FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

September 19, 2017

sNDA 21938/S-033

Sutent (sunitinib)

Applicant: Pfizer Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the Sutent (sunitinib) sNDA to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

1. Introduction

On March 17, 2017, Pfizer and C.P. Pharmaceuticals International C. V. submitted an application for the use of sunitinib in the adjuvant treatment of renal cell carcinoma. The basis of efficacy and safety for this application is provided by the following applicant-conducted trial.

> S-TRAC: A Randomized Double-blind Phase 3 Study of Adjuvant Sunitinib versus Placebo in Subjects at High Risk of Recurrent Renal Cell Carcinoma

The following trial, conducted in an adjuvant setting by ECOG-ACRIN, provides additional information and will also be reviewed as part of the application.

> ASSURE: Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma

Issues that will be discussed with this application are based on:

- Examination of the results of S-TRAC; and
- Examination and comparison of the results of S-TRAC and ASSURE.

Issues for the Committee:

- Has an improvement in disease-free survival (DFS) been demonstrated in the S-TRAC trial?
- Can results from S-TRAC be explained in the context of the other adjuvant trials with sunitinib in renal cell carcinoma (RCC)?
- Is disease-free survival as defined in S-TRAC a clinically relevant endpoint?

2. Background

Sunitinib is a tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3 and platelet derived growth factor receptors α and β as well as many other tyrosine kinase receptors. Sunitinib was approved in 2006 for the treatment of advanced RCC. S-TRAC was initiated in 2007 and ASSURE in 2006 to study the effect of sunitinib in the adjuvant treatment of RCC.

It is unclear whether VEGF/VEGFR inhibitors are well suited to the treatment of adjuvant disease. In the adjuvant setting, small areas of disease may not require extensive vasculature. However, sunitinib, which acts primarily through VEGFR inhibition, also affects other tyrosine kinase receptors and is able to inhibit RCC proliferation and induce apoptosis in vitro (Can J Urol 2011 18:5819). Clinically, sunitinib, sorafenib, and pazopanib (all primarily VEGFR inhibitors) have been previously examined in the adjuvant setting in RCC. ASSURE was a three-arm trial of adjuvant sunitinib, sorafenib, or placebo in patients with resected RCC. ASSURE showed no improvement, with either sunitinib or sorafenib, in DFS or overall survival (OS) compared to placebo. PROTECT was an adjuvant trial of pazopanib 600 mg versus placebo in patients with resected RCC. The primary analysis was conducted in those who received 600 mg

pazopanib (or placebo) and showed no improvement in DFS. An exploratory analysis of 403 patients treated with pazopanib 800 mg found a HR of 0.69 (95% CI: 0.51, 0.94).

Table 1: Adjuvant Trials in Renal Cell Carcinoma			
ASSURE[1]			
	Sunitinib N = 647	Sorafenib N = 649	Placebo N = 647
5 Year DFS	54.3%	54.0%	56.4%
Hazard Ratio vs. Placebo (97.5% CI)	1.02 (0.85, 1.23)	0.97 (0.80, 1.17)	
p-value	0.80	0.72	
5 Year OS	77.9%	80.5%	80.3%
Hazard Ratio vs. Placebo (97.5% CI)	1.17 (0.90, 1.52)	0.98 (0.75, 1.28)	
PROTECT[2]			
	Pazopanib 600 mg N = 571	Placebo N = 564	
3 Year DFS	67%	64%	
Hazard Ratio (95% CI)	0.86 (0.70, 1.06)		
p-value	0.165		

[1] Lancet 2016 387:2008; [2]ASCO 2016 Abstract # 4507

This document will examine the effect of sunitinib in the adjuvant treatment of RCC in S-TRAC, but will also incorporate information from ASSURE. Both S-TRAC and ASSURE enrolled patients who had undergone nephrectomy, randomized them to sunitinib or placebo, and followed them for DFS and OS.

Differences in S-TRAC and ASSURE include:

- Patient population;
- Dose of sunitinib;
- Definition of disease recurrence; and
- Outcome.

To define the extent of disease prior to nephrectomy, S-TRAC employed the University of California Los Angeles Integrated Staging System (UISS). The UISS uses the 1997 TNM classification system, Fuhrman grade, and pre-operative performance status (PS). Detailed information on the 1997, 2002, and 2010 TNM classification systems are included in Appendix I. S-TRAC enrolled those with T3 and T4 disease and with regional nodal involvement. T3 is defined as involvement of the perinephric tissue, renal veins, or inferior vena cava and T4 as disease that extends beyond Gerota's fascia. The Fuhrman nuclear grading system extends from grade 1 (well differentiated) to grade 4 (poorly differentiated). The table below illustrates how these components are incorporated into 3 risk groups for node negative disease. S-TRAC included patients at intermediate (T3N0, Grade any, PS any) and high risk for recurrence. Five

year disease-free survival is expected to be 55% in high risk and 80% in intermediate risk N0 disease (JCO 2004 22:3316, JCO 2002 20:4559).

Figure 1: UISS Risk Categories for N0 Disease

T stage	1				2	3				4
Grade	1-2		3-4		↓	1		>1		↓
ECOG PS	0	≥1	0	≥1		0	≥1	0	≥1	
Risk	Low	Intermediate							High	

JCO 2002 20:4559

There are separate UISS Risk Categories for those with node positive and metastatic disease. S-TRAC included patients (8%) with regional nodal involvement, but did not include those with metastatic disease. In S-TRAC, these patients were included in their own stratum.

ASSURE used the 2002 TNM classification system and enrolled those with T1b to T4 disease as well as those with regional lymph node involvement (9%). T1b disease is defined as tumors > 4 and ≤ 7 cm and limited to the kidney while T2 disease includes tumors > 7 cm and limited to the kidney. The 2002 definitions of T3 and T4 disease are similar to the 1997 definitions above. Additionally, ASSURE enrolled patients with both clear cell and non-clear cell histology while S-TRAC was confined to those with clear cell RCC.

Initially, both S-TRAC and ASSURE administered sunitinib 50 mg orally 4 weeks on/2 weeks off (4/2). However, after enrollment of 453 patients, ASSURE was modified to begin treatment at 37.5 mg of sunitinib. An additional 194 pts were enrolled at this dose. There were also differences in dose reduction with sunitinib decreased to 37.5 mg in S-TRAC and 37.5 and 25 mg in ASSURE. A publication which examined data from those with RCC or gastrointestinal stromal tumors found a relationship between increased exposure, response rate, and OS (Cancer Chemother Pharmacol 2010 66:357).

A further difference in these studies is in the mechanism of determination of disease recurrence. The primary endpoint of S-TRAC was DFS as determined by an independent review committee (IRC). Investigator-determined DFS was considered a secondary analysis with no allocation of alpha. Further, the S-TRAC Investigators were asked to have patient scans centrally reviewed prior to any changes in administration of study drug. The primary endpoint of ASSURE was Investigator-determined DFS. The actual definition of disease recurrence used in these two trials was similar. Most adjuvant trials have used Investigator-determined recurrence. However, the recent approval of ipilimumab in the adjuvant treatment of melanoma used IRC-determined DFS. Details concerning the definition of disease recurrence by IRC in S-TRAC are provided in Appendix II. Note that there is no widely agreed upon definition of DFS in RCC as there is in breast cancer (JCO 2007 25:2127).

While there is no widely agreed upon definition of disease recurrence, RCC is expected to recur in the lung, bone, liver, and brain as well as the renal bed (Expert Rev Anticancer Ther 2007 6:847). It is unclear whether contralateral renal cancers should be considered metastatic disease or a second primary, but would be considered an event in the S-TRAC definition of recurrent disease. Several unusual sites of recurrence were seen in S-TRAC. In the literature, metastatic RCC has been reported in the thyroid, breast, pancreas, spermatic cord, bladder, and muscle at the case report level (Surg Today 1995 25:1015, Breast 2006 15:426, Eur J Surg Oncol 1995 21:683, Clin Genitourin Cancer 2009 7:E101, Br J Urol 1997 79:650, Tumori 1990 76:407).

Regulatory History

During initial review of S-TRAC in 2007, the Agency expressed concern about the use of DFS as the sole primary endpoint and whether DFS correlated with OS in RCC. It was noted that the study was not powered to detect a statistically significant difference in OS and that regular approval, based on a prolongation in DFS, would be a review issue.

3. Clinical/Statistical- Efficacy Evaluation

Study Designs

The study designs of S-TRAC and ASSURE are provided below. Only the sunitinib and placebo arms of ASSURE are described. The bullets below summarize the key differences between study designs of S-TRAC and ASSURE.

- S-TRAC was limited to those with T3-T4 disease while ASSURE included patients with T1b-T4 disease.
- S-TRAC initiated dosing with sunitinib 50 mg/placebo while ASSURE administered sunitinib 50 mg (N = 453), sunitinib 37.5 mg (N = 194), and placebo.
- On S-TRAC, follow up scans were obtained every 12 weeks for 3 years and then every 6 months during years 4 and 5. On ASSURE, follow up scans were obtained every 18 weeks during dosing, six weeks after the last dose, every 6 months for 2 years , and then yearly for 8 years.
- Recurrent disease was determined by the Investigator and an Independent Review Committee on S-TRAC and by the Investigator on ASSURE.

Table 2: Eligibility Criteria	
S-TRAC	ASSURE
Predominate (> 50%) clear cell	Clear cell and non-clear cell No collecting duct or medullary histology
pT3N0M0, Grade any, PS any[1] pT4N0M0, Grade any, PS any TanyN1-2M0, Grade any, PS any	pT1bN0M0, Grade 3-4[1] pT2-4N0M0, Grade any TanyN1-2M0, Grade any
Microscopic disease at surgical margins allowed	Microvascular invasion of the renal vein at the surgical margin allowed
PS 0-2	PS 0-1
3-12 weeks post-surgery	4-12 weeks post-surgery
No evidence of disease by IRC review of post-operative CT of chest, abdomen, pelvis within 8 weeks of surgery	No evidence of disease by Investigator review of CT of chest, abdomen and pelvis within 4 weeks of randomization
Bone scan and Head CT if clinically indicated	Bone Scan and Head CT if clinically indicated

[1]Clinically N0, patients may not have had nodal sampling

- Patients on S-TRAC could only be randomized after surgery.
- Patients on ASSURE could be randomized prior to or after surgery.

Table 3: Stratification and Treatment		
	S-TRAC	ASSURE
Strata	1. UISS Risk Groups a. T3N0, Grade 2-4, PS 1-2 b. T3N0, Grade any, PS 0 OR T3N0, Grade 1, PS 1-2 c. T4N0, Grade any, PS any d. TanyN1-2, Grade any, PS any 2. PS 0/1 vs. 2 3. Country	1. Risk Group a. Intermediate High Risk i. T1bN0, Grade 3-4 ii. T2N0, Grade 1-4 iii. T3aN0, Grade 1-2[1] b. High Risk i. T3aN0, Grade 3-4[2] ii. T3b or T3cN0, Grade any iii. T4N0, Grade any iv. TanyN1-2, Grade any 2. PS 0 vs. 1 3. Clear cell vs. other 4. Open vs. laparoscopic nephrectomy
Treatment	1. Sunitinib a. 50 mg po 4/2 x 1 year, N = 309 2. Placebo po 4/2 x 1 year, N = 306	1. Sunitinib a. 50 mg po 4/2 x 9 cycles, N = 453 b. 37.5 mg po 4/2 x 9 cycles, N = 194 2. Placebo po 4/2 x 9 cycles, N = 647

[1]Intermediate High Risk-pT3a not due to adrenal involvement; High Risk-pT3a due to adrenal involvement

- There is no information concerning patient compliance on S-TRAC.

The table below provides information on differences in the dose modification criteria.

Table 4: Dose Modification[1]

	S-TRAC	ASSURE
Dose Levels	Sunitinib 37.5 mg	Sunitinib 37.5 mg Sunitinib 25 mg
Discontinuation	If toxicity not resolved > 6 weeks	If toxicity not resolved > 4 weeks
Hematologic Toxicity	1st occurrence Gr 3 neutropenia: resume at same dose unless > 5 d then resume at lower dose Gr 3 platelets: resume at same dose	1st occurrence Gr 3 neutropenia: resume at same dose Gr 3 platelets: resume at lower dose
Re-escalation	After dose reduction: Only if no > Gr 1 heme toxicity in previous cycle	Starting dose 37.5 mg: Escalation to 50 mg after Cycle 1 if Gr 0-1 toxicity, optional if Gr 2 toxicity

[1]Both trials allowed dose reduction at Investigator discretion.

The table below provides information on the monitoring program for S-TRAC and ASSURE. A key difference is in the frequency of disease assessment. During year 1, scans are done every 12 weeks on S-TRAC and every 18 weeks on ASSURE. During years 2-3, scans are done every 12 weeks on S-TRAC and every 6 months on ASSURE. During years 4-5, scans are done every 6 months on S-TRAC and yearly on ASSURE. Note that on S-TRAC Investigators were to await IRC input prior to a change in study drug.

Table 5: Study Monitoring

	S-TRAC	ASSURE
CBC Chemistries	Baseline, D28, q cycle, EOT	Baseline, q cycle, EOT Then q 6 mos x 1 year Then q year
INR, PT, PTT		Baseline, further testing if on warfarin
Urine Dipstick	Baseline, q cycle, EOT	
Thyroid	Baseline, D28, C3, 5, 7, 9, EOT	Baseline, C2, then as needed
MUGA/Echo	Baseline, C2, 4, 8, EOT	Baseline, C2, 4, 8, EOT
EKG	Baseline, D28, C2, 4, 8, EOT	Baseline
CT Chest, Abdomen, Pelvis	Baseline, q 12 weeks x 3 years, q 6 months x 2 years	Baseline, q 3 cycles during dosing, 6 wks after last dose, q 6 months x 2 years, then q year x 8 years
Bone Scan	If clinically indicated	If clinically indicated
Head CT	If clinically indicated	
Survival	q 12 weeks until final analysis	q 3 months x 2 years, q 6 months x 3 years. q year x 5 years

C-cycle; D-day; q-every; EOT-end of treatment; wks-weeks

Protocol Amendments
Both trials had 14 protocol amendments. Substantive amendments are included below.

S-TRAC
- Amendment 4: either pre-operative PS or PS at study entry to determine randomization strata
- Amendment 6: patients with T3N0M0, Grade any, PS 0 and T3N0M0, Grade 1, PS 1-2 added
- Amendment 9: changed the CT schedule from even to odd number cycles
- Several amendments changed sample size and timing of the interim and final analyses. Due to low event rate, the primary analysis of DFS was changed from an event-driven analysis to one performed 5 years after the last subject first visit or when approximately 258 DFS events are observed, whichever was later.

ASSURE
- Amendment 2: changed CTs from every 2 to every 3 cycles during treatment
- Amendment 5: changed to sunitinib from 50 to 37.5 mg

Radiology Review

The criteria for disease recurrence were similar between the S-TRAC Independent Review Committee, the S-TRAC Investigators, and the ASSURE Investigators. Only the IRC review of disease recurrence on S-TRAC has been closely examined.

S-TRAC Independent Radiology Committee (IRC)
Two radiologists read each scan and scans were adjudicated by a third radiologist. Scans were read prior to study entry to determine whether residual local disease or metastatic disease was present. The radiologist's reading and the patient's clinical information were reviewed by an oncologist who made the final determination concerning disease recurrence and date. Clinical information included on study surgery, biopsy reports, radiation, and anti-cancer medication as well as new lesions and physical findings per Investigator.

The IRC determination of disease recurrence was based on the criteria in Appendix II (summarized below) or biopsy. In general, the IRC definition of disease recurrence included:

- Multiple small ($\leq$ 1 cm) lung lesions or a single lung lesion > 1 cm
- Enlarging lesions in the renal bed, lymph nodes, liver, and soft tissue; enlarged lymph nodes were required to be $\geq$ 1.5 cm, long axis
- Pleural effusion with an associated soft tissue mass/enhancing rim or ascites
- Brain lesion(s)
- Multiple areas of bone uptake, Solitary bone lesions typically required additional imaging

The S-TRAC IRC could also state that there was conclusive evidence of disease recurrence based on a single scan and this date was used. If enlargement was required, the date of the

second scan (showing enlargement compared to the first scan) was used. S-TRAC Investigators were asked to continue study drug until the results of central review were available.

The definitions of recurrent disease used by the S-TRAC Investigators and by the ASSURE Investigators are shown in Appendix II.

Statistical Analysis Plan

S-TRAC
Primary Endpoint

- Disease-free survival was defined as the time from randomization to the date of recurrence as determined by the IRC, a second primary malignancy, or death. The analysis was conducted in all randomized patients.
- Censoring: Observations on patients without an event were censored at their last assessment date. Observations on patients alive and without a post-baseline assessment were censored at Day 1. Observations on patients who received anticancer therapy prior to an event were censored at their last assessment prior to anticancer therapy. If an event occurred after ≥ 2 consecutive missed assessments, the observation for that patient was censored at the last assessment date prior to the event.
- Test Statistic: A stratified (by modified UISS risk category) logrank test was used to test the null hypothesis that the hazard ratio = 1. The hazard ratio (HR) was estimated using a stratified (modified UISS risk category) Cox proportional hazards model. The medians were estimated using the Kaplan-Meier method. Although four UISS risk strata were used during randomization, the analyses were conducted using three risk strata. Patients with T4N0 and TanyN1-2 disease were included in the same stratum.
- There were 2 interim analyses. A significance level of 0.0476 was allocated for the final analysis after adjustment for the interim analyses.

Secondary endpoints included Investigator-determined DFS and OS. An interim analysis of OS was done at the time of the final analysis of DFS, and the final OS analysis will be conducted 3 years after the final DFS analysis. The overall type I error rate for both analyses of OS is controlled at 5%; however, there was no alpha allocation specified for the Investigator analysis of DFS. Exploratory endpoints included evaluation of the EORTC QLQ-C30 and EQ-5D.

ASSURE
The primary endpoint, DFS, was defined as the time from randomization to Investigator-determined recurrence, a second primary cancer, or death from any cause. Second primary cancers were further defined to include a rising PSA, but did not include localized breast or prostate cancer or non-melanoma skin cancer. Observations on patients without an event were censored at the date of last contact. A stratified (stratification factors at randomization) logrank test was used. The hazard ratio was estimated using a stratified Cox proportional hazards model. Interim analyses were conducted yearly beginning at ~ 33% of events. A one-sided alpha of 0.0125 was used for the comparison of sunitinib vs. placebo.

Disposition

S-TRAC was conducted at 97 centers with 48 patients (8%) accrued in the US. The trial was initiated in 2007 and the data cutoff date was April 2016. Updated information on OS was provided with a cutoff date of January 2017. The table below provides information on the patient disposition during the treatment period. This table differs from the Applicant's in that several patients who discontinued due to "Other" were reassigned based on additional information included in the dataset. Close to half the patients discontinued treatment on the sunitinib arm. Note that in the sunitinib arm, 36% of patients discontinued due to an adverse event or patients withdrawal.

Table 6: Disposition on S-TRAC

	Sunitinib	Placebo
Enrolled	309	306
Treated	306	304
Completed	167 (55%)	209 (69%)
Discontinued	139 (45%)	95 (31%)
Reasons for Discontinuation		
Adverse Event	93 (30%)	17 (6%)
Recurrence[1]	23 (8%)	61 (20%)
Patient Withdrawal/Lost to Follow Up	19 (6%)	11 (4%)
Other/Protocol Violation	3 (1%)	5 (2%)
Death	1 (0.3%)	1 (0.3%)

[1]Includes Investigator-suspected recurrence that was not confirmed by IRC. Data Cutoff: 4-16

ASSURE was conducted at 476 registering affiliates and 254 registering institutions with 1795/1943 (92%) patients accrued in the US. Initially, the protocol began dosing at sunitinib 50 mg (N = 453) and subsequently lowered the starting dose to 37.5 mg (N = 194). Among those on ASSURE who started treatment at sunitinib 50 mg, 45% completed treatment compared to 55% on S-TRAC. Even among those on ASSURE who started dosing at sunitinib 37.5 mg, the percentage who completed treatment, 51%, was lower than S-TRAC. It is unclear if this difference is related to the countries included in the trials or due to other differences between an industry-sponsored and cooperative group trial.

Demographics

On S-TRAC, the median ages were 57 and 58 years on the sunitinib and placebo arms, respectively. Patients ≥ age 65 made up 25% of the sunitinib and 27% of the placebo arm. On both arms, 72-75% of patients were male and 82-86% were White. The UISS risk strata were based on PS prior to nephrectomy. However, this PS was not separately recorded. The PS prior to randomization was 0 in 74% of patients on sunitinib and 72% on placebo. A PS of 1 was reported in most of the remaining patients. One patient on the sunitinib arm had a PS of 2.

Baseline Disease Characteristics

The Applicant collected the patient risk strata at randomization and later, on FDA request, collected the TNM classification.

A key difference in S-TRAC and ASSURE that may have led to the difference in study findings is that the patients on S-TRAC were at higher risk for recurrence. The table below provides the distribution among the risk strata on S-TRAC. S-TRAC used four risk strata at randomization, but the Applicant found that few patients were included in the T4N0 and the Node positive strata. The Applicant combined these groups in their analyses. Therefore, only three strata are shown. The table below also applies these risk strata to the patients on ASSURE. The patients from ASSURE who are included in the table are limited to those with clear cell histology who began dosing with sunitinib/placebo 50 mg. These patients will be used in an exploratory analysis of DFS (see below). Note that the distribution of patients among the risk strata differs substantially in the two trials.

Table 7: UISS Risk Strata

	S-TRAC		ASSURE[2]	
	Sunitinib N = 309 (%)	Placebo N = 306 (%)	Sunitinib N = 229 (%)	Placebo N = 231 (%)
UISS Risk Strata[1]				
T3N0, Grade Any, PS 0 OR T3N0, Grade 1, PS ≥ 1	115 (37)	112 (37)	176 (77)	174 (75)
T3N0, Grade ≥ 2, PS ≥ 1	165 (53)	166 (54)	38 (17)	32 (14)
T4N0, Grade any, PS any OR TanyN1-2, Grade any, PS any	29 (9)	28 (9)	15 (7)	25 (11)

[1]The UISS strata are N0-X and M0. [2]Baseline PS was missing in 8 patients and PS at the beginning of C1 was substituted.

As noted above a key difference between S-TRAC and ASSURE is the risk group in ASSURE including those with T1b and T2 as well as, T3 and T4 disease. Patients on S-TRAC were to have T3N0, T4N0, or TanyN1-2 disease. The table below provides information on the TNM classification as well as the Fuhrman grade.

Table 8: S-TRAC TNM Staging[1]

	Sunitinib N = 309 (%)	Placebo N = 306 (%)
T Stage		
T1	5 (2)	3 (1)
T2	5 (2)	3 (1)
T3	274 (89)	282 (92)
T4	5 (2)	5 (2)
TX or Missing	20 (6)	13 (4)
N Stage		
N0	156 (50)	169 (55)
N1	14 (5)	15 (5)
N2	12 (4)	9 (3)

Table 8: S-TRAC TNM Staging[1]		
	Sunitinib N = 309 (%)	Placebo N = 306 (%)
NX or Missing	127 (41)	113 (37)
M Stage		
M0	288 (93)	292 (95)
M1	3 (1)	2 (0.7)
MX or Missing	18 (6)	12 (4)
Fuhrman Grade		
1	11 (4)	8 (3)
2	104 (34)	104 (34)
3	139 (45)	141 (46)
4	54 (17)	52 (17)
Missing	1 (0.3)	1 (0.3)

[1]S-TRAC used the 1997 TNM staging system (see Appendix I).

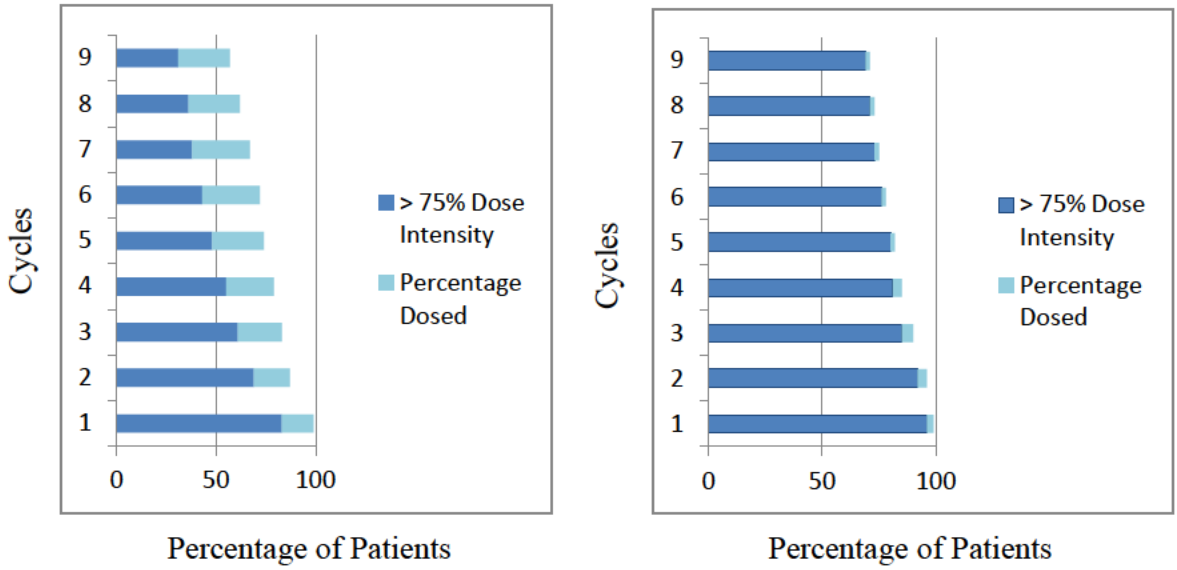
Dosing

Another key difference between S-TRAC and ASSURE is in the dose of sunitinib. The overall dose intensity/exposure was higher on the S-TRAC trial. S-TRAC initiated dosing at sunitinib 50 mg in all patients and allowed dose reductions to 37.5 mg. ASSURE initiated dosing at sunitinib 50 mg (N = 453) and later at sunitinib 37.5 mg (N = 194). On ASSURE, dose reductions to 37.5 and 25 mg were permitted. The decision to lower the starting dose to 37.5 mg was based on a 44% rate (as reported by ECOG-ACRIN) of treatment discontinuation due to adverse events and patient withdrawal.

The figures below provide information on sunitinib and placebo dosing by cycle on S-TRAC. This includes the percentage of patients starting each cycle and the percentage with > 75% dose intensity. Seventy-five percent was chosen because this is the dose intensity of a patients receiving 37.5 mg. In the sunitinib arm, < 60% of patients completed 9 cycles. Among those receiving sunitinib, overall dose intensity was > 90% in 46% and > 75% in 75% of patients.

Figure 2: Completion of the Treatment Period and Dose Intensity on S-TRAC

Sunitinib Placebo



Primary Analysis

The table below provides the Applicant's primary analysis of DFS based on the blinded IRC assessment. The analysis shows a statistically significant improvement in DFS. Since most events were diagnosed radiologically, we examined the scanning intervals and found that 70-100% of scans were obtained within the protocol-specified windows and that this was balanced between arms.

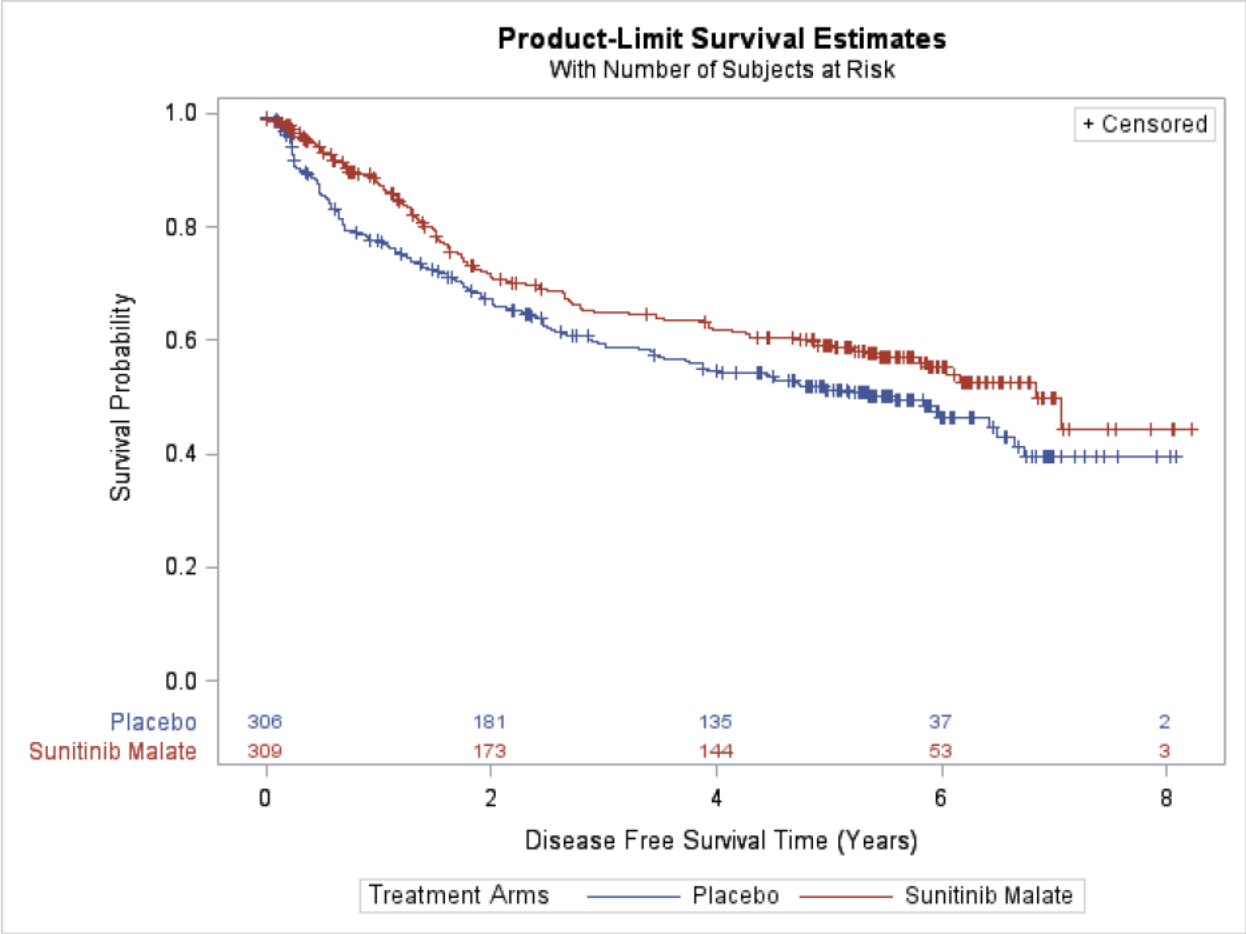
Table 9: Primary DFS Analysis-IRC Assessment

	Sunitinib N = 309	Placebo N = 306
Events	113 (37%)	144 (47%)
Recurrent Disease by Scan	86	126
Recurrent Disease by Biopsy	16	12
Deaths	8	4
Second Primary	4	11
Metastases at Diagnosis	3	2
Median DFS	6.8 years	5.6 years
5-year DFS	59%	51%
Hazard Ratio (95% CI)[1]	0.76 (0.59, 0.98)	
p-value[2]	0.03	

[1]Cox regression model using 3 UISS risk strata
[2]Stratified logrank test using 3 UISS risk strata

Data Cutoff: 4-2016

Figure 3: Disease-free Survival by Independent Review



Data Cutoff: 4-2016

During the blinded IRC review, either a single scan or an initial scan followed by a second scan with enlargement of the lesion could be used to determine disease recurrence. In the IRC analysis, for patients who required a second scan to determine disease recurrence, the date of recurrence was the date of the second scan.

- Among those on sunitinib with radiological recurrence, this was based on a second scan in 14 patients with a median time between scans of 86.5 days (range: 21, 186).
- Among those on the placebo arm with radiological recurrence, this was based on a second scan in 24 patients with a median time between scans of 89 days (range: 57, 401).

In the FDA analysis, based on Investigator comments and the AE dataset, there are 8 patients on sunitinib and 20 on placebo with a second primary cancer. These twenty patients on the placebo arm who had a second primary includes two patients with basal cell carcinoma and one patient with DCIS. In both the Applicant and FDA analyses, there is an imbalance in the number of second primary malignancies with an increase in the placebo arm. In animal studies, gastroduodenal carcinomas and an increased incidence of hemangiosarcomas have been seen

with sunitinib. These tumor types were not seen on the current trial. In the sunitinib arm, second primary tumors included (1 each) prostate, bladder, contralateral kidney, squamous cell cancer of the skin, breast, endometrium, brain, and leukemia.

Investigators were to send their scans for central review prior to discontinuation of study drug. Therefore, Investigator-determined DFS is not independent of the IRC. Nonetheless, the Investigator's assessment of DFS reported 290 events (257 in the IRC analysis). The results of this analysis are shown in the table below. Note that the median DFS in the placebo arm differed substantially between the IRC and Investigator (5.6 versus 4.5 years). This may be due to censoring by the IRC of Investigator-determined events in the placebo arm.

Table 10: DFS Analysis-Investigator Assessment

	Sunitinib N = 309	Placebo N = 306
Events	132 (43%)	158 (52%)
Median DFS	6.5 years	4.5 years
Hazard Ratio (95% CI)[1]	0.81 (0.64, 1.02)	

[1]Cox regression model using 3 UISS risk strata Data Cutoff: 4-2016

Sensitivity and Subgroup Analyses

A series of sensitivity analyses were conducted concerning the primary endpoint. One analysis did not censor patients with an IRC-determined event after $\geq$ 2 missed assessments or after additional anti-cancer therapy. The HR for this analysis is 0.81 (95% CI: 0.64, 1.02). An analysis of time to recurrence, excluding deaths and second primary malignancies as determined by the IRC, found a HR of 0.76 (95% CI: 0.59, 0.99). The results of both of these analyses are consistent with the Applicant's primary analysis.

S-TRAC was conducted primarily in Western Europe with few US patients. This is a difference between S-TRAC and ASSURE since 92% of those on ASSURE were enrolled in the US. A subgroup analysis of patients from the US (N = 48) found an unstratified HR of 1.32 (95% CI: 0.49, 3.55), while the subgroup enrolled in Western Europe (N = 364) had a HR of 0.71 (95% CI: 0.52, 0.98). While the result among US patients is of concern, given the small number enrolled in the US, the results of this analysis should be viewed cautiously. The result among those enrolled in Western Europe, a region similar to the US, is supportive of the primary analysis.

Exploratory Analyses of Patient Population, Dose, and Disease-free Survival

There are several differences between the designs of the S-TRAC and ASSURE trials which may explain the difference in study outcomes. These include the patient population, dose of sunitinib, and determination of DFS. This section explores these differences.

Patient Population

S-TRAC enrolled patients at a higher risk for recurrence than those enrolled on ASSURE. We, therefore, conducted an exploratory analysis of DFS in patients on ASSURE who: 1) had T3 or T4N0-X or TanyN1-2 disease, 2) had clear cell histology, 3) received sunitinib/placebo 50 mg as their initial dose, and 4) and did not have M1 disease at entry. Note that when these criteria were applied, the distribution of patients among the UISS risk strata differed between S-TRAC and ASSURE (Table 7). The result of this analysis is shown below.

ASSURE: T3-4N0 or Node Positive Clear Cell RCC Starting Dose Sunitinib/Placebo 50 mg

- The unstratified HR for DFS was 0.92 (95% CI: 0.71, 1.19) (N = 229 sunitinib/231 placebo).
- The stratified HR for DFS was 0.98 (95% CI: 0.75, 1.28) (N = 229 sunitinib/231 placebo).

This analysis suggests that sunitinib had a minimal effect on DFS among the patients on ASSURE who met the entry criteria for S-TRAC.

An additional difference between S-TRAC and ASSURE is that ASSURE included patients with non-clear cell carcinoma. The analysis of DFS in patients from ASSURE with clear cell histology, as conducted by the ECOG-ACRIN, is shown below.

ASSURE: Clear Cell Histology (Lancet 2016 387:2008)

- The HR for DFS was 1.01 (97.5% CI: 0.84, 1.22) (N = 1021 on sunitinib or placebo).

The analysis suggests that sunitinib had no effect on DFS in ASSURE despite limitation of the analysis to those with clear cell RCC.

Dose

S-TRAC and ASSURE differed in that 194 patients on ASSURE began dosing at sunitinib 37.5 mg while all patients on S-TRAC received sunitinib 50 mg. There was also a difference in the extent of dose reduction between these two trials. There is data to support a dose response effect of sunitinib and an increased dose could have contributed to a difference in outcome. We, therefore, examined the effect of dose intensity on DFS within S-TRAC. A dose intensity of 75% was chosen because those who received sunitinib 37.5 mg would receive 75% of the intended dose of sunitinib 50 mg. In this analysis, the outcome of patients on sunitinib with different dose intensities was compared to all patients in the placebo group. Finally, we also examined the ECOG-ACRIN analysis of those on ASSURE who began dosing at sunitinib 50 mg and those who began dosing at sunitinib 37.5 mg.

Dose Intensity on S-TRAC

- Dose Intensity > 75%: HR = 0.84 (95% CI: 0.64, 1.09) for DFS, (N = 232 sunitinib)
- Dose Intensity $\leq$ 75%: HR = 0.55 (95% CI: 0.34, 0.88) for DFS (N = 74 sunitinib)

Both analyses favor sunitinib. These exploratory analyses may suggest that those with a lower dose intensity receive greater benefit from sunitinib. However, this analysis should be viewed with caution since only 74 patients on sunitinib had a dose intensity $\leq$ 75%.

ASSURE: Starting Dose (Lancet 2016 387:2008)

- Sunitinib 50 mg: HR = 0.94 (97.5% CI: 0.76, 1.18) for DFS (N = 883 sunitinib/placebo)
- Sunitinib 37.5 mg: HR = 1.12 (97.5% CI: 0.76, 1.65) for DFS (N = 380 sunitinib/placebo)

The results of this analysis are unclear. Patients who receive 50 mg of sunitinib may benefit more from the drug, but this cannot be concluded with a HR of 0.94.

Overall, the data are mixed concerning the effect of dose on outcome.

Disease-free Survival

The primary differences in the determination of DFS between S-TRAC and ASSURE is the use of an Independent Review Committee to evaluate the results of S-TRAC and a difference in scanning intervals. There is, however, little difference in the actual definition of disease recurrence by scan. Appendix II provides detailed information concerning the definition of disease recurrence in the two trials. The extent to which the definition was followed on ASSURE is unknown. Since S-TRAC Investigators were to have the scans reviewed centrally prior to discontinuation of study drug, the results of Investigator review in S-TRAC and ASSURE cannot be directly compared.

Sites of Recurrent Disease

The table below provides information on the sites of recurrent disease in S-TRAC. This table does not include patients with second primary malignancies per FDA review.

Table 11: Sites of Recurrence Reported in S-TRAC

	Sunitinib N = 309 (%)	Placebo N = 306 (%)
Lung/Pleura/Pleural Fluid	41 (13)	54 (18)
Lymph Nodes/Spleen	24 (8)	27 (9)
Retroperitoneum/Renal Bed[1]	16 (5)	22 (7)
Liver	11 (4)	14 (5)
Adrenal Gland	10 (3)	7 (2)
Abdomen[2]	6 (2)	7 (2)
Bone	6 (2)	9 (3)
Pancreas	4 (1)	4 (1)
Brain	2 (0.6)	4 (1)
Kidney	2 (0.6)	7 (2)
Other	3 (1)	5 (2)
Mediastinum	1 (0.3)	4 (1)

[1]Includes celiac region nodule
[2]Includes abdominal wall, ascites, peritoneum/omentum, and small intestine

Data Cutoff: 4-2016

Most recurrences were in the lung, lymph nodes, or retroperitoneum with only 4-5% recurring in the liver. There was some imbalance between arms in the number with disease recurrence within the lung. This may be due to the small study size. Among the 8 patients who recurred within the pancreas, 1 patient in each arm had a biopsy-proven recurrence. In addition to the pancreas, there were several unusual sites of recurrence grouped under the category "Other." In the sunitinib arm, these included the thyroid, muscle, and maxillary sinus. Only the maxillary sinus lesion was biopsied. In the placebo arm, unusual sites of recurrence included the muscle, skin, thyroid, gonadal vein, and trachea. None of these sites were biopsied.

Overall Survival

By the cutoff date of January 31, 2017, deaths occurred in 21% on sunitinib and 24% on placebo. The hazard ratio for this analysis was 0.92 (95% CI: 0.66, 1.28). Estimated five-year OS was 81.4% in the sunitinib and 81.9% in the placebo arm.

Subsequent Therapy

By the data cutoff date of January 31, 2017, i.e., approximately 8 months after the cutoff for the primary analysis, 68 patients on sunitinib and 87 patients on placebo had received systemic anti-cancer therapy for metastatic disease. It is noted that 102 patients on sunitinib and 138 patients on placebo were reported to have recurrence events based on IRC assessments. The most commonly used agents were everolimus and sunitinib in the sunitinib and placebo arms, respectively. This brings into question the relevance of DFS as defined, if it does not lead to an immediate intervention in all patients with recurrence.

4. Safety

Safety Summary

The table below provides a safety summary of adverse events (AEs) during the treatment period and for 28 days after the last dose of study drug. See Appendix III at the end of this review for the grouping of preferred terms.

Table 12: Safety Summary for the S-TRAC trial

	Sunitinib N = 306 (%)	Placebo N = 304 (%)
Deaths	3 (1)	0
Permanent Discontinuation	85 (28)	15 (5)
Perm. Discon. due to Grade 3-4 AE	46 (15)	9 (3)
Dose Interruption of Reduction	186 (61)	44 (14)
Dose Interruption	142 (46)	40 (13)
Dose Reduction	106 (35)	6 (2)
Serious Adverse Events	57 (19)	30 (10)
Grade 3-4 Adverse Events	183 (60)	46 (15)

Data cutoff: 4-2016

Death: There were no deaths due to AEs that could be attributed to study drug.

Permanent Discontinuation: Permanent discontinuation due to an AE occurred in 28% of patients on sunitinib and 5% on placebo. In the AE dataset, many of the causes of permanent discontinuation were grade 1-2 events. Causes of permanent discontinuation in > 2% of patients on sunitinib were PPE and fatigue. No cause of permanent discontinuation was reported in > 2% of those on placebo.

Dose Interruption and Reduction: The incidence of dose interruption or reduction due to an adverse event is 61% in the sunitinib and 14% in the placebo arm. Causes of dose interruption in > 5% of patients on sunitinib included mucositis, PPE, fatigue, neutropenia, hypertension, and nausea. Causes of dose reduction reported in > 5% of patients on sunitinib were PPE and fatigue. No cause of dose interruption or reduction was reported in > 5% of those on placebo.

Serious Adverse Events: Serious adverse events occurred in 18% of patients on the sunitinib and 10% on the placebo arm. Serious adverse events in > 2 % of patients on sunitinib included hypertension and thrombocytopenia. No SAEs occurred in > 2% of those on placebo.

Grade 1-4 Adverse Events

The table below provides information on grade 3-4 and grade 1-4 AEs. The AE profile is, in general, consistent with the known toxicity of sunitinib. The incidence of mucositis in the current study (61%) is higher than the 47% (package insert) reported in patients with newly diagnosed metastatic RCC treated with sunitinib. This may be due to a difference in the grouping of terms collected under the category mucositis. In the current trial, the incidence of palmar-plantar erythrodysesthesia (PPE) is greater than the incidence of PPE in metastatic RCC (52% vs. 29%) reported in the package insert. This difference cannot be explained by the grouping of terms or a marked difference in exposure. Further, this increase is not due to increased reporting of grade 1-2 events on an adjuvant trial since the incidence of grade 3-4 PPE was also increased (17% in the current trial versus 8% in the metastatic setting). Also note that PPE was reported in 11% of patients on placebo, including 1 grade 3 event. The patient with the grade 3 event developed PPE shortly after the use of Hirucreme. Hirucreme has been reported to cause a contact dermatitis similar to eczema.

Table 13: Grade 1-4 Adverse Reactions in ≥ 20% of Patients Who Received Sunitinib

	Sunitinib N = 306		Placebo N = 304	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Any	99%	60%	88%	20%
Mucositis	61%	6%	13%	0
Fatigue	58%	8%	34%	2%
Diarrhea	57%	4%	21%	0.3%
PPE	52%	17%	11%	0.3%
Hypertension	39%	8%	14%	1%

Table 13: Grade 1-4 Adverse Reactions in ≥ 20% of Patients Who Received Sunitinib				
	Sunitinib N = 306		Placebo N = 304	
Dysgeusia	38%	0	6%	0
Nausea	34%	2%	14%	0
Dyspepsia	33%	1%	9%	0
Rash	29%	2%	14%	0
Abdominal Pain	27%	2%	11%	0.3%
Neutropenia	26%	10%	2%	0
Hypothyroidism	24%	0.3%	4%	0
Thrombocytopenia	23%	7%	2%	0.3%
Hair Color Changes	22%	0	2%	0
Hemorrhage	22%	0.7%	5%	0.3%

CTCAE Version 3 Data Cutoff: 4-2016

During the treatment period, hemorrhagic events occurred in 22% of patients on sunitinib. This included 2 grade 3 events. Both grade 3 events were an upper gastrointestinal hemorrhage. Grade 2 wound necrosis was reported in 1 patient. He began sunitinib 67 days after surgery and developed wound necrosis on Day 146 of treatment. The event required 107 days to resolve.

Thyroid Disease: During the treatment period, hypothyroidism, defined as either the adverse event hypothyroidism or a TSH > 10xULN, was present in 26% of patients on sunitinib and 4% on placebo. During the treatment period, the adverse event hyperthyroidism was reported in 6% of patients on sunitinib and 1% on placebo.

Heart Failure/Ejection Fraction Decreased: Eleven patients on each arm reported a decreased ejection fraction, left ventricular dysfunction, or cardiac failure. Of the 11 on sunitinib, 5 had an ejection fraction (EF) decrease ≥ 15%. Of these 5, 4 had resolution of their EF to baseline or ≥ 50%. One patient had a decrease from a baseline of 52% to 41% and had an EF of 47% at the end of treatment assessment.

Grade 3-4 Laboratories: Few grade 3-4 laboratory abnormalities occurred in ≥ 2% of patients on sunitinib. These included neutropenia (13%), thrombocytopenia (5%), lymphopenia (3%), and an increase in alanine aminotransferase (2%).

Adverse Events > 28 Days After Discontinuation of Study Drug

Issues to consider when using adjuvant treatment are the long-term consequences of therapy such as thyroid disease, decreased ejection fraction, and the long-term consequences of hypertension. There is little information concerning late events.

Thyroid Disease: A TSH level was drawn > 6 weeks after the last dose of sunitinib in 6 patients on thyroid replacement. Four who continued and 1 who discontinued thyroid replacement had an elevated TSH. TSH levels were also drawn > 6 weeks after the last dose of sunitinib in 19 patients who were not on thyroid replacement and did not have a thyroid-related AE. Most of

these 19 had an elevated TSH during treatment. Six of the 19 had an elevated TSH and 1 a low TSH > 6 weeks after discontinuation of sunitinib.

Summary

S-TRAC was a randomized, international trial that demonstrated a statistically significant increase in DFS on the sunitinib arm when compared to placebo (median DFS: 6.8 years vs 5.6 years, HR 0.76 [95% CI: 0.59, 0.98]; p = 0.03) in patients with high-risk, clear cell renal cancer in the adjuvant setting. All patients initiated dosing with sunitinib/placebo 50 mg on the 4/2 schedule. The Investigator-assessed DFS analysis and several sensitivity and exploratory analyses have been conducted as described in this document, and they all show an observed improvement in DFS on sunitinib. Overall survival was similar on the two arms [HR: 0.92 (95% CI: 0.66, 1.28)] with approximately 23% events. A substantial number of patients with recurrent disease did not receive antineoplastic therapy within the 8 month follow-up period.

On S-TRAC, 45% of patients discontinued treatment on the sunitinib arm; 30% due to adverse reactions. Dose interruption and/or reduction was required in 60% of those on sunitinib. No new adverse reactions were identified for sunitinib. With the exception of PPE, adverse reactions were less frequent in the adjuvant setting compared to the metastatic setting. There is little information on long-term adverse reactions to adjuvant therapy with sunitinib.

ASSURE was a randomized, cooperative group trial conducted mostly in the US in patients with RCC who were at a lower risk for disease recurrence than those enrolled in the S-TRAC trial. Dosing was initiated with sunitinib 50 mg in 70% and sunitinib 37.5 mg in 30% of patients. Both doses were administered on the 4/2 schedule. No difference was reported for DFS on the sunitinib arm compared to placebo (HR: 1.02 [97.5% CI: 0.85, 1.23]) in the adjuvant setting. The analysis of OS found a HR of 1.17 (97.5% CI: 0.90, 1.52). In a post hoc exploratory analysis on a subgroup of patients similar to those enrolled on S-TRAC, there was no improvement in DFS with the use of sunitinib.

The FDA review is ongoing and further/updated analyses may be presented at the ODAC meeting.

5. Issues for the Committee

- Has an improvement in DFS been demonstrated in the S-TRAC trial?
- Can results from S-TRAC be explained in the context of the other adjuvant trials with sunitinib in RCC?
- Is disease-free survival as defined in S-TRAC a clinically relevant endpoint?

Appendix I: TNM Staging

AJCC Staging System for Renal Carcinoma by Year of Initiation			
	1997	2002	2009
Tumor			
TX	Cannot be assessed	Cannot be assessed	Cannot be assessed
T0	No evidence of tumor	No evidence of tumor	No evidence of tumor
T1	≤ 7 cm, limited to kidney		
T1a		≤ 4 cm, limited to kidney	≤ 4 cm, limited to kidney
T1b		> 4 - ≤ 7 cm, limited to kidney	> 4 - ≤ 7 cm, limited to kidney
T2	> 7 cm, limited to kidney	> 7 cm, limited to kidney	
T2a			> 7 - ≤ 10 cm, limited to kidney
T2b			> 10 cm, limited to kidney
T3			
T3a	Adrenal or perinephric tissue Not beyond Gerota's fascia	Perirenal or renal sinus fat or adrenal extension	Renal vein or segmental branches or perirenal and/or renal sinus fat Not beyond Gerota's fascia
T3b	Grossly extends into renal veins or vena cava below the diaphragm	Renal vein or vena cava below the diaphragm	Grossly extends into vena cava below the diaphragm
T3c	Grossly extends into vena cava above the diaphragm	Vena cava above diaphragm	Grossly extends into vena cava above the diaphragm or invades the wall of the vena cava
T4	Beyond Gerota's fascia	Beyond Gerota's fascia	Beyond Gerota's fascia Includes contiguous adrenal
Node			
NX	Cannot be assessed	Cannot be assessed	Cannot be assessed
N0	No regional node metastases	No regional nodal metastases	No regional nodal metastases
N1	Single regional node	Single regional node	Single regional node
N2	> 1 regional mode	> 1 regional node	> 1 regional node
Metastases			
MX	Cannot be assessed	Cannot be assessed	Cannot be assessed
M0	No distant metastases	No distant metastases	No distant metastases
M1	Distant metastases	Distant metastases	Distant metastases

Stage	1997	2002	2009
III	T1-2N1M0 T3N0-1M0	T1-2N1M0 T3N0-1M0	T1-2N1M0 T3N0-1M0
IV	T4N0-1M0 TanyN2 M0 TanyNanyM1	T4N0-1M0 TanyN2M0 TanyNanyM1	T4NanyM0 TanyNanyM1

Appendix II: Definition of Disease Recurrence

The requirement for enlargement on serial scans prior to the determination of disease recurrence is at the discretion of the radiologist.

S-TRAC Independent Review Committee Charter
Local Relapse
• Lesions in the renal bed consistent with renal cell carcinoma and not consistent with post-surgical and or inflammatory changes • Invasion of the renal vein or inferior vena cava • Locoregional lymph node ≥ 1.5 cm in long axis
Metastatic Relapse
• Most non-cystic, non-calcified lesions of the chest or abdomen • Pulmonary nodules ≤ 1 cm o > 3 non-calcified pulmonary nodules all > 0.8 cm in long axis o Must have a definite soft tissue component • Pulmonary nodules > 1 cm • Pleural effusion with a soft tissue mass or an enhancing rim • Multiple, enlarging soft tissue masses in the liver; not compatible with benign process • Progressively enlarging solid mass(es), solid subcutaneous mass(es) or lymph nodes • Ureteral obstruction with soft tissue mass • Most bone lesions; Supportive images should be considered o Not a focus of uptake in anterior rib/ costochondral junction o Not focal distal uptake o Not consistent with a benign condition o Not a single focus of uptake in the spine (without confirmation on additional imaging) o Not consistent with stress fractures o Not a single focus in the proximal femur or humerus (without confirmation) o Not focus of uptake in sternum or clavicle (without confirmation) • Most brain lesions • Ascites • Most adrenal lesions; not contralateral hyperplasia of the adrenal gland

S-TRAC Investigator Radiology Review
Investigators could determine that the patient had recurrent disease by biopsy or by the following changes on scan: 1) Lung lesions consistent with metastases, 2) Multiple and enlarging liver lesions, 3) Enlarging solid mass or lymph node(s), 4) Urinary obstruction by a soft tissue mass, 5) Bone lesions with confirmatory imaging or biopsy required in some instances, or 6) Brain lesion(s).

ASSURE Investigator Radiology Review
The protocol recommended that disease recurrence be proven by biopsy when possible. Evidence of disease recurrence on scan was defined as: 1) Multiple lung lesions consistent with metastases, 2) Enlargement on 2 images ≥ 4 week apart of multiple liver defects, a subcutaneous/ soft tissue mass, lymph nodes, or a lesion(s) in the renal bed, 3) Diagnosis of a malignant pleural

effusion or ascites required cytology/histology, 4) Brain lesion(s), or 5) Multiple bone scan lesions; single or equivocal lesions-additional imaging or biopsy.

Appendix III: Grouped Preferred Terms

Adverse events can be broken down into multiple similar preferred terms (e.g., hypertension and blood pressure increased). To obtain a more accurate incidence of some adverse events, the preferred terms are groups. The groupings used in this document are listed below.

Term Used	Preferred Terms Grouped Under this Term
Abdominal pain	Abdominal discomfort or pain, abdominal pain lower or upper, gastrointestinal pain
Diarrhea	Colitis, diarrhea
Dysgeusia	Ageusia, dysgeusia
Dyspepsia	Dyspepsia, GE reflux disease
Ejection fraction decreased	Ejection fraction decreased, left ventricular dysfunction, left ventricular systolic dysfunction
Fatigue	Fatigue, asthenia, malaise
Hemorrhage	Anal hemorrhage, epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhagic gastritis, rectal hemorrhage, upper gastrointestinal hemorrhage
Hepatotoxicity	Abnormal liver function, acute hepatitis, elevated AST, hypertransaminasemia, transaminase high
Hypertension	Blood pressure increased, blood pressure systolic increased, blood pressure diastolic increased, hypertension, hypertensive crisis
Hyperthyroidism	Blood TSH decreased, hyperthyroidism
Hypothyroidism	Blood TSH increased, hypothyroidism
Mucositis	Aphthous ulcer, gingival ulceration glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal edema, mucosal inflammation, mucositis, mucositis-anus, oral discomfort, oral disorder, oral mucosal blistering, oral mucosal erythema, oral pain, oral toxicity, oropharyngeal pain, sore tongue, stomatitis, tongue discomfort, tongue disorder, tongue ulceration
Neutropenia	Neutropenia, neutrophil count decreased, neutrophil count
Palmar-plantar erythrodysesthesia (PPE)	PPE, palmar erythema, plantar erythema, erythema (involving hand or foot), skin exfoliation (desquamation of palm or foot, hands or fingers peeling)
Rash	Acne, dermatitis, eczema, erythema (not of palms or soles), erythema multiforme, exfoliative rash (not of palms or soles), rash, erythematous, follicular, generalized, macular, maculo-papular, and papular rash, genital rash, seborrheic dermatitis, skin exfoliation (if includes rash, redness, flakiness and does not involve the palms or soles)
Renal Impairment	Acute renal failure, creatinine increased, high creatinine,

	hypercreatininemia, nephrotic syndrome
Thrombocytopenia	Thrombocytopenia, platelet count decreased

Appendix IV: Abbreviations

Abbreviation	Complete Name
AE	Adverse event
ASSURE	Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Cell Carcinoma
CI	Confidence interval
DFS	Disease-free survival
ECOG-ACRIN	Eastern Cooperative Oncology Group-American College of Radiology Imaging Network
EF	Ejection fraction
EKG	Electrocardiogram
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30
EOT	End of treatment
EQ-5D	European Quality of Life-5 Dimensions
HR	Hazard ratio
IRC	Independent Radiology Committee
MUGA/Echo	Multiple gated acquisition scan/echocardiogram of the heart
ODAC	Oncologic Drugs Advisory Committee
OS	Overall survival
PPE	Palmar-plantar erythrodysestheia
PROTECT	A Randomized, Double-blind, Placebo-controlled Phase III Study to Evaluate the Efficacy and Safety of Pazopanib as Adjuvant Therapy for Subjects With Localized or Locally Advanced RCC Following Nephrectomy
PS	Performance status
PSA	Prostate specific antigen
q	Every
RCC	Renal cell carcinoma
SAE	Serious adverse event
S-TRAC	Sunitinib Treatment of Renal Adjuvant Cancer: A Randomized Double-blind Phase 3 study of Adjuvant Sunitinib vs. Placebo in Subjects at High Risk of Recurrent Renal Cell Carcinoma
TNM	Tumor, node, metastasis staging system
UISS	University of California Los Angeles Integrated Staging System
US	United States
VEGF/VEGFR	Vascular endothelial growth factor/Vascular endothelial growth factor receptor
X	Times