=number of patients with observations; S-TRAC= Sunitinib Treatment of Renal Adjuvant Cancer. Treatment-Emergent Adverse Events (TEAEs) are all AEs (serious and non-serious) that occurred, for the first time, on or after the first day of study treatment. AEs that started before the first dose of study treatment but increased in severity (CTCAE grade) over baseline were also considered TEAEs.
Includes data up to 9999 days after last dose of study drug.
Patients are counted only once in each row.
CTCAE v3.0 was used.
MedDRA (v19.0) coding dictionary applied.

3.7.2. Deaths

As of 31 January 2017, a numerically lower number (and proportion) of deaths were reported over the treatment and follow-up periods in the sunitinib arm (66 [21.6%]) than in the placebo arm (74 [24.3%]). No deaths in either treatment arm were attributed to study treatment toxicity, and the most common cause of death in both treatment arms was disease under study (49 [16.0%] patients in the sunitinib arm and 50 [16.4%] patients in the placebo arm). A summary of deaths reported on treatment and during the follow-up period in S-TRAC is provided in Table 10.

Two (2) patients in the sunitinib arm died on study treatment or within 28 days of their last dose of study drug. The cause of death was reported as disease under study for both patients. These events were also reported as Grade 5 AEs, neither of which was attributed to study treatment.

No deaths were reported in the placebo arm on study treatment or within 28 days after their last dose of study drug.

A total of 64 (20.9%) patients in the sunitinib arm and 74 (24.3%) patients in the placebo arm of S-TRAC died during the follow-up period (defined as after 28 days after the last dose of study drug), including 7 patients (2 in the sunitinib arm and 5 in the placebo arm) who died during the follow-up period but were reported as Grade 5 events, none of which were considered treatment-related. The majority of these deaths in the sunitinib arm (47 [15.4%]) and placebo arm (50 [16.4%]) were attributed to the disease under study, and no deaths in the follow-up period were attributed to study treatment toxicity.

Table 10. Summary of Deaths in S-TRAC – As-Treated Population

	Sunitinib (N=306) n (%)	Placebo (N=304) n (%)
Number (%) of patients:		
Deaths[a]	66[b] (21.6)	74 (24.3)
Patients who died while on treatment[c]	2 (0.7)	0
Disease under study	2 (0.7)	0
Study treatment toxicity	0	0
Unknown	0	0
Other	1 (0.3)	0
Patients who died during follow-up[d]	64 (20.9)	74 (24.3)
Disease under study	47 (15.4)	50 (16.4)
Study treatment toxicity	0	0
Unknown	9 (2.9)	9 (3.0)
Other	10 (3.3)	16 (5.3)

a. Some patients could have had multiple reasons for death.
b. One (1) patient was randomized to the sunitinib arm but not treated. Two (2) years after randomization, the patient died. By definition, this patient was excluded from the As-Treated population.
c. On-treatment deaths were those that occurred after the first dose of study drug and within 28 days after the last dose.
d. Follow-up deaths were those that occurred after 28 days after the last dose.
As-Treated population included all patients who received at least 1 dose of study drug with treatment assignments designated according to actual study drug received.
Abbreviations: N = number of patients in arm; n = number of patients with observations; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

3.7.3. Other Serious Adverse Events

Approximately one-fifth of patients in both treatment arms experienced all-causality treatment-emergent SAEs (21.9% and 17.1%, respectively). The most common SAEs were Hypertension (2.6% in the sunitinib arm vs 0.7% in the placebo arm), Thrombocytopenia (2.3% in the sunitinib arm vs 0.3% in the placebo arm), Pulmonary embolism (1.6% in the sunitinib arm vs 0.3% in the placebo arm), and Pyrexia (1.6% in the sunitinib arm vs 0% in the placebo arm). Hospitalization for any reason was similar between both treatment arms (18.9% in the sunitinib arm vs. 17.1% in the placebo arm).

The most common SAEs were consistent with the known safety profile of sunitinib.

3.7.4. Discontinuations and Dose Reductions Due to Adverse Events

Permanent Discontinuations

More patients in the sunitinib arm permanently discontinued treatment due to AEs. The mean and median times from randomization to permanent discontinuation due to an AE in the sunitinib arm were 5.1 months and 4.5 months, respectively. A total of 86 (28.1%) patients in the sunitinib arm and 18 (5.9%) patients in the placebo arm permanently discontinued treatment due to an AE. AEs leading to permanent discontinuation in ≥1% of patients in the sunitinib arm were PPE syndrome (4.2%), Hypertension (2.0%), Asthenia

(1.3%), Fatigue (1.0%), Pulmonary embolism (1.0%), and Gastroesophageal reflux disease (1.0%). Many AEs leading to permanent discontinuation were Grade 1 and 2 in severity, which was not unexpected in this adjuvant RCC patient population without radiological evidence of metastatic disease, and most events resolved or were resolving (87%). For the remaining 13% (11 patients), review of these AEs did not reveal any new safety concerns; 8 of these events were reported due to underlying illness/disease-related or identified with potential contributory factors (Section 6.4). Although no additional AE information was retrievable for 3 patients at the last patient contact (Grade 2 and 3 PPE syndrome, and Grade 2 Unexpected therapeutic effect [increased thyroid function]), these AEs are known to be manageable.

As observed in the mRCC treatment setting, a higher number (and proportion) of permanent treatment discontinuations occurred in Cycle 1 (8.2%) compared to subsequent cycles (2% - 3%). The majority of AEs leading to permanent discontinuation in Cycle 1 were reported in 1 patient each.

Temporary Discontinuations and Dose Reductions

AEs were managed by treatment interruption with or without dose reduction to 37.5 mg once daily on Schedule 4/2 (Table 8).

A total of 142 (46.4%) patients in the sunitinib arm and 40 (13.2%) patients in the placebo arm temporarily discontinued treatment in response to an AE. The mean time and median time to the first dosing interruption in the sunitinib arm were 3.8 months and 3.0 months, respectively. The most common AEs leading to temporary discontinuation in (>5% of patients in either arm) were PPE syndrome (6.2% of patients in the sunitinib arm vs 0% in the placebo arm), Hypertension (5.6% of patients in the sunitinib arm vs 0% in the placebo arm), and Neutropenia (5.2% of patients in the sunitinib arm vs 0% in the placebo arm). The mean and median duration of dosing interruptions in the sunitinib arm were 15.7 days and 9.5 days, respectively.

A total of 106 (34.6%) patients in the sunitinib arm and 6 (2.0%) patients in the placebo arm had a dose reduction due to an AE. The mean and median time to the first dose reduction in the sunitinib arm were 4.0 months and 2.9 months, respectively. The most common AE (>5% of patients in either arm) associated with a dose reduction was PPE syndrome (11.8% of patients in the sunitinib arm vs 0.7% of patients in the placebo arm).

3.7.5. Safety in Special Groups and Situations

The AEs and SAEs reported in S-TRAC were analyzed to determine whether the safety profile of sunitinib was affected by gender, age, race, or geographical region. There were no notable findings in these analyses with the exception of the higher frequency of PPE syndrome reported in Asia compared with North America and Europe (Asia 82.2%, North America 59.1%, Europe 43.8%); however, as there were only 45 patients treated with sunitinib in the Asia region, a meaningful review by geographical region was limited.

3.7.6. Adverse Events of Special Interest

AEs of special interest for sunitinib included neutropenia, hypertension, PPE syndrome, fatigue/asthenia, diarrhea, thyroid disorders, liver test abnormalities, cardiovascular events, and second primary malignancy.

Overall, the AEs of special interest are well-known risks for sunitinib with the exception of second primary malignancy. There is currently no clinical evidence associating second primary malignancies with sunitinib use. However, it is considered a potential risk for sunitinib and has been included as an AE of special interest based on non-clinical findings which showed potential carcinogenic effects in mice and rats. A review of the AEs of special interest in S-TRAC did not identify any new safety concerns. Analysis of AEs of special interest over time showed that only the AEs of thyroid dysfunction, which primarily consisted of Hypothyroidism, increased steadily in subsequent cycles of therapy. This is consistent with what has been observed in the mRCC patient population. Hypothyroidism can be readily monitored and treated as per standard medical practice. AEs of special interest are summarized in Table 16 in Section 6.5.

3.7.7. Long-Term Safety

AEs reported after sunitinib treatment was completed or permanently discontinued for any reason were reviewed to help characterize long-term safety in the RCC population receiving approximately 1 year of adjuvant treatment. Overall, no new safety signals with respect to AEs after permanent sunitinib discontinuation were identified based on the AEs and deaths reported in the follow-up period. However, it should be noted that this analysis was limited because investigators were only required to report treatment-related SAEs during the follow-up period.

In the adjuvant RCC population, patients were treated for up to 9 cycles (approximately 1 year) with sunitinib. Only thyroid dysfunction increased in frequency with treatment in this patient population. This is consistent with long-term safety experience in the mRCC population. Porta et al. conducted interval and cumulative time period analyses of long-term safety for sunitinib using pooled data in patients with mRCC enrolled in 9 prospective clinical trials.[49] The authors concluded that sunitinib was not associated with any new types or increased severity of treatment-related AEs. With the exception of hypothyroidism, toxicity was not cumulative.

As the adjuvant RCC population may inherently be a healthier population compared to those with mRCC, it is likely that patients treated in the adjuvant setting for up to 9 cycles with sunitinib would have a better long-term safety profile compared to those treated in the mRCC setting, who are treated for much longer and reported treatment durations have exceeded 6 years.[50]

3.8. Patient-Reported Outcomes

Patient-reported outcomes (PROs) provide a direct assessment of the patient experience at baseline, while on treatment, and at the end of treatment, and are intended to provide some insight into how patients are feeling and functioning. In an adjuvant treatment setting, the

goal is to evaluate whether or not there are clinically meaningful declines in health-related QoL measures of functioning and treatment-related symptoms.

PROs were assessed using 2 instruments, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the EuroQoL Group health status questionnaire (EQ-5D). A brief description of these measures is provided below.

The EORTC QLQ-C30 consists of 30 items grouped into 15 scales: global health status/QoL, 5 functional scales (physical, role, cognitive, emotional, and social) and 9 symptom scales (fatigue, nausea/vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact of cancer). All 15 scales are normalized to 0 to 100 with higher scores corresponding to better QoL, better functioning for functional scales and, conversely, more extreme symptom for symptom scales.

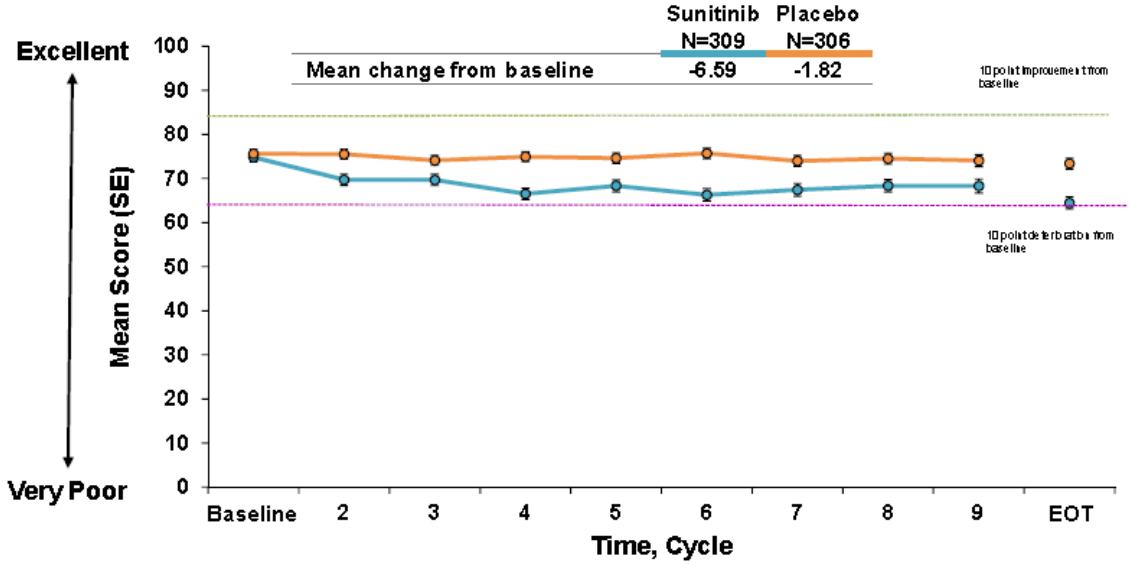
The EuroQol EQ-5D consists of 2 parts, EQ-5D index based on scores from 5 individual items and EQ-VAS based on a visual analog scale where the patient places a mark between 0 (worst imaginable health state) to 100 (best imaginable health state) to indicate his/her health state. The EQ-5D index is calculated based on country-specific utility scores and ranges generally between 0 and 1, with higher values indicating better health states.

The published clinically important difference (CID) for the EORTC scales is 10 points,[51,52] and this was pre-specified in the S-TRAC SAP. This is conservative, as in the literature, 10-20 points represent moderate change, and changes above 20 points are considered large changes.[51,52] The CID for EQ-5D index depends on the country-specific utility scores used. It is, for example, 0.06 for US and 0.08 for UK (S-TRAC used UK utility scores). The CID for EQ-VAS is between 7 to 12 points.[53] As is generally the case, the CID is roughly 10% of the score range.

In the S-TRAC study, PRO data were collected at baseline and on the first day of each cycle while on treatment. An End of Treatment assessment was also performed when patients permanently discontinued treatment either at the end of the 9th cycle, or if they permanently discontinued treatment at any time during the treatment period of the trial. Thus, the PRO data in this trial primarily represent the self-reported experience of patients who stayed on treatment in the 2 treatment arms. The dropout rate was higher in the sunitinib arm than in the placebo arm, with 59.2% and 70.6% remaining at Cycle 9, respectively, the last cycle while on treatment. The PRO completion rate was high in both treatment arms (>89% of available patients) at every cycle. End of Treatment assessment (which could occur at any time during the 9 cycles) were also completed for 79% - 82% of patients who entered the study.

The mean scores from baseline in the EORTC QLQ-C30 global health status/QoL score over time is graphically presented in Figure 13 for the sunitinib and placebo arms.

Figure 13. EORTC QLQ-C30 Mean Scores Over Time: Global Health Status/Quality of Life Domain (S-TRAC) - Intent-To-Treat Population



Number at Risk										
Sunitinib	292	260	241	227	219	210	200	185	177	250
Placebo	288	274	265	249	234	231	220	212	203	250

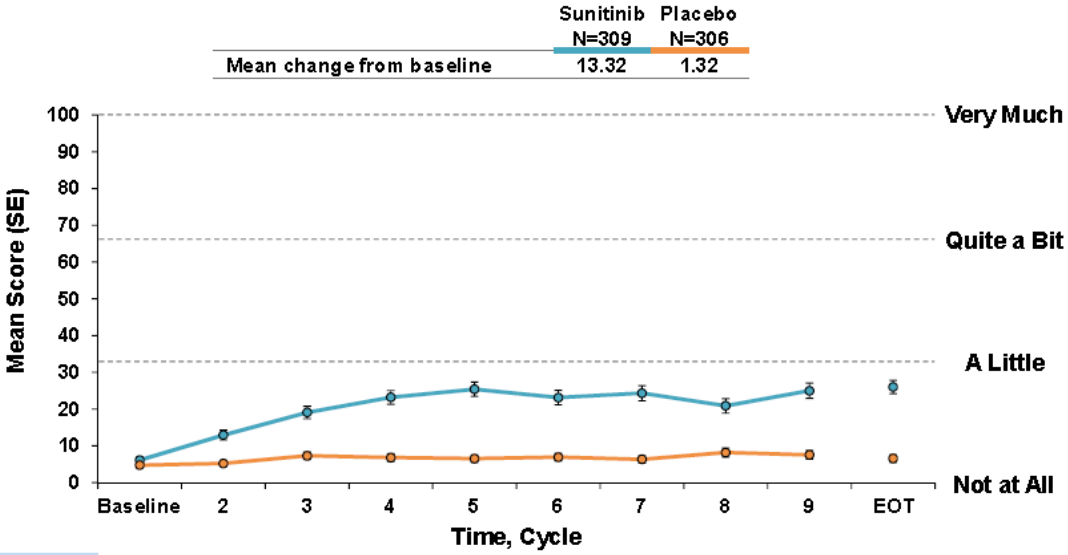
Green (upper) dotted line: 10 point improvement from baseline; Purple (lower) dotted line: 10 point deterioration from baseline.

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= European Organization for Research and Treatment of Cancer; EOT = end of treatment; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

Application of a repeated measures longitudinal model to these data yielded a mean (95% CI) difference in the overall means of -4.76 (-6.82, -2.71) favoring placebo. While statistically significant, the point estimate of the difference was below the published CID of 10 points, indicating no clinically meaningful deterioration in global health status/QoL with sunitinib treatment. These results observed for global health status/QoL are consistent with the pattern of changes observed in the other EORTC scales, including the physical, social, and emotional functioning scales; symptoms such as fatigue and pain all indicated a statistically significant difference but without reaching the threshold of clinical significance (Table 18, Section 6.7). The 2 exceptions to this trend were the PRO scores for diarrhea and loss of appetite, as displayed in Figure 14 and Figure 15, respectively.

Figure 14. Change from Baseline in Diarrhea Over Time (S-TRAC) – Intent-To-Treat Population

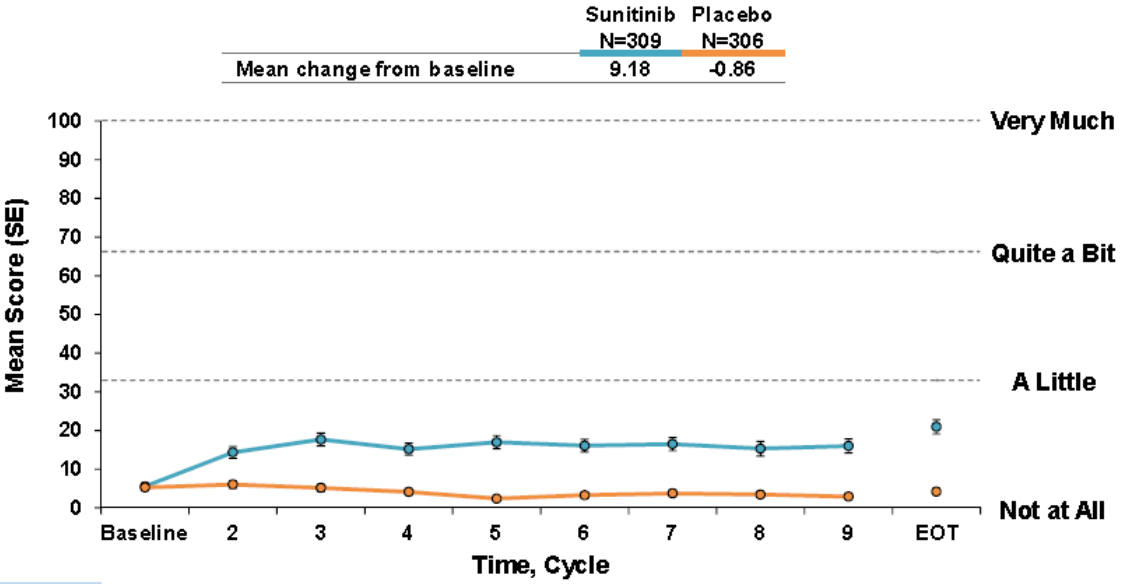


Number at Risk										
Sunitinib	293	260	241	227	219	209	200	185	176	250
Placebo	288	274	264	249	234	231	220	212	203	249

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. S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

Figure 15. Change from Baseline in Loss of Appetite Over Time (S-TRAC) – Intent-To-Treat Population



Number at Risk										
Sunitinib	294	260	241	228	222	211	200	185	177	251
Placebo	289	274	269	249	234	232	221	212	203	251

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. S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

The changes from baseline in diarrhea appeared early in the sunitinib arm and further increased until reaching a plateau by Cycle 5. The changes in loss of appetite were also apparent early (by Cycle 2) but did not appear to further increase through the rest of the treatment period. The model-estimated differences between the sunitinib and placebo arms were 12.00 (95% CI: 9.62, 14.38) for diarrhea and 10.04 (95% CI 7.88, 12.20) for loss of appetite, both exceeding the pre-specified CID.

While it is difficult to tie AE-related permanent treatment discontinuation (which can occur at any time during the 54 weeks) with a change in a PRO measure (reported by patients every 6 weeks), both diarrhea and loss of appetite were reported independently as AEs and permanent discontinuation data were collected. The AE of Diarrhoea led to permanent discontinuation in only 1 patient, and no patient permanently discontinued from treatment due to the AE of Loss of appetite. As described in Section 3.7, the common AEs of sunitinib, consistent with the known safety profile in the mRCC setting, were effectively managed with dosing interruption, dose reduction, and/or standard supportive medical therapy.

PRO measures, however, appeared to be sensitive to the impact of AEs on how the patients are feeling and functioning. Post-hoc exploratory analyses assessed the impact of selected AEs (all grades) reported in the previous cycle on all 15 PRO scores of the EORTC

QLQ-C30 measured in the subsequent cycle. This was done for each of the 9 cycles. Patients with any-grade AEs of Diarrhoea, PPE syndrome, Loss of appetite, and Fatigue reported a consistent negative impact on many symptom and functioning scales (at the beginning of the next cycle when the PRO instruments was administered) compared to patients who did not experience these AEs. By contrast, patients with the AE Hypertension (all grades) did not have any impact on PROs, and their ratings on the PROs were similar to those who did experience the AE. This suggests that the PRO instrument was responsive to symptomatic AEs that might have been expected to impact how a patient feels and functions but not to asymptomatic AEs which would not be expected to have an impact on how a patient feels or functions.

Results from the second PRO instrument (EQ-5D) used in S-TRAC showed that the changes in EQ-5D index and EQ-VAS were consistent with those observed with global health status/QoL in that statistically significant differences were noted in both endpoints favoring placebo, but neither was considered clinically meaningful, as the differences were less than the published CID.

A limitation of this analysis is that PROs were only obtained during and at the end of the 1-year treatment period 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.

In summary, while patients who received sunitinib treatment did experience symptoms related to the treatment, patients reported that these were largely at a mild to moderate level. It is likely that active management through the use of dosing interruptions and dose reductions, contributed to the preservation of global health status/QoL, and the alleviation of treatment-related symptoms, thereby enabling patients to remain on effective adjuvant therapy. The analysis of PROs in S-TRAC indicated that adjuvant sunitinib therapy is not associated with a clinically meaningful deterioration in most QoL measures. The clinically meaningful changes observed in the PROs of diarrhea and loss of appetite are associated with known AEs of sunitinib and are clinically manageable and reversible.

4. COMPARISON WITH OTHER ADJUVANT RENAL CELL CANCER STUDIES

The S-TRAC study was the first trial to demonstrate a statistically significant and clinically meaningful improvement in DFS in the adjuvant RCC treatment setting. In addition to S-TRAC, there have been 5 randomized Phase 3 clinical trials evaluating the role of various VEGFR-targeted TKIs or mammalian target of rapamycin (mTOR) inhibitors in the adjuvant treatment of RCC, 2 of which have been completed and 3 of which are ongoing. The 2 completed trials are the ASSURE study,[14] which evaluated the use of adjuvant sorafenib or sunitinib versus placebo, and the PROTECT study,[15] which evaluated the use of adjuvant pazopanib versus placebo.

The purpose of this section is to discuss the differences between these trials and to contextualize the efficacy and safety profiles of sunitinib in the adjuvant RCC treatment setting.

4.1. ASSURE Study

The ASSURE study (ECOG 2805) led by the ECOG-ACRIN (Eastern Cooperative Oncology Group American - College of Radiology Imaging Network) (ClinicalTrials.gov Identifier: NCT00326898) was a randomized (1:1:1), double-blind, placebo-controlled Phase 3 study investigating adjuvant treatment with sunitinib or sorafenib versus placebo in previously untreated patients with resected RCC at intermediate risk or high risk of recurrence.

The primary objective of the ASSURE study was to demonstrate an improvement in DFS by investigator assessment in patients with locally advanced RCC randomly assigned to adjuvant treatment with sunitinib or sorafenib versus placebo after radical or partial nephrectomy.

Between 24 April 2006 and 01 September 2010, 1943 patients from the National Clinical Trials Network located at sites in the United States and Canada were randomly assigned to receive sunitinib (n=647), sorafenib (n=649), or placebo (n=647).

Patients were treated for 9 cycles or until disease recurrence or unacceptable toxicity, whichever occurred first. When the study began, the starting dose of sunitinib was 50 mg orally once daily on Schedule 4/2, and the starting dose of sorafenib was 400 mg orally twice daily (continuously). After observing a high rate of permanent treatment discontinuation due to AEs or patient refusal (44% of patients on sunitinib and 45% of patients on sorafenib) in the first 1323 patients enrolled, the protocol was amended to institute a starting sunitinib dose of 37.5 mg orally once daily or sorafenib dose of 400 mg orally once daily. If the patient did not experience any Grade ≥2 AEs, then the dose was to be escalated to the previous starting dose at the beginning of Cycle 2 or Cycle 3. Dose reductions were allowed for Grade 3 or 4 AEs as assessed by NCI CTCAE in decrements of 12.5 mg for sunitinib and 400 mg for sorafenib, with doses allowed as low as 25 mg for sunitinib daily or 400 mg sorafenib every other day.

The primary efficacy analysis showed no significant differences in DFS between either active treatment arm and placebo. Median DFS was 5.8 years (interquartile range [IQR] 1.6−8.2) for sunitinib (HR 1.02, 97.5% CI: 0.85–1.23, p=0.8038), 6.1 years (IQR 1.7–not estimable [NE]) for sorafenib (HR 0.97, 97.5% CI: 0.80–1.17, p=0.7184), and 6.6 years (IQR 1.5–NE) for placebo.

Differences between study design and exposure in the S-TRAC study and the ASSURE study are described in Section 4.1.1. These include differences in the RCC patient population, sunitinib dosing, and adjudication of the primary endpoint. Efficacy analyses based on a subset of patients from the ASSURE study who met the enrollment and dosing criteria from the S-TRAC study are also provided. A comparison of safety in the S-TRAC study and the ASSURE study is provided in Section 4.1.2.

4.1.1. Comparison of Study Design and Exposure in the S-TRAC Study and the ASSURE Study

The key differences in the study design between the S-TRAC and ASSURE studies are presented in Table 11.

Table 11. Key Study Design Differences Between the S-TRAC Study and the ASSURE Study

	S-TRAC Study	ASSURE Study
Patient Population	• T3, N0 or NX, M0, any G; • T4, N0 or NX, M0, any G; • Any T, N1-2, M0, any G.	• pT1b G3-4 N0 (or pNX where clinically N0) M0; • pT2 G (any) N0 (or pNX where clinically N0) M0; • pT3 G (any) N0 (or pNX where clinically N0) M0; • pT4 G (any) N0 (or pNX where clinically N0) M0; • T (any) G (any) N+ (fully resected) M0.
Central Review conducted to confirm lack of metastasis prior to randomization	Yes	No
Blinded Independent Central Review Post-Baseline	Yes	No
Histology	Preponderant (defined as >50%) clear cell RCC	Clear cell and non-clear cell RCC
Starting Dose (sunitinib arm)	50 mg once daily for all patients	Approximately one-third of patients received a starting sunitinib dose of 37.5 mg once daily and two-thirds of patients received 50 mg once daily
Dose Reductions (sunitinib arm)	1 dose reduction level (37.5 mg)	2 dose reduction levels (37.5 mg and 25 mg)

Abbreviations: ASSURE = Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; mg = milligrams; p = primary; RCC = renal cell carcinoma; S-TRAC= Sunitinib Treatment of Renal Adjuvant Cancer.

The S-TRAC study only included patients with locally advanced RCC (≥T3 and/or N1-2), while approximately one-third of patients included in the ASSURE study had localized RCC (T1 and T2 without nodal involvement). Additionally, the S-TRAC study only included patients with preponderant (defined as >50%) clear cell RCC, while the ASSURE study included approximately 21% of patients with a histology of non-clear cell RCC.

The median DFS based on investigator assessment in the placebo arm of the ASSURE study was higher (6.6 years) than that in the S-TRAC study (4.5 years). The difference in the performance of the placebo arms supports the conclusion that there were key differences between RCC patient populations, regardless of treatment, between the S-TRAC study and the ASSURE study.

A summary of the key differences in sunitinib exposure in the patients from the S-TRAC study and the ASSURE study is provided in Table 12. The median and mean duration of treatment was 1 month longer in the S-TRAC study than in the ASSURE study. Additionally, the differences in starting dose and dose reduction levels resulted in a 42% higher overall sunitinib exposure in the S-TRAC study compared to the ASSURE study (median cumulative dose of 9637.5 mg in S-TRAC compared to 6800 mg in ASSURE). Furthermore, a higher proportion of patients in the S-TRAC study completed 9 cycles of treatment (55.6% in S-TRAC compared to 49% in ASSURE), and a greater proportion patients who started on the 50 mg dose in the ASSURE study (44%) permanently discontinued due to AEs or patient refusal compared with the S-TRAC study (32%).

Table 12. Summary of Key Differences Between Patient Exposure to Sunitinib in the S-TRAC and ASSURE Studies

	S-TRAC Study Sunitinib	ASSURE Study Sunitinib
Median Relative Dose Intensity (%)	88.4	77.7
Median Cumulative Dose (mg)	9637.5	6800
Mean Duration of Treatment (months)	9.46	8.36
Median Duration of Treatment (months)	12.4	11.1
Range (months)	0.13 – 14.9	0.07 – 15.5
Completed 9 cycles (approximately 1 year) of Treatment (%)	55.6	49
Permanent Discontinuation due to AE or patient refusal for patients who started on 50 mg dose (%)	32	44

Abbreviations: AE = Adverse Event; ASSURE = Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; mg = milligrams; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

To further assess baseline characteristics and sunitinib dosing, patients from the ASSURE study who met S-TRAC study eligibility criteria and were prescribed sunitinib 50 mg in Cycle 1 and either 50 mg or 37.5 mg in subsequent cycles were identified (Table 13). Only 30% (394/1294 patients) of the patients enrolled in the sunitinib and placebo arms of the ASSURE study matched the protocol criteria for the S-TRAC study. However, within the context of these defined criteria, there was still a difference between the ASSURE study and the S-TRAC study in the number of patients categorized as T3-Low UISS Risk Group (i.e., T3 N0 or NX, M0, any Fuhrman's grade, ECOG PS 0 or Fuhrman's Grade 1, ECOG PS ≥1), with 74.4% in the ASSURE study compared to 37% in the S-TRAC study.

Table 13. Summary of Patients in the ASSURE Study Who Met the Study Eligibility and Dosing Criteria From the S-TRAC Study – As-Treated Population

	S-TRAC N=615 n (%)	ASSURE Subset N=394 n (%)
T3 Low[a]	227 (36.9)	293 (74.4)
T3 High[b]	331 (53.8)	57 (14.5)
T4 N0 or Nx, M0, any Fuhrman's grade, any ECOG PS	8 (1.3)	1 (0.3)
Any T, N1-2, M0, any Fuhrman's grade, any ECOG PS	49 (8.0)	38 (9.6)
T3 unknown (missing ECOG PS)	0	5 (1.3)

a. T3 Low=T3 N0 or Nx, M0, any Fuhrman's grade ECOG PS 0 or Fuhrman Grade - 1 ECOG PS ≥1.
b. T3 High= T3 N0 or Nx, M0, Fuhrman's Grade ≥2, ECOG PS ≥1.
Abbreviations: ASSURE = Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; ECOG = Eastern Cooperative Oncology Group; PS = performance status; S-TRAC= Sunitinib Treatment of Renal Adjuvant Cancer.

As described in a Journal of the American Medical Association (JAMA) publication[54] analysis of a subgroup of patients with high-risk (T3, T4, node-positive) clear cell (including mixed histology >25%) RCC from the ASSURE study did not elicit positive signals in this subgroup.

The risk group subpopulation identified in the JAMA publication was similar to the 30% of patients enrolled in the sunitinib and placebo arms in the ASSURE study who met the RCC patient population and sunitinib dosing criteria for the S-TRAC study identified above, with the exception that the JAMA publication included patients with RCC histology defined as clear cell >25% and patients with distant metastasis (cannot be assessed) (MX) status. These factors represent a small portion of patients from the overall population in the ASSURE study (2.8% of the ITT population were mixed, >25% clear cell, and 3.5% of the ITT population were MX). More importantly, analyses presented in the JAMA publication did not consider dosing criteria in analyses comparing sunitinib to placebo, and it should be noted that risk groups should not be viewed in isolation of dosing (as discussed below). Additionally, measured or unmeasured differences in subpopulations, such as the imbalance in the T3-Low UISS Risk-Group noted (37% vs 74% in S-TRAC vs ASSURE, respectively), limit the extrapolation of these results to the RCC patient population enrolled in the S-TRAC study.

Additional analyses in the JAMA article focused on quartiles of average dose defined as the total cumulative dose divided by the number of cycles, and comparisons were made within the sunitinib arm; however, quartiles defined in the JAMA article indicated dose ranges for the ASSURE study that were substantially lower than those observed in the S-TRAC study (Table 14). While the results of the dosing analyses in the JAMA article did not reach statistical significance (which is not unexpected given the small subset of patients in each

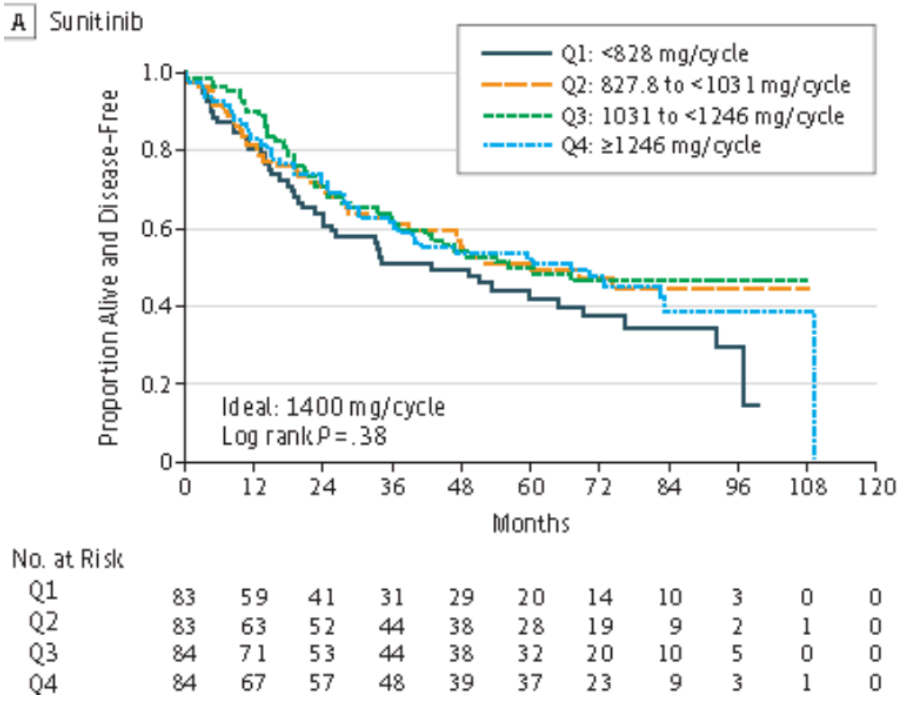
quartile), there was separation in the Kaplan-Meier curves for the lowest quartile compared with the other 3 quartiles indicating that patients with lower cumulative average dose had shorter DFS times (Figure 16).

Table 14. Summary of Cumulative Average Dose of Sunitinib Received per Cycle by Quartile in the ASSURE Study Subpopulation Identified in the JAMA Publication and the S-TRAC Study

Quartile	S-TRAC Study Sunitinib Cumulative Average Dose, mg	ASSURE Study Sunitinib Cumulative Average Dose, mg
Q1	<1052.78	<827.8
Q2	1052.78 to <1261.11	827.8 to < 1031
Q3	1261.11 to <1400	1031 to <1246
Q4	≥1400	≥ 1246

Abbreviations: ASSURE = Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

Figure 16. Disease-Free Survival by Quartile of Average Dose Received per 6-Week Cycle for Patients in the Sunitinib Arm of the ASSURE Study

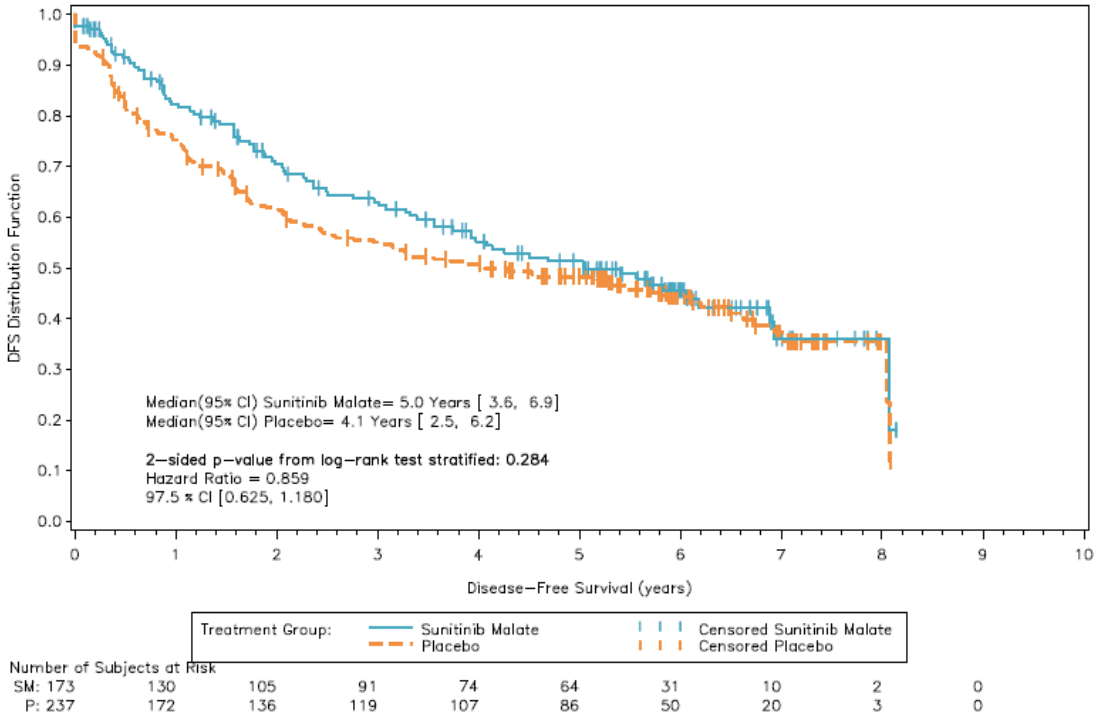


Source: Figure 3, Haas et al.[54]

To better align the ASSURE study subpopulation to that of the S-TRAC study population and to further examine the combined influence of patient population and sunitinib dosing, an analysis of DFS was performed for the subset of patients from the ASSURE study identified in the JAMA publication by a) excluding the small number of patients with MX status (both S-TRAC and ASSURE studies required patients to be metastasis free at study entry) and b) including only patients who had a starting dose of 50 mg without dose reductions below

37.5 mg. As shown in Figure 17, there was large separation in the curves through Year 4, which is in contrast to the primary analysis in the ITT population.[14]

Figure 17. Kaplan-Meier Plot of Disease-Free Survival for Patients in the ASSURE Study Who Met Study Eligibility and Sunitinib Dosing Criteria from the S-TRAC Study[a]



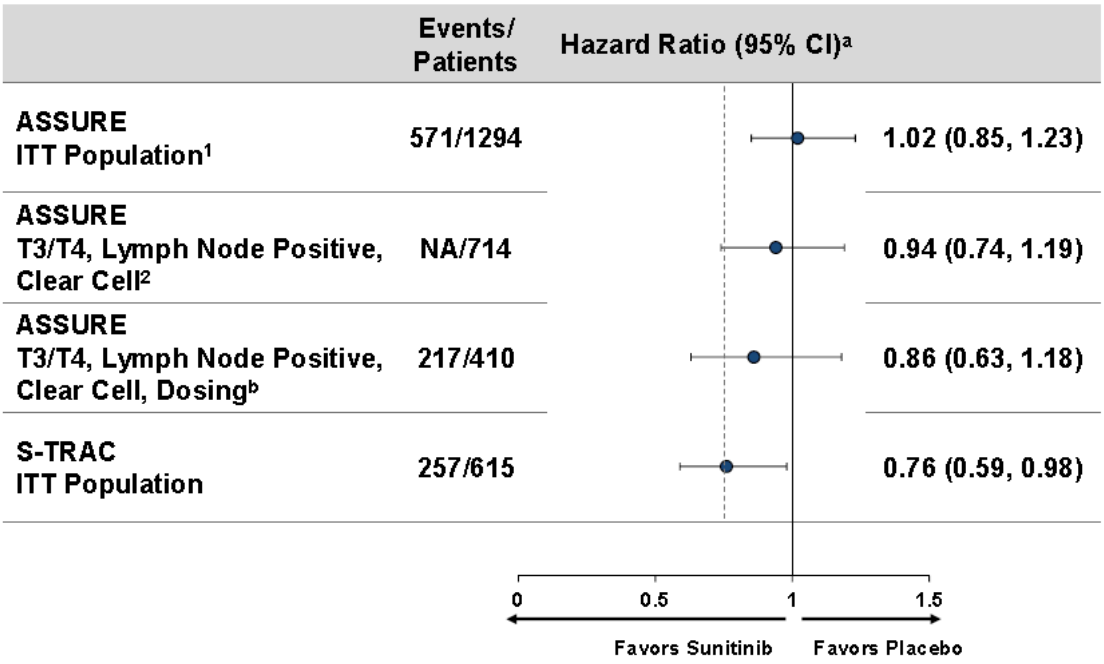
Abbreviations: ASSURE = Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; DFS = disease-free survival; P = placebo; SM = sunitinib malate; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

a. Including the >25% clear cell RCC population treated with a starting dose of 50 mg and no dose reductions below 37.5 mg.

2-sided p-value from the log-rank test stratified by pathologic stage, ECOG PS, histology, and surgical approach.

In summary, as illustrated in Figure 18, subgroup analyses of the ASSURE study indicated that the more closely the patients were aligned with those treated and enrolled in the S-TRAC study based on RCC patient population and sunitinib dosing, the more favorable the HRs were to sunitinib compared to placebo.

Figure 18. Outcomes from the ASSURE Study for Patients Who Met S-TRAC Study Eligibility and Sunitinib Dosing Criteria



1. Hass et al, Lancet[14]; 2. Hass et al, JAMA[54]; a. Confidence intervals are 95% for S-TRAC and 97.5% for ASSURE; b. Patients who started at 50 mg sunitinib and did not have their dose reduced below 37.5 mg.

Abbreviations: ASSURE = Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; NA = not available; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

4.1.2. Comparison of Grade 3, Grade 4, and Grade 5 Adverse Events in the S-TRAC Study and the ASSURE Study

Limited safety data were collected on the ASSURE study case report forms (CRFs). Specifically, only Grade 3 to 5 all-causality non-hematologic AEs and infection AEs and Grade 4 and 5 hematologic and chemistry laboratory events were collected. Blood pressure results, left ventricular ejection fractions (LVEFs), and drug exposure data were also collected. No laboratory data (other than for reported Grade 4 and 5 AEs) were collected on the ASSURE study CRFs.

A summary of Grade ≥3 all-causality TEAEs in the S-TRAC and ASSURE studies (including all patients in the ASSURE patient population regardless of starting dose) is provided in Table 19 (Section 6.8). Although not all Grade 3 events were to be reported in the ASSURE study, the overall frequencies of Grade 3 all-causality TEAEs were lower in the S-TRAC study, with Grade 3 AEs of Hypertension, Fatigue, and Diarrhoea reported at a higher frequency in the ASSURE study, but consistent with frequencies observed in the mRCC treatment setting. The overall frequencies of Grade 4 all-causality TEAEs was higher in the S-TRAC study, but there were no notable differences identified in the frequencies of the Grade 4 AE terms that could be matched in the S-TRAC study and the ASSURE study. The overall frequencies of all-causality Grade 5 TEAEs were low in both the S-TRAC and ASSURE studies.

Overall, where it was possible to match AE terms, a similar pattern of Grade ≥3 AEs was observed between the S-TRAC and ASSURE studies.

4.2. PROTECT Study

PROTECT was a double-blind, placebo-controlled, randomized Phase 3 study sponsored by Novartis to evaluate whether pazopanib, another VEGFR TKI approved for the treatment of mRCC, administered for 12 months could prevent or delay recurrence of RCC as compared to placebo in patients with moderately high or high risk of developing recurrence following nephrectomy.[15] Patients with non-metastatic disease (M0) fulfilling any of the following combinations of pathologic staging based on AJCC TNM staging version 2010 and Fuhrman's nuclear grading met the inclusion criteria:

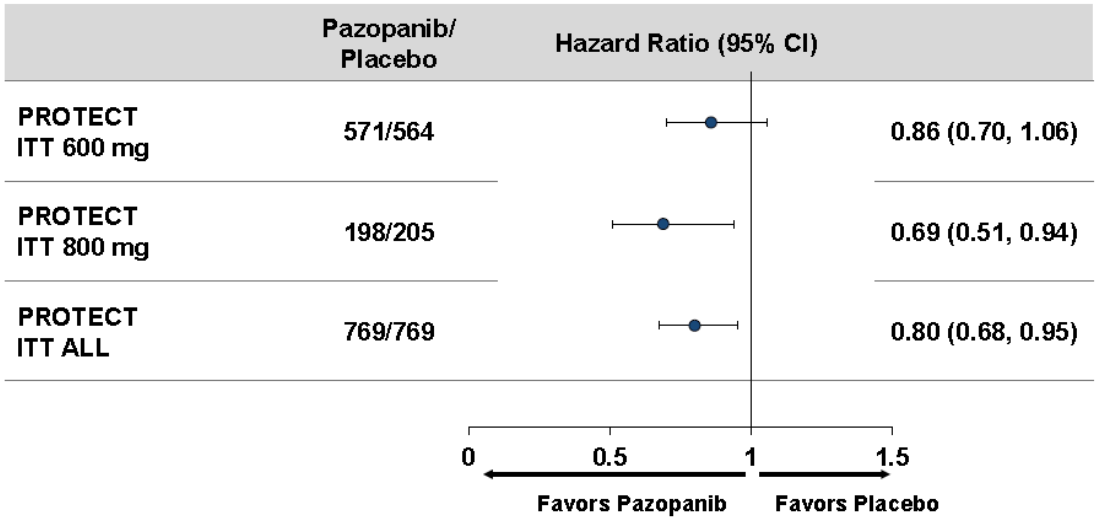
- pT2, G3 or G4, N0; or
- pT3, G any, N0; or
- pT4, G any, N0; or
- pT any, G any, N1.

Patients in the PROTECT study were largely similar to those in the S-TRAC study, with 86% of the patients having RCC with ≥T3 or N+ and clear cell histology.

The starting pazopanib dose was amended from the higher 800 mg daily (approved dose in mRCC) to 600 mg daily based on an unacceptably high permanent treatment discontinuation rate due to AEs. When the protocol was amended to enroll patients at the reduced dose of 600 mg daily, the primary population was specified as the patients enrolled at the reduced starting dose. The majority of patients in PROTECT study (1135/1538 [73.8%]) received the reduced starting dose. The pazopanib dose could be escalated to 800 mg daily based on safety evaluations after the patient had received the initial dose of 600 mg daily for 8-12 weeks. The median treatment duration was 10.6 months in the pazopanib 600 mg daily arm and 10.2 months in the pazopanib 800 mg daily arm.

The primary analysis did not show a significant difference in DFS between the reduced 600 mg daily dose and placebo (HR 0.862; 95% [CI: 0.699, 1.063]; p = 0.165). However, a statistically significant decrease in the risk of recurrence was observed in the secondary endpoint of DFS with pazopanib 800 mg daily (HR 0.693 [95% CI: 0.510, 0.943]) and in the combined analysis of both doses versus placebo (Figure 19).

Figure 19. Disease-Free Survival by Dose in PROTECT– Intent-to-Treat Population[55]



Abbreviations: CI = confidence interval; ITT = intent-to-treat

Analysis of pazopanib concentrations for the 600 mg daily starting dose also showed that longer DFS times were observed in patients achieving higher C_{trough} quartiles and those achieving C_{trough} >20.5 µg/mL.[55] These results, obtained with pazopanib, further support the importance of patient population and dose to demonstrate a treatment benefit in the adjuvant RCC setting.

4.3. Conclusions

Based on the multiple differences between the S-TRAC study and the ASSURE study, including the limited percentage of patients (30%) enrolled in the sunitinib and placebo arms in the ASSURE study who met the RCC patient population and sunitinib dosing criteria for the S-TRAC study, the efficacy results of the ASSURE study are not indicative of the efficacy in the high-risk RCC population enrolled in the S-TRAC study, and cross-study comparisons of efficacy are not reliable.

The differences between the RCC patient populations and TKI dosing must be considered together and not in isolation. A subgroup analysis of the ASSURE study data taking into account both RCC patient population and sunitinib dosing to align with those in the S-TRAC study suggested a treatment difference favoring sunitinib. The results from the PROTECT study provide an external corroboration of the importance of patient selection and dosing on DFS outcomes in the adjuvant treatment setting.

5. BENEFIT/RISK ASSESSMENT

While mRCC prognosis has improved in the past decade with the availability of a number of molecularly targeted agents and immunotherapies, none of these therapies are curative. Given the poor outcome of metastatic disease and lack of screening programs for RCC, there is an unmet medical need for the adjuvant treatment of patients at high risk of recurrence following nephrectomy that can reduce the risk of or delay disease relapse and change the natural progression of the disease.

Adjuvant sunitinib administered orally at a dose of 50 mg daily on Schedule 4/2 demonstrated statistically significant efficacy in patients at high risk of recurrent RCC following nephrectomy. The primary endpoint of BICR-assessed DFS as compared with placebo demonstrated an HR of 0.761 (95% CI: 0.594, 0.975, 2-sided p-value=0.030), corresponding to a relative risk reduction of DFS event of 24%. DFS improvement in favor of sunitinib was maintained across secondary analyses of DFS by investigator assessment as well as multiple sensitivity analyses. The significant prolongation of the primary DFS endpoint obtained with 1 year of adjuvant sunitinib treatment in patients at high risk of recurrent RCC was also maintained over time with a higher proportion of patients who received sunitinib being disease-free at 5 years (59.3% vs 51.3% in the placebo arm, corresponding to an absolute improvement favoring sunitinib of 8.0%). This magnitude of DFS benefit in the S-TRAC study (24% relative risk reduction and 8% absolute improvement at 5 years) was within the range of those reported across other solid tumor adjuvant trials both in relative (17-65%) and absolute (2-15%) terms (Section 6.9). In addition, this benefit was demonstrated in a population with a substantial unmet medical need and high risk of poor long-term outcomes.

The OS data are immature in the S-TRAC study, as the median OS was not reached in either treatment arm (Section 3.6.5). Available data indicates that sunitinib did not have a detrimental effect on OS compared to placebo.

Sunitinib has a well-characterized safety profile based on extensive safety experience in clinical studies and post-marketing exposure. In the S-TRAC study, no new safety signals were identified with sunitinib use in the adjuvant treatment setting for RCC; AEs were consistent with the known safety profile of sunitinib in the mRCC treatment setting. The most common AEs of sunitinib in the S-TRAC study were Diarrhoea, PPE syndrome, Hypertension, and Fatigue. Effective therapy management via dosing interruption, dose reduction, and/or standard supportive medical therapy enabled resolution of these events and continuation of effective adjuvant therapy, with <5% of patients permanently discontinuing treatment due to any of these events. The overall rate of permanent discontinuations due to AEs in the sunitinib arm (28%) was comparable to that observed in the metastatic disease setting.[17] As described in section 3.7.4, most of the AEs leading to permanent treatment discontinuation recovered or were recovering at the time of last known outcome. No new safety concerns were identified in patients who permanently discontinued treatment due to AEs with an outcome of ongoing (Section 3.7.4). There were no treatment-related deaths as well as no differences in cardiovascular events between the 2 treatment arms. Hepatic events in the sunitinib arm were primarily Grade 1 or 2 elevations in liver transaminases. No Hy's

Law cases were observed in either treatment arm. Overall, the maximum 9 cycles (1 year) of study treatment was completed by 55.6% patients in the sunitinib arm, while 70.9% of patients in the sunitinib arm were on treatment during Cycle 6 (8 months) of treatment.

Patient-reported outcomes (PROs) were evaluated using 2 QoL instruments. Sunitinib treatment was associated with statistically significant differences favoring placebo that were not considered clinically meaningful in the majority of QoL measures, including global health status/QoL. Two (2) exceptions to this were the PROs of diarrhea and loss of appetite, both of which exceeded the published threshold for clinical relevance. Diarrhea and loss of appetite are known AEs of sunitinib and were clinically manageable. Overall, patients maintained a relatively high level of quality of life and functioning and low level of symptoms throughout the treatment period.

In summary, the randomized Phase 3 S-TRAC study demonstrated that 1 year of adjuvant sunitinib treatment in patients at high risk of recurrent RCC resulted in a 24% reduction in the risk of a DFS event as assessed by BICR, which was maintained over time, with an absolute improvement of 8.0% in favor of sunitinib in the probability of being event-free at 5 years. No new safety signals were observed in the S-TRAC study and the AEs observed were consistent with the well-characterized safety profile of sunitinib based on more than 11 years of post-marketing and clinical trial experience.

The selection of a patient population with high-risk RCC, initiating patients on the approved full dose, and maintaining patients on treatment through effective therapy management were key factors in demonstrating a statistically significant and clinically meaningful DFS benefit. Together with its well-characterized and generally manageable and reversible safety profile, sunitinib has a favorable benefit/risk relationship for the adjuvant treatment of patients with high risk of recurrent RCC following nephrectomy. Therefore, physicians should be fully informed through the product label for this already approved treatment in the metastatic RCC setting in order to optimize the benefit/risk assessment for their patients as an adjuvant treatment option in RCC.

6. APPENDICES

6.1. Phase 3 Studies Evaluating Adjuvant Targeted Therapies in Renal Cell Carcinoma

Published Studies	Treatment Arms	Modified Dosing (Y/N)	Treatment Duration	Type of Renal Cell Carcinoma[a]	Risk Group (UISS)
ASSURE	Sunitinib Sorafenib Placebo	Y	1 year	CC or nCC	≥T1b, FG 3-4, PS0-1, and/or N+
PROTECT	Pazopanib Placebo	Y	1 year	CC	≥T2, FG 3-4, PS0, and/or N+
Study Enrollment Complete	**Treatment Arms**	**Modified Dosing (Y/N)**	**Treatment Duration**	**Type of Renal Cell Carcinoma**	**Risk Group (UISS)**
SORCE	Sorafenib 1 year Sorafenib 3 years Placebo	Y	1 or 3 years	CC or nCC	Leibovich[56] (Score 3-11)
ATLAS	Axitinib Placebo	N	3 years	CC	≥T2, FG any, PS0-1, and/or N+
EVEREST	Everolimus Placebo	N	54 weeks	CC or nCC	≥T1b, FG 3-4, PS0-1, and/or N+

a. Varying percentage of clear cell.
Source: www.clinicaltrials.gov. Date accessed 25 July 2017.
Abbreviations: CC = clear cell; FG = Fuhrman's grade; N = no; nCC = Non-clear cell; PS = Eastern Cooperative Oncology Group performance score; UISS = University of California, Los Angeles Integrated Staging System; Y = yes.

6.2. Key S-TRAC Protocol Amendments

Protocol Amendment Number (Date)	Summary of Key Changes
6, Global (20 June 2008)	• Group a. T3 N0 or Nx, M0, Fuhrman's grade ≥ 2 and ECOG general status ≥1, was extended to T3 N0 or NX, M0, any Fuhrman's grade, and any ECOG PS
7, Global (29 April 2009)	• Sample size was re-calculated based on population changes in Amendment 6 and updated survival analysis in the mRCC patient population. • The assumptions of 2-year DFS rates for the placebo arm and sunitinib arm for the 3 risk groups were revised. • The minimal number DFS events required to detect the statistical difference in DFS between the 2 treatment arms was increased from 101 to 320 DFS events. • The estimated number of patients to enroll increased from 236 to 500 patients.
10, Global (05 October 2010)	• The timing of the first interim analysis was adjusted. • Total number of patients was increased from 500 to 600.
14, Global (18 July 2014)	• Time for final analysis was changed to 5 years after LSFV or when approximately 258 DFS events had occurred.

Abbreviations: DFS=disease-free survival; ECOG= Eastern Cooperative Oncology Group; LSFV=last subject first visit; mRCC= metastatic renal cell carcinoma; PS=performance status

6.3. Adverse Events in S-TRAC and mRCC Study A6181034

Table 15. Summary of Treatment-Emergent Adverse Events (All Grades and Grades ≥3) Reported in the S-TRAC Study and mRCC Study A6181034

Adverse Event	S-TRAC Sunitinib (n=306)[a] n (%)		mRCC A6181034 Sunitinib (n=375)[b] n (%)	
	All Grades	Grades≥3	All Grades	Grades≥3
Any AEs	305 (99.7)	190 (62.1)	372 (99.2)	312 (83.2)
Diarrhoea	174 (56.9)	12 (3.9)	246 (65.6)	37 (9.9)
Palmar-plantar erythrodysaesthesia syndrome	154 (50.3)	49 (16.0)	108 (28.8)	32 (8.5)
Hypertension	113 (36.9)	24 (7.8)	127 (33.9)	50 (13.3)
Fatigue	112 (36.6)	15 (4.9)	233 (62.1)	55 (14.7)
Nausea	105 (34.3)	6 (2.0)	216 (57.6)	21 (5.6)
Dysgeusia	103 (33.7)	0	174 (46.4)	1 (0.3)
Mucosal inflammation	103 (33.7)	14 (4.6)	100 (26.7)	8 (2.1)
Dyspepsia	82 (26.8)	4 (1.3)	128 (34.1)	8 (2.1)
Stomatitis	81 (26.5)	7 (2.3)	114 (30.4)	5 (1.3)
Neutropenia	72 (23.5)	26 (8.5)	70 (18.7)	41 (10.9)
Asthenia	69 (22.5)	11 (3.6)	96 (25.6)	42 (11.2)
Hair colour changes	68 (22.2)	0	75 (20.0)	0 (0.0)
Thrombocytopenia	64 (20.9)	19 (6.2)	69 (18.4)	33 (8.8)

a. Median duration of treatment 12.4 months.
b. Median duration of treatment 11.1 months.
Abbreviations: AE=adverse event; n=number of patients in arm.

6.4. Patients Who Permanently Discontinued Sunitinib Due to Adverse Events: Summary of Potential Contributing Factors Identified for Adverse Events Recorded as Not Resolved at the Last Patient Follow-Up

Patient Identification	MedDRA Preferred Term	CTCAE Grade	Potential Contributory Risk Factors/ Co-Morbidities
10361015	Asthenia	3	Concomitant medicines included tramadol/acetaminophen combination product. Sunitinib does was decreased to 37.5 mg; however asthenia worsened from Grade 2 to Grade 3 suggesting a relationship to study treatment was less likely.
10251011	Blood creatinine increased	2	Creatinine 1.87 mg/dL at baseline. Medical history included hypertension, diabetes mellitus, and blood urea nitrogen increased.
10131010	Ejection fraction increased	1	Left ventricular ejection fraction of 59% (Grade 1) at screening. Medical history included hemochromatosis and hypertension.
10171007	Electrocardiogram QT prolonged	3	Medical history included coronary artery disease (Percutaneous Transluminal Coronary Angioplasty stenting) and hypertension.
10071005	Hypercreatininaemia	2	Medical history included hypertension, atherosclerosis, peripheral edema, and urinary tract obstruction.
11481006	Proteinuria	3	Medical history included hypertension and diabetes mellitus.
10461022	Pulmonary embolism	3	Medical history included lung metastasis.
11431004	Embolism venous	3	Event was considered related to the underlying disease by the investigator. Pathology report: tumor thrombus in inferior vena cava and renal vein stump.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities.

6.5. S-TRAC Adverse Events of Special Interest

Table 16. Summary of S-TRAC Adverse Events of Special Interest

Adverse Event of Special interest	Summary
Neutropenia	• Neutropenia reported in 72 (23.5%) patients in the sunitinib arm and 2 (0.7%) patients in the placebo arm. • One (1) patient discontinued due to Grade 3 Neutropenia in the sunitinib arm, the event resolved after discontinuation of treatment. • The majority of TEAEs of neutropenia in the sunitinib arm were Grade 2 (34 [11.1%]) or Grade 3 (23 [7.5%]) in severity. • No cases of febrile neutropenia/neutropenic infections or neutropenia requiring hospitalization. • Occurrence of neutropenia in the sunitinib arm was consistent with the known safety profile of sunitinib.
Hypertension	• Known side effect of medications that block the action of human VEGF; although the mechanism of the effect is not known.[57] • Hypertension reported in 113 (36.9%) patients in the sunitinib arm and 36 (11.8%) patients in the placebo arm. • The rate of permanent discontinuations from treatment associated with Hypertension was low (6 [2.0%] patients), all events resolved after treatment discontinuation. • Managed effectively during treatment with standard medical therapy and dosing interruption with or without dose reduction. • Consistent with the known safety profile of sunitinib and it was manageable with antihypertensives medications in the adjuvant RCC population.
PPE syndrome	• Second most common TEAE reported in sunitinib arm of S-TRAC. • Approximately two-thirds (68%) of all-causality TEAEs of PPE syndrome in the sunitinib arm were Grade 1 or 2 in severity. • No action was taken with sunitinib treatment in the majority of patients (68%) who experienced PPE syndrome. • PPE syndrome was reported at a higher frequency in S-TRAC than in patients with mRCC. However, PPE syndrome is a common risk associated with sunitinib. In the adjuvant RCC population PPE syndrome was manageable and resulted in low (4.2%) frequency of permanent treatment discontinuations. PPE syndrome resolved after treatment discontinuation in all patients with follow-up information available, but additional information was not available for 2 patients at the last contact.
Fatigue/Asthenia	• Fatigue and Asthenia were common TEAEs reported in the sunitinib arm (36.6% and 22.5%, respectively) and placebo arm (24.3% and 12.2%, respectively). • The majority of all-causality TEAEs of Fatigue (87%) and Asthenia (84%) in the sunitinib arm were Grade 1 or 2 in severity. • In the sunitinib arm, only 4 and 3 patients permanently discontinued treatment in response to AEs of Asthenia and Fatigue, respectively, all events resolved except for one event of asthenia, which was identified with a potential contributory factor. • AEs of Fatigue/Asthenia were manageable and consistent with the known safety profile of sunitinib.
Diarrhea	• In S-TRAC, Diarrhoea was the most common TEAE in the sunitinib arm (56.9%). • The majority (93%) of all-causality TEAEs of Diarrhoea in the sunitinib arm were Grade 1 or 2 in severity. • One (1) patient who experienced Diarrhoea permanently discontinued treatment, the event resolved after discontinuation of treatment. • AEs of Diarrhoea were consistent with the known safety profile of sunitinib.

Table 16. Summary of S-TRAC Adverse Events of Special Interest

Adverse Event of Special interest	Summary
Thyroid disorders	• Thyroid disorders are commonly observed during sunitinib treatment and patients in S-TRAC. • The most frequent thyroid disorder in both treatment arms was Hypothyroidism (56 [18.3%] patients in the sunitinib arm vs 4 [1.3%] patients in the placebo arm). • The frequency of thyroid disorder steadily increased from Cycle 4 through Cycle 9. The majority of AEs of thyroid dysfunction were Grade 1 or Grade 2 in severity. No Grade 4 or Grade 5 AEs of thyroid dysfunction were reported. • One (1) patient who experienced hypothyroidism permanently discontinued treatment, the event was recorded as recovering at the last patient contact. • Overall, the thyroid disorders reported in S-TRAC were consistent with the known safety profile of sunitinib.
Liver test abnormalities	• In S-TRAC, the majority of instances of elevated liver tests from baseline were Grade 1 or Grade 2 in severity. • No Hy's Law cases were observed in either treatment arm. • Overall, the liver test abnormalities reported in the sunitinib arm in S-TRAC are consistent with the known hepatic safety profile of sunitinib.
Cardiovascular events	• The overall frequency of cardiovascular events was similar in both treatment arms (sunitinib arm 9.8 % vs 8.9% placebo arm). • The most common cardiovascular event reported was Angina pectoris (sunitinib arm 1.6% vs 0.7% placebo arm) and Myocardial infarction (sunitinib arm 1.0% vs 0.3% placebo arm). • No clinically meaningful risk differences for sunitinib versus placebo were identified for cardiovascular events of interest.
Second primary malignancy	• In S-TRAC, second primary malignancies were reported as part of the disease assessment for the primary efficacy endpoint of DFS. There were more reports of second primary malignancy in the placebo arm than in the sunitinib arm. Nine (9 [2.9%]) patients in the sunitinib arm and 20 (6.6%) patients in the placebo arm experienced second primary malignancies based on efficacy assessments by BICR (Table 17 in Section 6.6). • Overall, there were no trends noted in the type of second primary malignancies reported. • Review of reports of second primary malignancies did not identify any trends in the type of second primary malignancies reported or safety issues with sunitinib use.

Abbreviations: AE = adverse event; BICR = blinded independent central review; DFS = disease-free survival; mRCC = metastatic renal cell carcinoma; PPE = palmar-plantar erythrodysaesthesia syndrome; RCC = renal cell carcinoma; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer; TEAE = treatment-emergent adverse event; VEGF = vascular endothelial growth factor; vs = versus.

6.6. Second Primary Malignancies in the S-TRAC Study Based on Efficacy Assessments

Table 17. Summary of Second Primary Malignancies in the S-TRAC Study Based on Efficacy Assessments – As-Treated Population

Treatment Arm Diagnosis (Preferred Term)	Time to Onset (Years)[a]
Sunitinib	
Squamous cell carcinoma	0.9
Uterine cancer	1.7
Prostate cancer	2.6
Invasive ductal breast carcinoma	3.0
Bladder cancer	4.1
Brain neoplasm malignant	4.2
Leukaemia	5.0
Ovarian cancer	5.5
Renal cell carcinoma	6.6
Placebo	
Bladder neoplasm	1.3
Thyroid cancer	1.5
Endometrial adenocarcinoma	2.1
Gastrointestinal stromal tumour	1.8
Prostate cancer (2 patients)	1.8, 4.7
Bladder cancer (2 patients)	2.3, 5.9
Basal cell carcinoma	2.6
Lung neoplasm malignant	2.8
Adenocarcinoma gastric (2 patients)	2.9, 3.9
Adenocarcinoma	3.4
Colon cancer metastatic	4.1
Follicle centre lymphoma, follicular grade I, II, III (2 patients)	5.1, 5.9
Rectal cancer	5.5
Renal neoplasm	6.4
Leukaemia	6.6
Acute promyelocytic leukaemia	6.7

a. Time to onset (years) is defined as (Date of second primary malignancy – Date of randomization +1)/365.4
MedDRA (v19.0) coding dictionary applied.

6.7. Pre-Specified Analysis of Patient-Reported Outcomes in the S-TRAC Study

Table 18. Pre-Specified Analysis of Patient-Reported Outcomes in S-TRAC[a]

	Sunitinib (n=309) Model Estimated Mean	Placebo (n=306) Model Estimated Mean	Difference (Sunitinib – Placebo)	95% Confidence Interval
EORTC QLQ-C30				
Global Health status/QoL (large values better)	69.07	73.84	**-4.76****	-6.82, -2.71
Functional scales (large values better)				
Physical functioning	83.54	87.53	**-3.98****	-5.57, -2.39
Role functioning	78.94	85.46	**-6.52****	-9.05, -4.00
Emotional functioning	80.92	82.97	**-2.05***	-3.93, -0.17
Cognitive functioning	85.50	87.43	**-1.93***	-3.79, -0.07
Social functioning	80.62	87.99	**-7.36****	-9.58, -5.15
Symptom items/scales (large values worse)				
Fatigue	29.94	21.74	**8.21****	5.95, 10.46
Nausea and vomiting	7.35	3.46	**3.90****	2.53, 5.26
Pain	21.81	16.63	**5.18****	2.79, 7.57
Dyspnea	14.97	11.89	**3.08***	0.85, 5.31
Insomnia	22.22	20.73	**1.49**	-1.26, 4.24
Appetite loss	14.66	4.62	**10.04 **†**	7.88, 12.20
Constipation	11.24	9.83	**1.41**	-0.80, 3.62
Diarrhea	19.25	7.25	**12.00 **†**	9.62, 14.38
Financial difficulties	15.12	13.92	**1.19**	-1.19, 3.57
EQ-5D (large values better)				
EQ-5D Index	0.79	0.83	**-0.04****	-0.06, -0.02
EQ-VAS	73.28	77.09	**-3.80****	-5.57, -2.04

a. A repeated measures longitudinal analysis with an intercept term, and treatment, time, treatment by time, and baseline as covariate over all cycles.
*: P <0.05
**: P <0.001
†: Clinically meaningful difference:
≥10 points for EORTC QLQ-C30 subscales
≥0.08 points for EQ-5D index
≥10 points for EQ-VAS
P-values not adjusted for multiplicity.

6.8. All-Causality Treatment-Emergent Adverse Events in the Sunitinib Arms of the S-TRAC and the ASSURE Studies

Table 19. Summary of Grade 3, Grade 4, and Grade 5 All-Causality Treatment-Emergent Adverse Events, Reported in ≥1% of Patients in the Sunitinib Arms of the S-TRAC and the ASSURE Studies[a]

Preferred Term	S-TRAC (N=306) n (%)			Adverse Event Term	ASSURE Study (N=625) n (%)		
	Grade 3	Grade 4	Grade 5		Grade 3	Grade 4	Grade 5
Any AEs	148 (48.4)	37 (12.1)	5 (1.6)		359 (57.4)	31 (5.0)	4 (0.6)
Palmar-plantar erythrodysaesthesia syndrome	46 (15.0)	3 (1.0)	0	Hand-foot reaction	94 (15.0)	0	0
Neutropenia	23 (7.5)	3 (1.0)	0	-	-	-	-
Hypertension	24 (7.8)	0	0	Hypertension	104 (16.6)	1 (0.2)	0
Thrombocytopenia	15 (4.9)	4 (1.3)	0	Platelets	N/A	8 (1.3)	0
Fatigue	13 (4.2)	2 (0.7)	0	Fatigue	106 (17.0)	4 (0.6)	0
Mucosal inflammation	14 (4.6)	0	0	-	-	-	-
Diarrhoea	12 (3.9)	0	0	Diarrhoea w/o prior colostomy	62 (9.9)	0	0
Asthenia	11 (3.6)	0	0	Nonneuropathic upper extremity muscle weakness	1 (0.2)	0	0
				Nonneuropathic right-side muscle weakness	1 (0.2)	0	0
				Nonneuropathic generalized weakness	1 (0.2)	0	0
Stomatitis	5 (1.6)	2 (0.7)	0	Muco/Stomatitis by exam, oral cavity	2 (0.3)	0	0
				Muco/Stomatitis (symptom) oral cavity	3 (0.5)	0	0
				Muco/Stomatitis (symptom) pharynx	24 (3.8)	1 (0.2)	0
Vomiting	7 (2.3)	0	0	Vomiting	14 (2.2)	0	0
Nausea	6 (2.0)	0	0	Nausea	23 (3.7)	0	0
Proteinuria	5 (1.6)	1 (0.3)	0	Proteinuria	N/A	1 (0.2)	0
Pulmonary embolism	2 (0.7)	4 (1.3)	0	Thrombosis/thrombus/embolism	2 (0.3)	2 (0.3)	1(0.2)
Abdominal pain	4 (1.3)	1 (0.3)	0	Abdomen, pain	5 (0.8)	1 (0.2)	0
Anaemia	4 (1.3)	1 (0.3)	0	Hemoglobin	N/A	3 (0.5)	0
Dyspepsia	4 (1.3)	0	0	Dyspepsia	15 (2.4)	0	0
Leukopenia	3 (1.0)	1 (0.3)	0	Leukocytes	N/A	1 (0.2)	0
Neutrophil count decreased	4 (1.3)	0	0	Neutrophils	N/A	0	0

Table 19. Summary of Grade 3, Grade 4, and Grade 5 All-Causality Treatment-Emergent Adverse Events, Reported in ≥1% of Patients in the Sunitinib Arms of the S-TRAC and the ASSURE Studies[a]

Preferred Term	S-TRAC (N=306) n (%)			Adverse Event Term	ASSURE Study (N=625) n (%)		
	Grade 3	Grade 4	Grade 5		Grade 3	Grade 4	Grade 5
Alanine aminotransferase increased	3 (1.0)	0	0	ALT, SGPT	N/A	1 (0.2)	0
Hyponatraemia	3 (1.0)	0	0	Hyponatremia	N/A	0	0
Hypophosphataemia	3 (1.0)	0	0	-	-	-	-
Oesophagitis	3 (1.0)	0	0	Esophagitis	1 (0.2)	0	0
Rash	2 (0.7)	0	0	Rash/desquamation	15 (2.4)	0	0
Decreased appetite	2 (0.7)	0	0	Anorexia	12 (1.9)	0	0
Dehydration	2 (0.7)	0	0	Dehydration	12 (1.9)	0	0
Arthralgia	1 (0.3)	0	0	Joint, pain	10 (1.6)	0	0
Dyspnoea	0	0	0	Dyspnea	9 (1.4)	1 (0.2)	0
Headache	2 (0.7)	0	0	Head/headache	8 (1.3)	0	0
Renal failure	0	1 (0.3)	0	Renal failure	7 (1.1)	0	1 (0.2)
Back pain	0	0	0	Back, pain	6 (1.0)	0	0

a. Hematologic and other laboratory events were only collected at Grade 4 and higher in the ASSURE study.
CTCAE v3.0 was used in both studies.
MedDRA (v19.0) coding dictionary applied to Study A6181109.
Abbreviations: ASSURE = Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma; CTCAE= Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in arm; n=number of patients with observations; N/A=not applicable; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer.

6.9. Disease-Free Survival Results from the S-TRAC Study in the Context of Disease-Free Survival or Recurrence-Free Survival Results from Other Adjuvant Cancer Drug Trials

Disease	Drug	Primary Endpoint/ Number of Patients	Relative Risk Reduction	Absolute Risk Reduction
Renal Cell Carcinoma	Sunitinib (S-TRAC)	DFS/ 615	**24%** HR = 0.76 (95% CI 0.59 – 0.98) 2-sided p-value = 0.030	**8.0%** at 5 years
Colon Cancer	Oxaliplatin[8]	DFS/ 2246	**23%** HR = 0.77 (95% CI 0.65 – 0.91) p-value = 0.002	**5.3%** at 3 years
Breast cancer	Letrozole[58]	DFS/ 8010	**21%** HR = 0.79 (95% CI 0.68 – 0.92) p-value = 0.002	**1.7%** at 2 years[63] **2.6%** at 5 years[63]
	Exemestane[59]	DFS/ 4724	**31%** HR = 0.69 (95% CI 0.58 – 0.82) p-value = 0.00003	**3.1%** at 2 years[63]
	Docetaxel[60]	DFS/ 1491	**28%** HR = 0.72 (95% CI 0.59 – 0.88) p-value = 0.001	**7%** at 5 years
	Trastuzumab[61]	DFS/ 3752	**52%** HR = 0.48 (95% CI 0.39 – 0.59) p-value = <0.0001	**15.3%** at 3.5 years
	Trastuzumab[61] AC→TH[a]	DFS/ 3386	**46%** HR = 0.54 (95% CI 0.44 – 0.67) p-value = <0.0001	**7.6%** at 2 years
	Trastuzumab[61] AC→TH[b]	DFS/ 3222	**40%** HR = 0.60 (95% CI 0.48 – 0.76) p-value = <0.0001	**5.7%** at 3 years
	TCH		**33%** HR = 0.67 (95% CI 0.54 – 0.84) p-value = 0.0006	**4.0%** at 3 years
	Anastrazole[62]	DFS/ 9366	**17%** HR = 0.83 (95% CI 0.71 – 0.96) p-value = 0.013	**2.0%** at 3 years

Disease	Drug	Primary Endpoint/ Number of Patients	Relative Risk Reduction	Absolute Risk Reduction
	Neratinib[63]	DFS/ 2840	**34%** HR = 0.66 (95% CI 0.49 – 0.90) p-value = 0.008	**2.3%** at 2 years
GIST	Imatinib[64]	RFS/ 713	**65%** HR = 0.35 (95% CI 0.22 – 0.53) one-sided p-value <0.0001	**15%** at 1 year
Melanoma	Ipilimumab[65]	RFS/ 951	**25%** HR = 0.75 (95% CI 0.64 – 0.90) p-value = 0.0013	**10.5%** at 5 years[66]

a. AC→TH = doxorubicin and cyclophosphamide followed by paclitaxel plus trastuzumab (Herceptin).
b. AC→TH = doxorubicin and cyclophosphamide followed by docetaxel plus trastuzumab (Herceptin).
Abbreviations: CI = confidence interval; DFS = disease-free survival; HR= hazard ratio; RFS = recurrence-free survival; S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer; TCH = docetaxel and carboplatin plus trastuzumab (Herceptin).

6.10. List of Abbreviations

Acronym	Definition
ACRIN	American College of Radiology Imaging Network
AE	Adverse Event
ALT	Alanine aminotransferase
ASSURE	Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma
AT	As-Treated
ATP	Adenosine triphosphate
AUC	Area Under the Curve
BICR	Blinded Independent Central Review
CI	Confidence Interval
CRF	Case Report Form
CSF-R1	Colony-Stimulating Factor-1 Receptor
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-Free Survival
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQoL Group health status questionnaire
EQ-VAS	EuroQol-Visual Analogue Scale
FDA	Food and Drug Administration
FLT-3	Fms like Tyrosine Kinase 3
GIST	Gastrointestinal stromal tumor
IGF2	Insulin-like Growth Factor 2
HR	Hazard Ratio
IFN-α	Interferon-α
IL-2	Interleukin-2
IQR	Interquartile Range
ITT	Intent-to-Treat
JAMA	Journal of the American Medical Association
KIT	Receptor for stem cell factor
LSFV	Last Subject First Visit
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mRCC	metastatic Renal Cell Carcinoma
MRI	Magnetic Resonance Imaging
mTOR	mammalian Target of Rapamycin
MX	Distant Metastasis (cannot be assessed)
NCI	National Cancer Institute
NE	Not Estimable
NR	Not Reached
PDGF	Platelet-Derived Growth Factor
PDGFR	Platelet-Derived Growth Factor Receptor
PK-PD	Pharmacokinetic-pharmacodynamic

Acronym	Definition
PFS	Progression-Free Survival
pNET	Pancreatic Neuroendocrine Tumor
PO	Per os (oral)
PPE	Palmar-Plantar Erythrodysaesthesia
PRO	Patient-Reported Outcome
PROTECT	Pazopanib as an Adjuvant Treatment for Localized Renal Cell Carcinoma
PS	Performance Status
PT	Preferred Term
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
RCC	Renal Cell Carcinoma
RTK	Receptor Tyrosine Kinase
sNDA	Supplemental New Drug Application
SAE	Serious Adverse Event
SLD	Sum of Longest Diameter
SOC	System Organ Class
S-TRAC	Sunitinib Treatment of Renal Adjuvant Cancer
TAM	Tumor Associated Macrophage
TEAE	Treatment-Emergent Adverse Event
TKI	Tyrosine Kinase Inhibitor
TNM	Tumor, Nodes, Metastasis
TTR	Time to Recurrence
UCLA	University of California, Los Angeles
UISS	University of California, Los Angeles Integrated Staging System
US	United States
VAS	Visual Analog Scale
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor receptor
VHL	Von Hippel-Lindau
vs	versus

6.11. References

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