22 February 2018
EMA/CHMP/481973/2018
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Sutent

International non-proprietary name: sunitinib

Procedure No. EMEA/H/C/000687/II/0065

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACRIN	American College of Radiology Imaging Network
AE	Adverse Event
ALT	Alanine aminotransferase
ASSURE	Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BICR	Blinded Independent Central Review
BMI	Body-Mass Index
CI	Confidence Interval
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-Free Survival
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eNOS	Endothelial nitric oxide synthase
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQol-5 Dimensions questionnaire
EQ-VAS	EuroQol-Visual Analogue Scale
FDA	Food and Drug Administration
GIST	Gastrointestinal stromal tumour
HR	Hazard Ratio
IHC	Immunohistochemistry
ITT	Intent-to-Treat
LSFV	Last subject first visit
LVEF	Left ventricular ejection fraction
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
mRCC	Metastatic Renal Cell Carcinoma
NCI	National Cancer Institute
NDA	New Drug Application
NR	Not reached
PEP	Pharmacogenomic Evaluable Population
PPE	Palmar-plantar erythrodysesthesia syndrome
PRO	Patient reported outcomes
PS	Performance Status
PT	Preferred Term
QLQ	Quality of life questionnaire
QoL	Quality of Life
RCC	Renal cell carcinoma
RTK	Receptor tyrosine kinase
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SNP	Single nucleotide polymorphism
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TNM	Tumour, Nodes, Metastases
UISS	University of California Los Angeles Integrated Staging System
VEGF	Vascular endothelial growth factor
VEGFA	Vascular endothelial growth factor A
VEGFR	Vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Limited submitted to the European Medicines Agency on 16 March 2017 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include adjuvant treatment of patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy for Sutent; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated based on the study A6181109 (a randomized double-blind phase 3 study of adjuvant sunitinib vs. placebo in subjects at high risk of recurrent RCC). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the SmPC and Package Leaflet and in addition, to fulfil PAM (FU2 22.5). Furthermore, the PI is brought in line with the latest QRD template version 10. Moreover, updated RMP version 16 has been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Melchiorri Co-Rapporteur: Sinan B. Sarac

Timetable	Actual dates
Submission date	16 March 2017
Start of procedure	22 April 2017
CHMP Rapporteur's preliminary assessment report circulated on	16 June 2017
CHMP Co- Rapporteur's preliminary assessment report circulated on	19 June 2017
PRAC Rapporteur's preliminary assessment report circulated on	23 June 2017
PRAC Rapporteur's updated assessment report circulated on	29 June 2017
PRAC RMP advice and assessment overview adopted by PRAC on	6 July 2017
CHMP Rapporteurs' updated (joint) assessment report circulated on	13 July 2017
Request for supplementary information and extension of timetable adopted by the CHMP on	20 July 2017
The CHMP adopted a report on similarity of Sutent with Torisel on (Appendix 1)	20 July 2017
MAH's responses submitted to the CHMP on	7 September 2017
CHMP Rapporteurs' preliminary (joint) assessment report on the MAH's responses circulated on	10 October 2017
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	13 October 2017
CHMP Rapporteurs' updated (joint) assessment report on the MAH's responses circulated on	3 November 2017
Request for supplementary information and extension of timetable adopted by the CHMP on	9 November 2017
MAH's responses submitted to the CHMP on	21 December 2017
CHMP Rapporteurs' preliminary (joint) assessment report on the MAH's responses circulated on	24 January 2018
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	26 January 2018
PRAC RMP advice and assessment overview adopted by PRAC on	8 February 2018
CHMP Rapporteurs' updated (joint) assessment report on the MAH's responses circulated on	14 February 2018
An Oral explanation took place on	20 February 2018
CHMP opinion	22 February 2018

2. Scientific discussion

2.1. Introduction

Sunitinib is an oral, multi-targeted tyrosine kinase inhibitor (TKI) that targets and blocks the signalling pathways of multiple selected receptor tyrosine kinases (RTKs) that are implicated in tumour growth, neoangiogenesis, and metastatic progression of cancer. Through competitive inhibition ATP binding site, sunitinib inhibits the TK activity of a group of closely related RTKs, including VEGFR1, VEGFR2 and VEGFR3, PDGFRα and PDGFRβ, stem cell factor receptor (KIT), CSF-1R, FLT-3, and RET.

Sutent is currently approved for metastatic renal cell carcinoma, gastrointestinal stromal tumour (GIST) and for pancreatic neuroendocrine tumour (pNET).

Renal cell carcinoma (RCC) denotes cancer originated from the renal tubular epithelium. RCC accounts for about 90% of kidney cancer, and represents 2-3% of all cancer, presenting twice as common in men than women, with a median age of 61 years at diagnosis. RCC incidence varies across Europe, with the highest rate in Eastern countries (22.1/100,000 men and 9.9/100,000 women in Czech Republic) and lower in southern countries. RCC incidence has been increased over time, partly due to the widespread use of non-invasive radiological techniques leading to incidental diagnosis and downward shift of tumour stage and size. Well established risk factors for RCC are cigarette smoking, obesity and hypertension. Hereditary syndromes account for 3-5% of all RCC, most commonly presenting at younger age (< 45 years).

Approximately 80% of RCC are clear cell tumour (ccRCC). Recent genomic studies have revealed complex intra- and inter-tumour heterogeneity, which could contribute to the heterogeneous clinical outcome observed. VHL tumour suppressor gene is the most frequently mutated in ccRCC, involved in angiogenesis, glycolisis and apoptosis. Accordingly, ccRCC are highly vascular, and agents primarily inhibiting VEGF pathway are effective treatment for metastatic RCC.

Up to 70% of RCC are diagnosed when the disease is localized (Stages I-III). Surgical resection is the treatment of choice and the only curative therapy, including radical or partial nephrectomy. Staging according with TNM classification, grade, histological subtype, tumour size as well as patient performance status are known to be the predictor of oncological outcome after surgical treatment, with 10-50% of patients experiencing disease recurrence or progression depending on the individual risk profile. Different pre- and postoperative scores have been applied to assess prognosis in RCC. Integrated prognostic scores, composed of histological and clinical factors, offer some predictive advantages over single tumour characteristics and are used preferentially. The most recent modifications of the stage, size, grade and necrosis (SSIGN) score and the University of California Los Angeles Integrated Staging System (UISS) score are frequently used. ESMO guidelines (2016) are not giving clear preference for a specific prognostic model. More recently, molecular profiling and multigene assays have been also developed to provide prognostic information in addition to the traditional clinical and histological factors. However, as of today, no specific molecular marker can be recommended for clinical use (ESMO guidelines, 2016).

There are currently no approved adjuvant treatments for RCC and observation remains the standard of care after nephrectomy. Trials with IL-2 and IFN-α, as well as chemotherapy or other novel agents as adjuvant treatment, have been largely negative.

In an effort to transpose into the adjuvant setting the targeted agents which demonstrated to be active in the metastatic disease, several large phase III trials have been initiated (see table 1 below):

Trial (sponsor)	Treatment	N	Primary endpoint	Eligibility	Results
ASSURE (ECOG-ACRIN) Haas NB et al. (2016)	Sunitinib 50 mg/d 4/2 for 1 year* (decreased to 37.5 mg) or Sorafenib 400 mg/bid for 1 year* vs. placebo	1943	DFS (inv)	-clear and non-clear cell - pT1b G3-4 N0 M0 - pT2-3-4 N0 M0 -any T N+ M0	DFS (sunitinib vs. placebo) HR 1.02; 97.5% CI 0.85-1.23; p = 0.8 DFS (sorafenib vs. placebo) HR 0.97; 97.5% CI 0.80-1.17; p = 0.718
ATLAS[2] (Pfizer) Kwon TG et al. (2014)	Axitinib 5 mg bid for 3 years vs. placebo	692	DFS (indip)	- clear cell - pT2-3-4 N0 M0 - any T N+ M0	ongoing
EVEREST (SWOG) NCT01120249	Everolimus 10 mg/d for 1 year *vs.* placebo	1545	DFS	-clear and non-clear cell - pT1b G3-4 N0 M0 - pT2-4 N0 M0 - any T N+ M0	ongoing
PROTECT (Novartis) Moetzer RJ et al, (2017)	Pazopanib 800 mg/bid for 1 year** vs. placebo	1538	DFS**	- clear cell - pT2-3-4 N0 M0 - any T N+ M0	DFS (ITT PAZ 600): HR 0.862; 95% CI 0.699- 1.063; p = 0.165
SORCE (MRC) NCT00492258	Sorafenib 400 mg/bid for 1 year or Sorafenib 400 mg/bid for 3 years vs. placebo	1656	DFS	-clear and non-clear cell -intermediate or high risk (Leibovich score)	ongoing
S-TRAC[6] (Pfizer) Ravaud A et al. 2016	Sunitinib 50 mg/d 4/2 for 1 year vs. placebo	610	DFS (indip)	- clear cell - pT3-4 N0 M0 - any T N+ M0	DFS: HR 0.761; 95%CI 0.594, 0.975; p = 0.030

With regard to the trial of TKIs reported so far in the adjuvant RCC setting, ASSURE study did not demonstrated benefit from the use of sorafenib nor sunitinib. Pazopanib did not demonstrated statistical significant improvement in DFS at 600 mg dose in PROTECT trial. However, the secondary endpoints of DFS in pazopanib 800 mg ITT population and DFS in all patients yielded 31% and 20% risk reduction, respectively. In both PROTECT and ASSURE studies, TKIs starting dose of was lowered in order to improve tolerability of the drugs. S-TRAC is the pivotal trial supporting Sutent in the adjuvant setting in this application.

Adjuvant studies with immune checkpoint blockade are currently ongoing, expected to be completed toward 2022-2024 (data from Clinicaltrial.gov). The anti-PD1 pembrolizumab and the anti-PDL1 atezolizumab are evaluated as adjuvant treatment vs. placebo in KEYNOTE-546 (NCT03142334) and in IMmotion010 (NCT03024996) trials, respectively. Perioperative anti-PD1 nivolumab is tested in PROSPER trial vs. observation.

The MAH applied for the following extension of indication:

“Sutent is indicated for the adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy (see section 5.1)”.

2.2. Non-clinical aspects

No new non-clinical data (with the exception of a revised ERA) have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Introduction

A new Environmental Risk Assessment (ERA) is submitted as part of the Type II variation to extend the indication for SUTENT, for the adjuvant treatment of patients at high risk of recurrence of renal cell carcinoma (RCC) following nephrectomy.

ERA data coming from the first MAA demonstrate that, based on the estimated value of predicted environmental concentration (PEC surface water) for SUTENT of 0.38 µg/L phase II Environmental Effect Analysis has been performed. Both the PEC and the revised PEC are approximately 2 orders of magnitude lower than the lowest no observed effect concentration (NOEC) determined under the test conditions for various species tested. The PEC/PNEC surface water is determined to be 0.04. Therefore, SUTENT does not present an environmental risk following patient use.

2.2.2. Ecotoxicity / environmental risk assessment

Phase I: ENVIRONMENTAL EXPOSURE ASSESSMENT

Screening for Persistence, Bioaccumulation and Toxicity (PBT)

As Sunitinib is a ionisable compound, logD has been calculated and was shown to be < 4.5 at all environmentally relevant pHs. The log Kow was determined experimentally at pH 5, 7 and 9.

Calculation of the Predicted Environmental Concentration in Surface Water (PECsw)

Fpen Refinement

The refined Fpen value was determined based on the prevalence of RCC, with the defined posology taken into consideration assuming the worst case treatment scenario, as per ERA Q&A (EMA/CHMP/SWP/44609/2010 Rev. 1); the following equation is applied:

$$Fpen_{refined} = P_{region} \times \frac{(t_{treatment} \times n_{treatment})}{N_d}$$

Where:
P_{region} = 5-year prevalence (renal cancer) in the Czech Republic [106.5/100,000] (GLOBOCAN 2012)
$t_{treatment}$ = Duration of one treatment period [4 weeks x 7 days = 28 days]
$n_{treatment}$ = No. treatments per year [365 days year^{-1} / 42 days = 8.7 year^{-1}]
N_d = No. of days per year [365 days year^{-1}]

$$Fpen_{refined} = \frac{106.5}{100,000} \times \frac{(28 \times 8.7)}{365}$$

$$Fpen_{refined} = 0.00071$$

The PECsw based on prevalence data therefore is:

$$PECsw\,[mg/L] = \frac{DOSEai \times Fpen}{WASTEWinhab \times Dilution}$$

PECSW	Predicted environmental concentration in surface water	-- mg/L
DOSEai	Maximum daily dose consumed per inhabitant	50 mg/(inh·d)*
Fpen	Market penetration	0.00071
WASTEWinhab	Amount of wastewater per inhabitant per day	200 L/(inh·d) [Default]
DILUTION	Dilution factor	10 [Default]

*Maximum daily dose for all indications, including those previously approved as well as the indication for which approval is currently being sought (See Response to Question 4).

PECsw	Predicted environmental concentration in surface water	-- mg/L
DOSEai	Maximum daily dose consumed per inhabitant	50 mg/(inh·d)
Fpen	Market penetration	0.00071
WASTEWinhab	Amount of wastewater per inhabitant per day	200 L/(inh·d) [Default]
DILUTION	Dilution factor	10 [Default]

$$PECsw = \frac{50\,mg/(inh \cdot d) \times 0.00071}{}$$

$$PECsw = \frac{50\,mg/(inh \cdot d) \times 0.00071}{200\,L/(inh \cdot d) \times 10}$$

$$PECsw = 1.8 \times 10^{-5}\,mg/L = 0.018\,\mu g/L$$

The Fpen value was determined based on the highest per capita consumption in 2016 of 4.44 kg in Slovakia (IMS Health) and the maximum daily dose of 50 mg, using the following equation:

$$Fpen_{refined}\,[\%] = \frac{Consumption\,[mg \cdot year^{-1}] \times 100}{Daily\,dose\,[mg \cdot day^{-1} \cdot inhab] \times inhhab \times 365\,day \cdot year^{-1}}$$

Where:
Consumption = 4.44 kg = 4.44 x 10^6 mg
Daily dose = 50 mg/day
Inhabitants = 5,429,000 (total population, Slovakia, 2016)

Fpen = 0.0045% = 0.000045; therefore, PECsw based on approved indications = 0.0011 µg/L

PECsw based on use in new patients upon approval of Sutent for RCC = 0.018 µg/L

Total PECsw based on current consumption and estimated use in new patients upon approval of Sutent for RCC = 2.0 x 10-5 mg/L = 0.02 µg/L.

The PEC/PNEC Risk Quotient Summary is as shown below:

PEC/PNEC Risk Quotient Summary

	PEC/PNEC	Action Criteria	Outcome
Surface Water	7.4 x 10^{-3}	PEC/PNEC < 1.0	No further testing required
Ground Water	1.6 x 10^{-4}	PEC/PNEC < 1.0	No further testing required
Microorganisms	1.0 x 10^{-4}	PEC/PNEC < 0.1	No further testing required
Sediment	0.1	PEC/PNEC < 1.0	No further testing required

PHASE II TIER A: PHYSICAL-CHEMICAL PROPERTIES, ENVIRONMENTAL FATE AND EFFECTS ANALYSIS

Data coming from Phase II Tier A studies are shown below:

Sludge, Sediment and Soil Adsorption Coefficients

Sorption (OECD 106)[8]	K_d	K_{oc}
Sludge Sorption Coefficient		
Activated Sludge, Wareham WWTF, MA	1340	5700
Soil Sorption Coefficient		
Mutchler sandy loam	7820	412,000
Roger Myron loamy sand	5290	481,000
Ostlie East sandy clay loam	6670	185,000
Don Uglem loam	13,700	327,000
Valley Montana clay	7260	660,000
Geometric mean:	*7721*	*380,000*
WWTF = Wastewater Treatment Facility		

Environmental Fate

Study	Results	
Ready Biodegradation – 28 days[9]	Average cumulative biodegradation – 8.8% (CO_2 evolution)	
Sludge Die Away – 28 day sludge biodegradation[10]	Ultimate biodegradation (CO_2 evolution) 23.1% in 28 days 34.6% remaining with solids at Day 28 Loss of parent DT_{50} is 69 hours Elimination rate constant K_e 0.010 hrs^{-1}	
Photo-degradation in Water[11]	Environmental photolytic half-life ($t_{1/2}$)	pH 5 = 1.58 days
		pH 7 = 1.15 days
		pH 9 = 0.52 days
Aerobic Transformation in Aquatic-Sediment (OECD 308)[12]	Mineralization 3.9 – 6.7% over 100 days	
	Aqueous dissipation rate: 7.5 – 7.7 days (DT_{50} water)[a]	
	Sediment disappearance rate: 118 – 169 days (DT_{50} sediment)[a,b]	
	Total system disappearance: 11.4 – 11.8 days (DT_{50} total system)[a]	

[a] Kinetic results obtained from CAKE re-analysis of OECD 308 study data.
[b] Extrapolated beyond the 100 day study duration.

Aquatic Effects

Species	Exposure	L(E)C_{50} mg a.i./L	NOEC mg a.i./L
Acute			
Daphnids[15] *(Daphnia magna)*	48 hour OECD 202	3.1	1.4
Rainbow trout[16] *(Oncorhynchus mykiss)*	96 hour OECD 203	7.8	3.8
Chronic			
Green Alga[17] *(Pseudokirchneriella subcapitata)*	72 hour OECD 201	0.17 (biomass)	0.046 (biomass)
		0.32 (growth rate)	0.10 (growth rate)
		LOEC mg a.i./L	**NOEC mg a.i./L**
Daphnids[18] *(Ceriodaphnia dubia)*	7 day Survival and Reproduction EPA 1002.0	0.66 (reproduction)	0.32 (reproduction)*
Fathead Minnow[19] *(Pimephales promelas)*	Early lifecycle OCED 210	0.049 (growth)	0.027 (growth)**

*NOEC used to calculate $PNEC_{groundwater}$ and ** NOEC used to calculate $PNEC_{surfacewater;}$

Recalculation of the PECsw to account for total use of sunitinib resulted in revised PEC/PNEC values for surface water (0.0074), groundwater (0.00016), micro-organisms (0.0001) and sediment (0.1), all of which are below the respective action limits. Therefore sunitinib will not present an environmental risk to aquatic organisms following patient use. The extrapolated DT_{50} of 167 days in the Choptank River (loamy sand sediment) and 118 days in the Brandywine Creek (silt loam sediment), indicate that sunitinib may be considered persistent in some sediment compartments.

Phase II tier A was conducted in line with the requirements set forth by ERA Guideline. With regards to the long term toxicity test carried out on daphnia, a 48 hour test on Daphnia magna (OECD 202) and a

7 day survival and reproduction test on Ceriodaphnia dubia (EPA 1002.0) have been conducted instead of the 21-day reproduction test on Daphnia sp. (OECD 211) required by ERA guideline.

Considering the PEC/PNECgroundwater derived using the *C.dubia* NOEC is 0.00016, it is unlikely *D.magna* would be several orders of magnitude more sensitive to sunitinib than *C.dubia*, thereby supporting a PEC/PNECgw risk ratio less than the action limit of 1. In addition, as the fathead minnow was determined to be the most sensitive species, the PNECsurfacewater was calculated using the NOEC for fathead minnow. Therefore, it is unlikely that any further evaluation of chronic toxicity using *D.magna* would alter the overall outcome of the ERA.

Recalculation of the PECsw to account for total use of sunitinib resulted in revised PEC/PNEC values for surface water (0.0074), groundwater (0.00016), micro-organisms (0.0001) and sediment (0.1), all of which are below the respective action limits. Therefore it may be concluded that sunitinib will not present an environmental risk to aquatic organisms following patient use in the proposed indication.

2.2.3. Discussion on non-clinical aspects

No new non-clinical data have been submitted for this application with the exception of additional ERA studies.

Human metabolism and excretion profile of sunitinib has been evaluated in the original MAA. Following oral administration of [14C] labeled drug, the mean cumulative recovery was about 77% of the radioactive dose over 21 days, with approximately 16% of the dose recovered in urine and 61% in the feces. Approximately 62% of the dose is excreted, 20% as unchanged drug and 42% as metabolites. Once in the wastewater treatment facility, sunitinib will undergo primary and ultimate degradation. Sunitinib will also sorb to sludge solids, resulting in approximately 18% removal on wasted sludge based on a sludge sorption coefficient (K_d) of 1340. Exposure to the terrestrial compartment as a result of sludge application to land is not a concern. Sunitinib is hence considered the primary entity released into the environment following patient use.

As sunitinib is a ionisable compound, logD has been calculated in accordance with the ERA Q&A guideline and was shown to be < 4.5 at all environmentally relevant pHs, leading to the conclusion that Screening for PBT is not required. The refined Fpen value was determined based on the prevalence of RCC, with the defined posology taken into consideration assuming the worst case treatment scenario. Accounting for the consumption of sunitinib for the adjuvant treatment of RCC recurrence following nephrectomy, prevalence data obtained from GLOBOCAN (2012) shows that the highest 5-year prevalence of renal cancer (106.5 per 100,000 population) is reported for the Czech Republic. A PECsw value based on prevalence data was therefore extrapolated (0.018 µg/L). PECsw values have been calculated, which take into consideration both the approved indication and the one for which the variation is sought. The results clearly indicate that sunitinib is unlikely to represent a risk to the aquatic environment, groundwater, microorganisms and sediment, with no further testing required. The chronic aquatic effects of sunitinib were assessed in green algae, fish and daphnids. Sunitinib may be considered persistent in some sediment compartments, in light of the DT_{50} values extrapolated. The extrapolated DT_{50} of 167 days in the Choptank River (loamy sand sediment) and 118 days in the Brandywine Creek (silt loam sediment), indicate that sunitinib may be considered persistent in some sediment compartments.

Considering the PEC/PNECgroundwater derived using the *C.dubia* NOEC is 0.00016, it is unlikely *D.magna* would be several orders of magnitude more sensitive to sunitinib than *C.dubia*, thereby supporting a PEC/PNECgw risk ratio less than the action limit of 1. In addition, as the fathead minnow was determined to be the most sensitive species, the PNECsurfacewater was calculated using the

NOEC for fathead minnow. Therefore, it is unlikely that any further evaluation of chronic toxicity using *D.magna* would alter the overall outcome of the ERA. Recalculation of the PECsw to account for total use of sunitinib resulted in revised PEC/PNEC values for surface water (0.0074), groundwater (0.00016), micro-organisms (0.0001) and sediment (0.1), all of which are below the respective action limits. Therefore it may be concluded that sunitinib will not present an environmental risk to aquatic organisms following patient use in the proposed indication.

2.2.4. Conclusion on the non-clinical aspects

Considering the updated data submitted in this application the use of sunitinib in the proposed indication would not lead to a significant increase in environmental exposure.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

- The final bioconcentration potential evaluation study report will be submitted in the context of a Type II variation.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2: overview of clinical studies

Study Number	Study Design and Objectives	Type of Subjects	Treatment Groups	Number of Subjects	Demographics	Duration of Treatment	Study Start/ Status	Study Reporting Status (Type of Report/ Location)
Study Reports of Controlled Clinical Studies								
A6181109 (Sunitinib Treatment of Renal Adjuvant Cancer [S-TRAC])	A prospective, randomized, double-blind, placebo-controlled Phase 3 trial of oral sunitinib at a dose of 50 mg once daily given on Schedule 4/2 (4 weeks on, 2 weeks off for) 1 year vs placebo **Primary Objective** - To demonstrate an improvement in disease-free survival in patients at high risk of disease recurrence with renal cell carcinoma (per modified University of California Los Angeles Integrated Staging System [UISS] criteria) randomly assigned to adjuvant sunitinib 50 mg once daily on Schedule 4/2 for 1 year (9 cycles) vs placebo after nephrectomy **Secondary Objectives** - Compare overall survival associated with sunitinib treatment to that associated with placebo treatment; - Assess safety/toxicity profile of Schedule 4/2 administration of sunitinib; - Assess patient reported outcomes; - Assess the UISS Prognostic Model	Patients at high risk of recurrent renal cell carcinoma after nephrectomy	Patients received blinded study drug: sunitinib (at a dose of 50 mg) or matching placebo once daily (Schedule 4/2)	**Sunitinib**: 309 randomized, 306 treated **Placebo**: 306 randomized, 304 treated	**Gender:** Sunitinib 87 female/ 222 male Placebo 77 female/ 229 male **Mean age in years (minimum/ maximum):** Sunitinib 56.8 (25-83) Placebo 57.9 (21-82) **Race:** Sunitinib 254 White 43 Asian 3 Black 9 Other Placebo 263 White 33 Asian 1 Black 9 Other	9 cycles or until disease recurrence, occurrence of a secondary malignancy, significant toxicity, or withdrawal of consent	First Subject First Visit: 19 September 2007 Study ongoing	Primary CSR (global cohort) (07 April 2016 cutoff) completed/ Module 5.3.5.1 A6181109 Study Synopsis
Other Study Reports								
E2805 (Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma [ASSURE])	A double-blind, placebo-controlled, randomized, Phase 3 trial of adjuvant sunitinib or sorafenib vs placebo after radical or partial nephrectomy. **Primary Objective** - To demonstrate an improvement in disease-free survival in patients with locally advanced renal cell carcinoma randomly assigned to adjuvant sunitinib or sorafenib vs placebo after radical or partial nephrectomy **Secondary Objectives** - To compare overall survival of patients randomized to each of the two regimens with placebo. - To further define the toxicity of prolonged administration of sunitinib or sorafenib in this patient population	Patients at risk of recurrent renal cell carcinoma	Patients received blinded study drug: Sunitinib taken orally at 50 mg per day for the first 28 days of each 6 week cycle, or sorafenib taken orally at 400 mg twice per day throughout all cycles, or placebo After observing a high rate of treatment discontinuation due to adverse events or patient refusal, the protocol was amended to institute a starting dose of sunitinib/placebo of 37.5 mg orally once daily and sorafenib/placebo of 400 mg orally once daily. If the patient experienced no toxicities of Grade 2 or higher, then the dose was escalated to the previous starting dose at the beginning of cycle 2 or 3	**Sunitinib:** 647 allocated to treatment, 629 received allocated treatment, 625 included in safety analysis **Sorafenib:** 649 allocated to treatment, 632 received allocated treatment, 628 included in safety analysis **Placebo:** 647 allocated to treatment, 633 received allocated treatment, 626 included in safety analysis	**Gender:** Sunitinib 218 female/ 429 male Sorafenib 212 female/ 437 male Placebo 204 female/ 443 male **Median age in years (interquartile range):** Sunitinib 56 (49–64) Sorafenib 55 (48–63) Placebo 57 (49–64) **Race:** Sunitinib	54 weeks (9 cycles)	Study activated: 24 April 2006 Study completed	CSR (reflecting the database as of 27 August 2015) completed/ Module 5.3.5.4 E2805 (ASSURE) Study Synopsis

					598 White 27 African-American 11 Asian 1 Hawaiian/ Pacific Island 2 Native American 8 Unknown/ Missing Sorafenib 589 White 27 African-American 17 Asian 4 Native American 1 Other 11 Unknown/ Missing Placebo 585 White 31 African-American 15 Asian 5 Native American 11 Unknown/ Missing			

2.4. Clinical efficacy

2.4.1. Dose response studies

No formal dose-response studies have been carried out for the adjuvant RCC indication.

2.4.2. Main study

Study Title: Sunitinib Treatment of Renal Adjuvant Cancer (S-TRAC): A Randomized Double Blind Phase 3 Study of Adjuvant Sunitinib vs. Placebo in Subjects at High Risk of Recurrent Renal Cell Carcinoma (RCC) - Protocol A6181109

Methods

Figure 1: study design

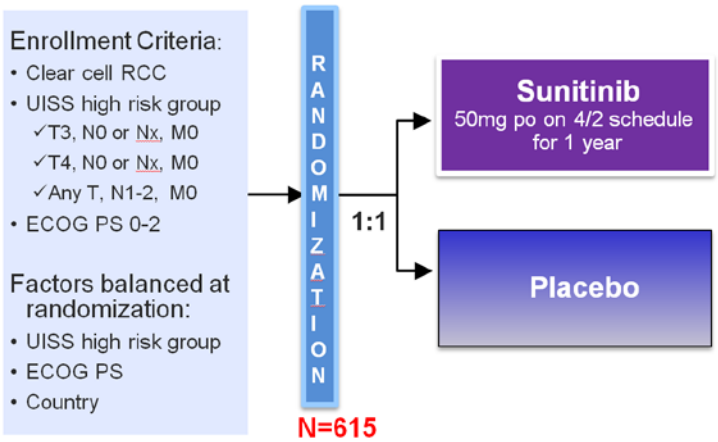
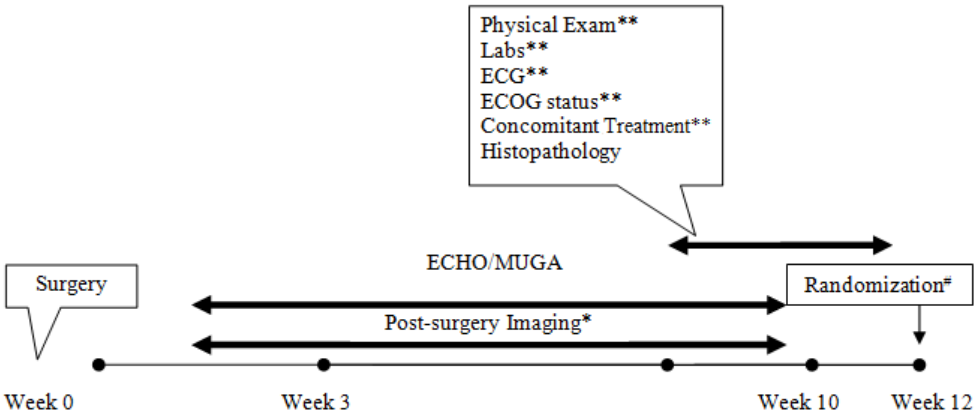


Figure 2: overview of screening procedures



Study participants

Main inclusion criteria were:

- Age ≥ 18 years
- ECOG PS 0 - 2 prior to nephrectomy
- Diagnosed utilizing the UISS staging system with one of the following:
    a. T3 N0 or Nx, M0, any Fuhrman's grade and any ECOG PS; or
    b. T4 N0 or Nx, M0, any Fuhrman's grade and any ECOG PS; or
    c. Any T, N1 2, M0, any Fuhrman's grade and any ECOG PS.
- Histologically confirmed preponderant, defined as >50%, clear cell RCC
- No evidence of macroscopic residual disease or metastatic disease. Patients having evidence of microscopic disease (histological classification of R1 disease) were acceptable
- No previous systemic (includes chemotherapeutic, hormonal or immunotherapeutic) treatment for RCC
- No previous anti-angiogenic treatment
- Adequate organs function. LVEF ≥ the lower limit of normal as assessed by either multigated acquisition (MUGA) scan or echocardiogram (ECHO)
- Used adequate contraception during the study

Main exclusion criteria:

- Histologically undifferentiated carcinomas, sarcomas, collecting duct carcinoma, lymphoma, or patients with any metastatic renal sites
- NCI-CTCAE Grade 3 haemorrhage <4 weeks of date of randomization
- Diagnosis of any second malignancy within the 5 years from 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

- Any of the following within the 6 months prior to study drug administration: severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, cerebrovascular accident, including transient ischemic attack, or pulmonary embolism
- Concurrent medication with known CYP3A4 inducers and potent inhibitors dosed 7 and 12 days before date of randomization, respectively
- Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2 or prolongation of the QTc interval to >500 msec
- Hypertension, defined as systolic >150 mmHg and/or diastolic >100 mmHg, that could not be controlled by medications
- Treatment with ≥2 mg of warfarin within 2 weeks prior to first day or concurrently with sunitinib administration was not recommended. Low-dose warfarin for DVT prophylaxis was permitted (<2 mg/day). Low-molecular weight heparin (fractionated) or aspirin were allowed
- Any illness that could have affected absorption
- Known HIV or AIDS-related illness. Known active or chronic active hepatitis B or C
- Pregnant or breastfeeding female patients; male patients with partners currently pregnant; male and female patients of childbearing potential who were unwilling or unable to use a highly effective method of contraception

Treatments

Patients received blinded study drug sunitinib 50 mg or matching placebo orally once daily (OD) for schedule 4/2 (4 weeks on, 2 weeks off) for 9 cycles (approximately 1 year). Subjects should begin protocol treatment on the date of randomization, which occurred no sooner than 3 weeks and no later than 12 weeks following nephrectomy.

Subjects requiring >6 weeks of dose interruption or dose reductions less than 37.5 mg (one dose level) should be considered for discontinuation from the study. Intra-patient re-escalation back to the previous dose level was permitted.

Subjects will be withdrawn from treatment in the case of: Disease recurrence or occurrence of a secondary malignancy; unacceptable toxicity; Need for anticancer therapy not specified in the protocol; congestive heart failure; noncompliance; lost to follow-up; choice to withdraw from treatment; withdrawal of consent (cessation of follow-up); completion of 1 year of sunitinib treatment.

Objectives

Primary objective:

- Demonstrate that adjuvant treatment with sunitinib is superior to placebo in prolonging disease-free survival (DFS) in patients with RCC at high risk of disease recurrence after nephrectomy (per modified University of California Los Angeles Integrated Staging System [UISS] criteria)

Secondary objectives:

- Compare overall survival (OS) associated with sunitinib treatment to that with placebo
- Assess safety/toxicity profile of Schedule 4/2 administration of sunitinib
- Assess patient-reported outcomes (PROs)
- Assess the UISS Prognostic Model

Outcomes/endpoints

Primary endpoint:

- DFS as assessed by BICR; defined as the time interval from randomization to the first date of recurrence (including relapse of the primary tumour in-situ or at metastatic site) or the occurrence of secondary malignancies or death.

Secondary endpoints:

- DFS as assessed by investigator
- OS - as defined as the time from date of randomization to date of death due to any cause.
- PROs - assessed using the EORTC QLQ-C30 and the EQ-5D questionnaires.
- AEs (graded by the CTCAE 3.0)

Exploratory biomarker analyses have also been submitted (see FUM 22.05 aimed at evaluating biomarkers predictive of safety and efficacy of sunitinib).

Sample size

Global Cohort

Based on initial assumptions, a total of 236 patients were to be enrolled, with the primary DFS analysis planned to occur when 101 events had occurred. Before Protocol Amendment #6 (June 2008), the patient population in this study was classified by modified UISS criteria into 3 risk group:

a. T3 N0 or NX, M0, Fuhrman's grade ≥2, ECOG ≥1; or

b. T4 N0 or NX, M0, any Fuhrman's grade, and any ECOG status; or

c. Any T, N1-2, M0, any Fuhrman's grade, and any ECOG status.

After Protocol Amendment #6, Group a. was extended to:

- T3 N0 or NX, M0, any Fuhrman's grade, and any ECOG status.

Sample size was then revised to account for the characteristics of the modified target population, and was determined based on the assumptions that time to DFS event follows an exponential distribution and on percentage of patients per risk groups as in table 3.

Table 3: Assumptions on the percentage of patients randomized from the 3 risk groups, 2-year DFS rates

Risk Groups	Percentage of patients	2-year DFS rate for placebo arm [7, 31*]	2-year DFS rate for sunitinib arm**
T3/N0 or NX/M0	90%	70%	78%
T4/N0 or NX/M0	1%	35%	60%
Any T/N1-2/M0	9%	33%	50%

* An important note, in the references the T3/N0 or NX/M0 risk group does not include ECOG=2 patients. However ECOG=2 patients will not be as common as ECOG 0 or 1 patients.

**2-year DFS rates for the sunitinib arm for the 3 risk groups are based on key opinion experts (personal communication with Global Steering Committee for A6181109) since no published data available on sunitinib treatment for RCC in the adjuvant setting.

According to the MAH, the assumptions of 2-year DFS rates for the placebo arm and sunitinib arm for the 3 risk groups are equivalent to the assumptions of hazard ratios to be 0.70, 0.49, and 0.63 for the 3 risk groups T3/N0 or NX/M0, T4/N0 or NX/M0, and Any T/N1-2/M0, respectively.

Based on the above assumptions and 1:1 randomization, the HR for the study population was estimated to be 0.69. A minimal number of 320 DFS events was required to detect this HR with 90% power at 2-sided significance level of 0.05. With a planned accrual period of 36 months, a minimum follow-up period of 60 months (5 years), it was estimated that 500 subjects would need to be enrolled. The sample size was calculated through simulation.

China cohort

120 subjects minimal will be randomized in China Cohort. The China cohort is NOT included in this submission, as it was added later to fulfill regulatory request of the Chinese Authority. All data and statistical analysis in the dossier are based on the Global cohort.

Randomisation

A centralized system was used to randomize patients at a 1:1 ratio to blinded sunitinib or placebo, from 3 to 12 weeks after nephrectomy and treatment should be started on the date of randomization. Subject eligibility was confirmed by BICR before randomization; minimization was to be used.

Stratification factors for Global Cohort were the following:

1. UISS high-risk group
    a. T3 N0 or NX, M0, Fuhrman's grade ≥2, and ECOG PS ≥1; or
    b. T3 N0 or NX, M0, any Fuhrman's grade and ECOG PS =0; or
    c. T3 N0 or NX, M0, Fuhrman's grade =1 and ECOG PS ≥1; or
    d. T4 N0 or NX, M0, any Fuhrman's grade, and any ECOG PS; or
    e. Any T, N1 2, M0, any Fuhrman's grade; and any ECOG PS.
2. ECOG PS (<2 versus 2).
3. Country

Blinding (masking)

This study was a double-blinded placebo-controlled study.

An external Data Monitoring Committee (DMC) had access to unblinded patient treatment assignment

information.

DFS primary analysis was based on independent blinded 3rd party review of tumour imaging (BICR).

Statistical methods

ITT population is the primary population for evaluating all efficacy endpoints as well as patient characteristics. The primary analysis for DFS was the comparison between treatment arms with a 2-sided log-rank test stratified by UISS high risk group.

Median DFS was estimated for each arm using Kaplan-Meier (KM) method. The corresponding 95% confidence intervals (CI) were estimated for each arm by Brookmeyer-Crowley method. The Cox regression model stratified by the factors used in the stratified log-rank test was used to estimate the treatment hazard ratio (Arm A/Arm B). The DFS rates at 2 years and 5 years were also estimated for each arm.

The study has two interim analyses and a final analysis for the primary endpoint. The first interim analysis (IA) was planned after 96 (30%) DFS events and the second IA after 192 (60%) DFS events. The aims of both IAs were: to allow early stopping of the study for futility, to assess safety, and to allow for sample size re-estimation applying the method outlined by Cui et al (1999) to preserve type I error. The O'Brien-Fleming stopping boundary was used. The nominal significance level for the final analysis on DFS was 0.0476 because of the two planned interim analyses. The same analysis for the primary endpoint was repeated based on investigator's assessment on DFS and on OS.

Tumour assessments were performed every 12 weeks for the first 3 years, then every 6 months thereafter until the time for final analysis, or recurrence of RCC or occurrence of a secondary malignancy, whichever came first. The assessment was made by an independent blinded 3rd party review (BICR).

Censoring rules for DFS were:

- Patients without a DFS event: DFS time was censored at the date of last disease assessment prior to the time for final analysis.
- Patients alive who did not have post-baseline disease assessment: DFS time was censored at randomization.
- Patients receiving further anticancer therapy prior to disease recurrence or occurrence of a secondary malignancy or death: DFS times were censored at the date of last disease assessment prior to taking the anti-tumour medication or cut-off date, whichever come first.
- DFS event occurred after missing 2 or more consecutive tumour assessments: DFS was censored at the date of last objective tumour assessment prior to the event.

Censoring rules for OS:

- In the absence of confirmation of death, survival time was censored at the last date the patient was known to be alive.
- Subjects lacking data beyond randomization have their survival times censored at Day 1.

PRO questionnaires were to be completed on Day 1 and approximately every 6 weeks thereafter until end of study treatment (i.e. up to 1 year), prior to having any tests or receiving any treatment on the day of that visit. For the 15 EORTC QLQ-C30 scales (global health status/QoL scale, 5 functional scales, 3 symptom scales, and 6 individual item scales) descriptive statistics were presented (means,

medians, standard deviations, and 95% CI at each assessment point). Comparisons between groups were based on a repeated measures analysis by a mixed effects model using the method of restricted maximum likelihood and assuming an unstructured covariance matrix. Analysis of the 2 EuroQoL components EQ-5D index and EQ-VAS (visual analog scale) used the same methods as described above for the 15 EORTC scales.

Table 4: Summary of SAP revisions

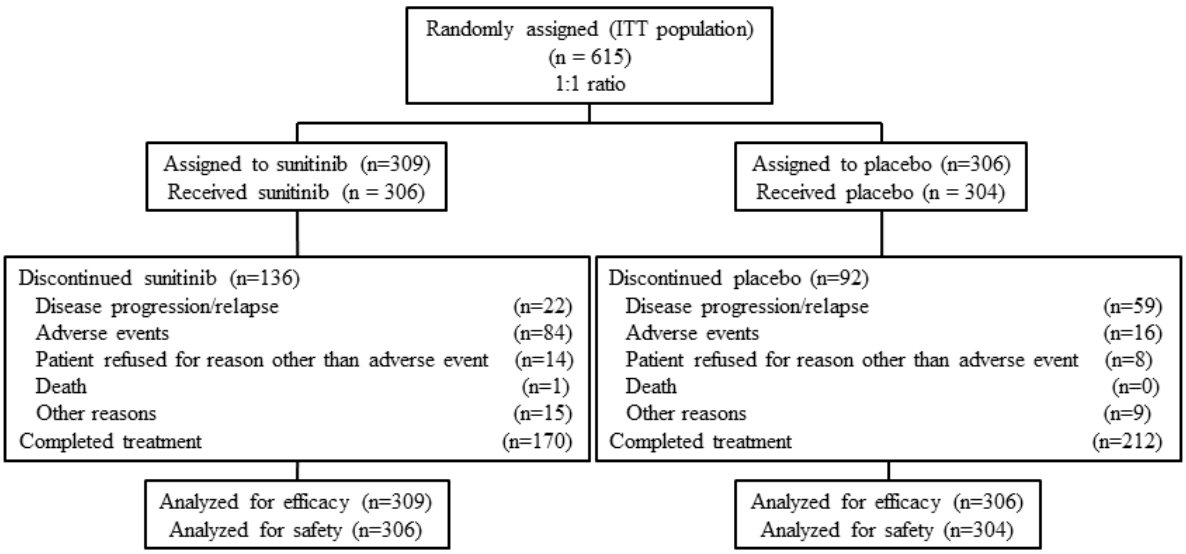
Version	Date	Summary of Changes/Comments
Version 1	Aug. 11, 2006	
Version 2	Jan. 31, 2007	Following changes are made to match the changes made in Protocol Amendment #1 (Jan. 29, 2007). 1) Removal of relapse-free survival (RFS) as a secondary parameter. 2) Conducting 2 interim analyses instead of 1 due to a FDA comment. 3) Change of assumptions for the sample size calculations due to updated information. 4) Disease free survival (DFS) based on independent 3rd party blinded review was identified as the primary parameter, and DFS based on investigator assessments as secondary.
Version 3	Aug. 20, 2009	1) Increase sample size from 101 DFS events (236 patients) to 320 DFS events (500 patients) due to extending the patient population following the Protocol Amendments #6 (June 20, 2008) and #7 (April 29, 2009). 2) Times of interim analyses have been changed accordingly. 3) For subjects receiving further anti-tumor therapy prior to disease recurrence or occurrence of a secondary malignancy or death, DFS will be censored on the date of the last tumor assessment prior to taking the anti-tumor medication. This change on definition of DFS, as the primary analysis, is made following the change made since Protocol Amendment #3 (July 25, 2007). 4) Add a supportive analysis to include all DFS events confirmed by independent third party review, regardless of other anti-tumor therapy. In the absence of DFS event, DFS time will be censored at the date of last disease assessment or cut-off date, whichever comes first. This analysis was the primary analysis on DFS in Version 2 of SAP. 5) Remove a sensitivity analysis on DFS when death occurs after 6 months from the last tumor assessment because this issue will be taken care of by Section 7 Handling of Missing Values.
Version 3.1	Oct. 18, 2010	1) Following Protocol Amendment #9, the follow up time for DFS and OS has been extended until the time for final analysis to collect more long term efficacy data. 2) Following Protocol Amendment #9, remove the requirement of minimum follow up time of 60 months between last subject first visit (LSFV) and the time of final analysis. 3) Following Protocol Amendment #9, add sample size re-estimation to the second interim analysis. Extending the follow up time on DFS makes this task be possible. 4) Remove ECOG performance status, and combine risk groups of "T4 N0 or NX, M0, any Fuhrman's grade and any ECOG status" and "Any T, N1-2, M0, any Fuhrman's grade, and any ECOG status" in the UISS high risk group factor in the stratified log-rank test due to small number of patients randomized in ECOG performance status=2 and "T4 N0 or NX, M0, any Fuhrman's grade and any ECOG status" sub-groups. 5) Add a secondary analysis on DFS excluding non-clear cell patients. 6) Add sensitivity analyses on DFS only for the patients before the extension of patient population, and only for the patients in the extended patient population,

		respectively. 7) An analysis of cure rate model of DFS may be added based on independent blinded 3rd party assessment of DFS as an exploratory analysis. 8) Remove the limit of up to 28 days after the last dose of study medication to follow up AEs and SAEs. 9) Following Protocol Amendment #10, the estimated number of subjects for this study will be increased from 500 to 600 due to lower than expected Disease-Free Survival (DFS) event rate. 10) Following Protocol Amendment #10, the first interim analysis will be performed no later than March 2011 and will be independent to the number of DFS events occurred. This change is based on the recommendations of Data Monitoring Committee made on Sep. 2, 2010.
Version 4.0	Aug 31, 2014	1) Following Protocol Amendment #14, time of the final analysis for DFS has been changed to at 5 years after LSFV, or when approximately 258 DFS events are observed, whichever is later. 2) A 3-tier safety analysis has been added following Pfizer SOP SAF09-GSOP-SD-GL18 3.0. 3) Time of final analysis for OS has been added. 4) Appendix D "Data Handling for DFS Events Occurred after Two or More Consecutive Missed Tumor Assessments" has been added. Decision rules described in Appendix D followed SAP Section 7 Handling of Missing Data, and were used for the first and the second interim analyses. 5) The 1st supportive analysis has been modified to include DFS events confirmed by 3rd party review not only regardless of whether other anti-tumor therapies were received, but also regardless whether DFS events occurred after 2 or more missed tumor assessments. 6) SAP for the previous versions was for Global Cohort only. SAP for China Cohort has been added to version 4.0 in Section 9.

Results

Participant flow

Figure 3: Participant flow



Nine hundred (900) patients were screened for eligibility; the main reason for screening failure was metastatic disease. Data on patients disposition, discontinuation from treatment and from study are presented in the tables below:

Table 5: patient disposition in Study A6181109

	Number (%) of Patients	
Population Treatment arm	**Sunitinib N (%)**	**Placebo N (%)**
Intent-to-Treat	309	306
As-Treated	306	304
Not treated	3	2
Completed	170 (55.6)	211 (69.4)
Discontinued from Treatment	136 (44.4)	93* (30.6)

* patient died 1 year after treatment was completed.

Table 6: Patient Discontinuations from Treatment in Study A6181109 - As-Treated Population

	Number (%) of Patients	
	Sunitinib (N = 306)	**Placebo (N = 304)**
Patient Died	1 (0.3)	1* (0.3)
Relation to Study Drug not Defined	51 (16.7)	76 (25.0)
Global deterioration of health status	1 (0.3)	0
Lost to follow-up	1 (0.3)	1 (0.3)
Objective progression or relapse	22 (7.2)	59 (19.4)
Other	12 (3.9)	7 (2.3)
Protocol violation	1 (0.3)	1 (0.3)
Patient refused continued treatment for reason other than adverse event	14 (4.6)	8 (2.6)
Related to Study Drug	77 (25.2)	13 (4.3)
Adverse event	77 (25.2)	13 (4.3)
Not Related to Study Drug	7 (2.3)	3 (1.0)
Adverse event	7 (2.3)	3 (1.0)
Total	136 (44.4)	93 (30.6)

* Data issue: patient died 1 year after treatment was completed.

Table 7: Patient Discontinuations from Study A6181109 - ITT Population

Patient Population	Number (%) of Patients	
	Sunitinib (N = 309)	**Placebo (N = 306)**
Patient Died	61 (19.7)	64 (20.9)
Relation to Study Drug not Defined	62 (20.1)	51 (16.7)
Lost to follow-up	14 (4.5)	12 (3.9)
Other	24 (7.8)	16 (5.2)
Patient refused further follow-up	24 (7.8)	23 (7.5)
Total	123 (39.8)	115 (37.6)

Among patients who discontinued study, 24 patients in the sunitinib arm and 16 patients in the placebo arm were withdrawn from the study for "other" reasons. In the cases where "Other" were selected as the reason for withdrawal, the main reason was "withdrawal of consent".

Recruitment

Overall, 615 patients were randomized in 97 out of 101 activated sites worldwide (22 countries) between 19 September 2007 and 7 April 2011.

Two interim analyses were performed in March 2011 and in May 2013.

The data cut-off for the final analysis in this CSR is 7th April 2016 (time-driven, 5 years after last patient first visit).

Conduct of the study

Protocol amendments

A total of 14 protocol amendments to the original protocol (dated 18 July 2006), including global and country-specific changes, were implemented during the study. The first 3 amendments were released before accrual started.

Table 8: Summary of key changes introduced by the protocol amendments:

Document	Version Date	Summary of Changes
Amendment 14	18 July 2014 (Global)	Time for final analysis has been changed to 5 years after Last Subject First Visit (LSFV), Data analysis/statistical methods and trial design sections have been updated to be in line with new time for final analysis. Adverse event reporting period section has been updated. Medication errors section has been moved to section 8 and minor administrative changes were made align with the last version of the protocol template. Added China-specific trial design information. Revised exclusion criterion regarding contraception. Appendices 10, 11 and 12 have been removed and summary of changes for amendments 7, 8 and 9 have been included in this table.
Amendment 13	15 June 2012 (Global)	Updated Summary Rationale and Introduction safety and efficacy sections according to the most updated information. Updated medication errors language to align with CT3. Adverse event reporting section updated due to alignment with CT3 guidance (effective 11 June 2011) and US FDA Final Rule (effective 28 Sept. 2011) Minor administrative changes were made align with the last version of the protocol template.
Amendment 12	10 October 2011 (Global)	Addition of guidance for potential cases of Drug-Induced Liver Injury. Inclusion of Pfizer Internal Oncology Business Unit-Safety Data Monitoring Committee information. Clarification of AE reporting period. Update on publications.
Amendment 11	21 April 2011 (Country-specific: China)	Additional 120 China subjects to estimate an improvement of Disease Free Survival (DFS) in subjects at the high risk of recurrent RCC
Amendment 10	05 October 2010 (Global)	Adjust the timing of the first interim analysis. Increase # of subjects from 500 to 600. Correction collection timepoint of Prep D1 and blood volume of Molecular Profiling samples.
Amendment 9	21 June 2010 (Global)	The changes performed in amendment 8 (that was not released) have been included in this amendment. In addition, tumor images including CT or MRI of chest, abdomen and pelvis should be performed every 12 weeks at Day 1 of Cycle 3, 5, 7 & 9 (odd numbered cycles).
Amendment 8	17 February 2010 (Global) Not Implemented	Pharmacogenomics blood samples increased. Updated end of study/withdrawal procedures

		section. Added 21 new sites and 1 Country (China). Statistical analysis has been updated and some clarifications added.
Amendment 7	29 April 2009 (Global)	Sample Size was re-calculated based on population changes in Amendment 6 and updated survival analysis in the mRCC population. Removal of coagulation tests (PT and INR) at screening. Minor administrative changes were made to correct typographical errors, emphasize sub-points or improve internal consistency and clarity of the protocol.
Amendment 6	20 June 2008 (Global)	
Amendment 5	01 January 2008 (Country-specific: United Kingdom)	
Amendment 4	01 January 2008 (Global)	
Amendment 3	25 July 2007(Global) Not released	
Amendment 2	19 April 2007 (Country Specific: United Kingdom)	
Amendment 1	29 January 2007 (Global)	
Original protocol	18 July 2006	N/A

Protocol deviations

Table 9: Protocol deviations – ITT population

	Number (%) of Patients	
	Sunitinib (N = 309)	**Placebo (N = 306)**
Potentially Important or Major Protocol Deviations	66 (21.4)	70 (22.9)
Disallowed medications	33 (10.7)	32 (10.5)
Inclusion/exclusion criteria	14 (4.5)	11 (3.6)
Informed consent	2 (0.6)	1 (0.3)
IP administration/study treatment	3 (1.0)	2 (0.7)
Procedures/tests	12 (3.9)	15 (4.9)
Randomization	4 (1.3)	3 (1.0)
Visit schedule	2 (0.6)	6 (2.0)
Withdrawal criteria	5 (1.6)	7 (2.3)
Minor protocol deviations	296 (95.8)	299 (97.7)
AE SAE	20 (6.5)	23 (7.5)
Disallowed medications	8 (2.6)	0
Inclusion/exclusion criteria	7 (2.3)	12 (3.9)
Informed consent	182 (58.9)	184 (60.1)
IP administration/study treatment	110 (35.6)	90 (29.4)
Procedures/tests	281 (90.9)	287 (93.8)
Randomization	12 (3.9)	6 (2.0)
Visit schedule	218 (70.6)	214 (69.9)
Withdrawal criteria	2 (0.6)	0

Source: Section 14.1, Table 14.1.1.6.1.
Patient could contribute to more than one deviation category.
Patients were counted only once in each row.
Abbreviations: AE = adverse event; IP = investigational product; SAE = serious adverse event.

Baseline data

Baseline data

The majority of enrolled patients were male (71.8% vs. 74.8%), White (82.2% vs. 85.9%), with ECOG 0 pre-nephrectomy (73.8% vs. 71.9%). Median age was 57 vs. 58 years old; patients ≥65 years old were 24.6% vs. 26.8%. With regard to the baseline medical history, subject with at least one

disease/syndrome were: past history 58.3% vs. 59.5%, present history 80.3% vs. 86.9% in sunitinib and placebo arm respectively.

Table 10: baseline subject characteristics in Study A6181109 – ITT population

	Sunitinib (N = 309)	Placebo (N = 306)
Age (years), n (%)		
<18	0	0
18-44	41 (13.3)	35 (11.4)
45-64	192 (62.1)	189 (61.8)
≥65	76 (24.6)	82 (26.8)
Age (years)		
Mean (SD)	56.8 (10.6)	57.9 (10.6)
Median	57.0	58.0
Minimum-Maximum	25-83	21-82
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)
Weight (kg)		
n (%)	307 (99.4)	302 (98.7)
Mean (SD)	79.5 (17.2)	81.1 (18.3)
Median	78.0	79.0
Minimum-Maximum	45.0-140.0	44.0-184.0
Height (cm)		
n (%)	304 (98.4)	304 (99.3)
Mean (SD)	171.3 (9.5)	171.4 (9.1)
Median	172.0	172.0
Minimum-Maximum	150.0–196.0	134.0–193.0
BMI at Baseline (BMI categories, kg/m^2), n (%)		
Normal weight (18.5≤ BMI <25)	108 (35.0)	96 (31.4)
Overweight (25≤ BMI<30)	122 (39.5)	145 (47.4)
Overweight + Obese (BMI ≥25)	189 (61.2)	204 (66.7)
Obese (BMI ≥30)	67 (21.7)	59 (19.3)
ECOG Performance Status, 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)

Table 11: Baseline disease characteristics in Study A6181109 – ITT population

	Sunitinib (N = 309)	Placebo (N = 306)
Primary Diagnosis, n (%)		
Renal Cell Carcinoma	309 (100.0)	306 (100.0)
Time from Diagnoses to Randomization (weeks) [a]		
Mean	10.4	10.2
Median	10.7	10.7
Minimum-Maximum	5.1–53.4	3.7–19.9
Disease of Body Site at Diagnosis, n (%)		
Right Kidney	165 (53.4)	148 (48.4)

Left Kidney	144 (46.6)	158 (51.6)
Both Kidneys	0	0
Histological Classification at Screening, n (%)		
Clear Cell Carcinoma	306 (99.0)	306 (100.0)
Other	3 (1.0)	0
Not Reported	0	0
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)
UISS High Risk group, n (%)		
T3 Low: 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	115 (37.2)	112 (36.6)
T3 High: T3 N0 or NX, M0, Fuhrman's Grade ≥2, ECOG PS ≥1	165 (53.4)	166 (54.2)
T4 N0 or NX, M0, and any Fuhrman's Grade, and any ECOG PS	4 (1.3)	4 (1.3)
Any T, N1-2, M0, and any Fuhrman's Grade, and any ECOG PS	25 (8.1)	24 (7.8)

Numbers analysed

Intention to treat population (ITT): 615 patients were randomized (309 in the Sunitinib arm and 306 in the placebo arm). ITT was the primary population for evaluating all efficacy endpoints, patient characteristics and PROs.

As-Treated population (AT): patients who received at least one dose of study medication, includes 610 subjects (306 in the Sunitinib arm and 304 in the placebo arm). AT was the primary population for safety assessment.

Outcomes and estimation

The data cut-off for the submitted final analysis was 7th April 2016.

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.

Primary endpoint

Disease Free Survival (according to BICR)

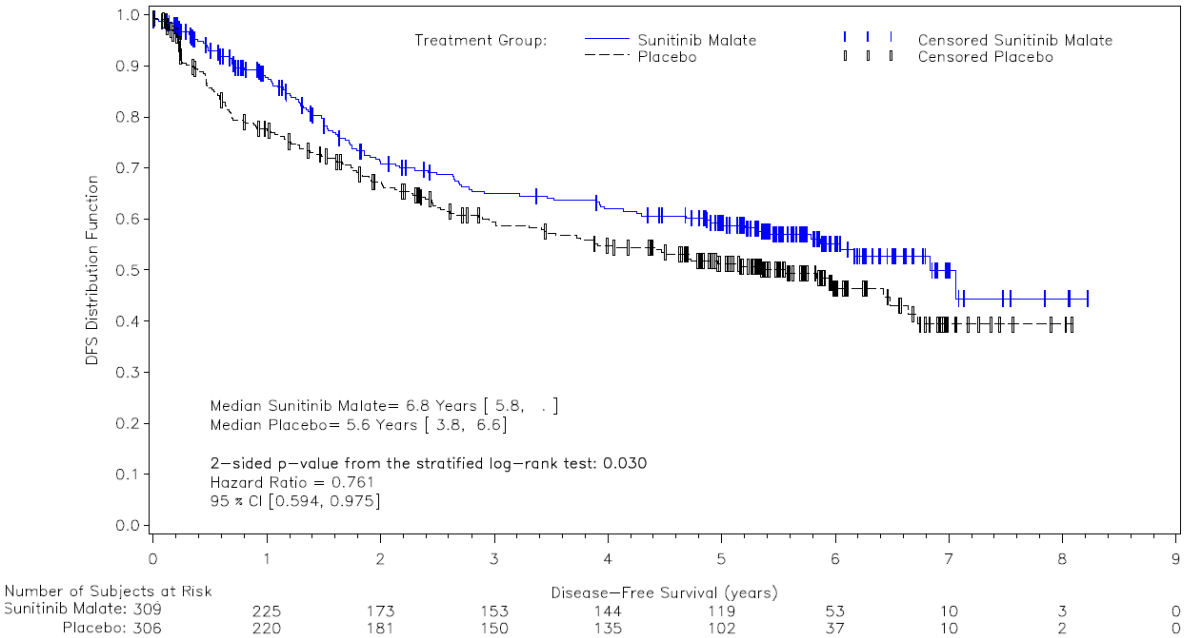
Table 12: DFS by BICR – study A6181109 – ITT population

	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 Cut-off	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)

Probability of Being Event Free		
Year 1a (95% CI)	87.7 (83.2, 91.1)	77.6 (72.4, 82.0)
Year 2a (95% CI)	71.3 (65.3, 76.4)	67.2 (61.4, 72.3)
Year 3a (95% CI)	64.9 (58.7, 70.5)	59.5 (53.5, 65.0)
Year 5a (95% CI)	59.3 (52.9, 65.1)	51.3 (45.1, 57.1)
Kaplan-Meier estimates of DFS (Year)		
50% Quartile (95% CI)b	6.8 (5.8, NR)	5.6 (3.8, 6.6)
Versus Placebo		
Hazard Ratioc (95% CI)	0.761 (0.594, 0.975)	
p-valued	0.030	

a. Estimated from the Kaplan-Meier curve.
b. Based on the Brookmeyer and Crowley method.
c. Based on the Cox Proportional Hazards model stratified by UISS High Risk Group.
d. 2-sided p-value from the log-rank test stratified by UISS High Risk Group.

Figure 5: Kaplan-Meier plot of DFS by BICR – study A6181109 – ITT population



Note: Patients with disease at baseline were included in the events and their DFS time was Day 1.

Details on type of DFS event in both arms is presented in the table below:

Table 13: DFS Events Based on Type of Event According to the BICR Assessment

	Sunitinib N=309 n (%)	Placebo N=306 n (%)
Patients with DFS Events	113 (36.6)	144 (47.1)
Deaths	8 (2.6)	4 (1.3)
Kidney	1 (0.3)	4 (1.3)
Local recurrence	3 (1.0)	3 (1.0)
Distant recurrence	97 (31.4)	122 (39.9)
Secondary malignancy	4 (1.3)	11 (3.6)
AML	1 (0.3)	1 (0.3)
Bladder	1 (0.3)	3 (1.0)
Prostate	1 (0.3)	2 (0.7)
Skin	1 (0.3)	0
Colon	0	2 (0.7)
Lung	0	1 (0.3)

Table 13: DFS Events Based on Type of Event According to the BICR Assessment

	Sunitinib N=309 n (%)	Placebo N=306 n (%)
Lymphoma	0	1 (0.3)
Thyroid	0	1 (0.3)

Secondary endpoints

Disease Free Survival (according to Investigator)

In the DFS analysis according to Investigator, median DFS was 6.5 years (95%CI: 4.7, 7.0) vs. 4.5 years (95%CI: 3.8, 5.9) for sunitinib and placebo respectively, HR 0.811 (95%CI: 0.643, 1.023), p= 0.077 (2-sided p-value from the log-rank test stratified by UISS High Risk Group).

Table 14: DFS by Investigator – study A6181109 – ITT population

	Sunitinib (N = 309)	Placebo (N = 306)
Number (%) with Event	132 (42.7)	158 (51.6)
Type of Event, n (%)		
Disease Recurrence or Occurrence of a Secondary Malignancy	125 (40.5)	153 (50.0)
Disease Present, Indeterminate if Recurrent or Secondary Primary	38 (30.4)	33 (21.6)
Recurrent Disease	80 (64.0)	102 (66.7)
Secondary Primary Malignancy Other Than Renal Cancer	7 (5.6)	18 (11.8)
Death	7 (2.3)	5 (1.6)
Number Censored, n (%)	177 (57.3)	148 (48.4)
Reason for Censorship, n (%)		
No Post-Baseline Cancer Event Assessments	16 (5.2)	7 (2.3)
No Event at Time of Data Cutoff	161 (52.1)	141 (46.1)
Withdrew Consent for Follow-Up	15 (9.3)	16 (11.3)
Lost to Follow-Up	8 (5.0)	6 (4.3)
Receiving Further Anti-Cancer Therapy Prior to an Event	4 (2.5)	5 (3.5)
Still in Disease Follow-up	122 (75.8)	109 (77.3)
Other	7 (4.3)	4 (2.8)
Disease Relapse or Death Occurred After ≥2 Consecutive Missed Assessments	5 (3.1)	1 (<1.0)
Probability of Being Event Free		
Year 1a (95% CI)	83.1 (78.2, 87.0)	75.8 (70.5, 80.3)
Year 2a (95% CI)	69.1 (63.3, 74.3)	65.3 (59.5, 70.4)
Year 3a (95% CI)	62.5 (56.3, 68.0)	59.4 (53.4, 64.8)]
Year 5a (95% CI)	54.8 (48.6, 60.6)	48.6 (42.6, 54.4)
Kaplan-Meier Estimate of DFS (Year)		
50% Quartile (95% CI)b	6.5 (4.7, 7.0)	4.5 (3.8, 5.9)
Versus Placebo		
Hazard Ratioc (95% CI)	0.811 (0.643, 1.023)	
p-valued	0.077	

a. Estimated from the Kaplan-Meier curve.
b. Based on the Brookmeyer and Crowley method.
c. Based on the Cox Proportional Hazards model stratified by UISS High Risk Group.
d. 2-sided p-value from the log-rank test stratified by UISS High Risk Group.

Figure 6: Kaplan-Meier plot of DFS by Investigator – study A6181109 – ITT population

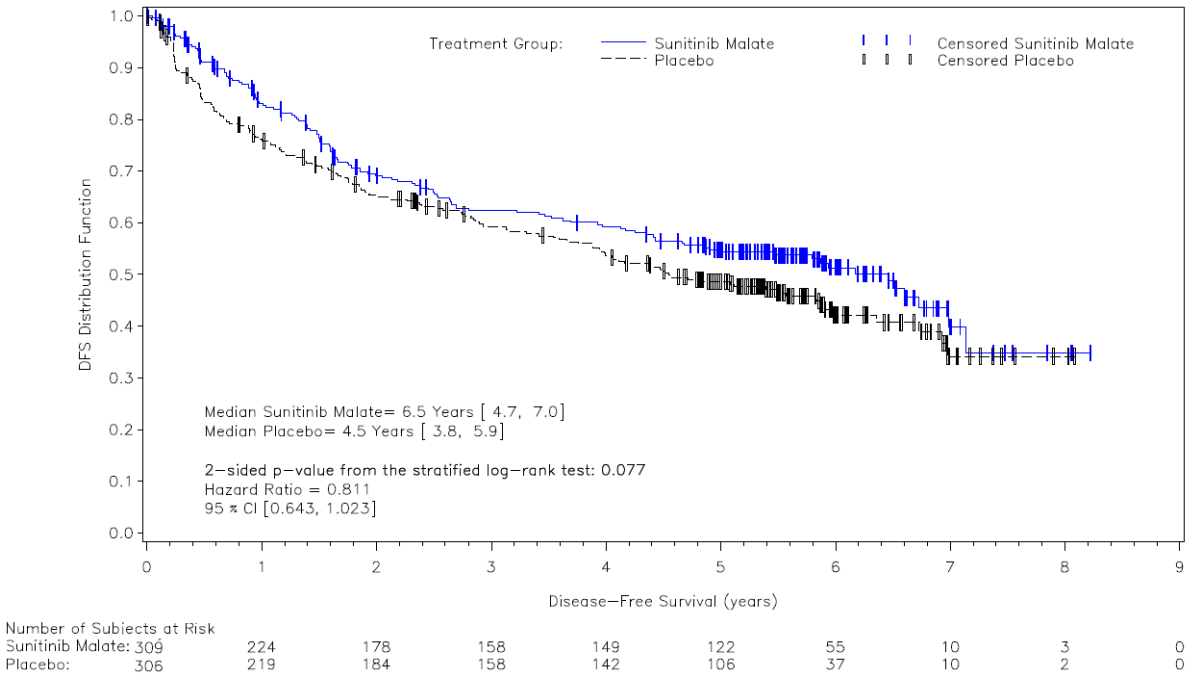
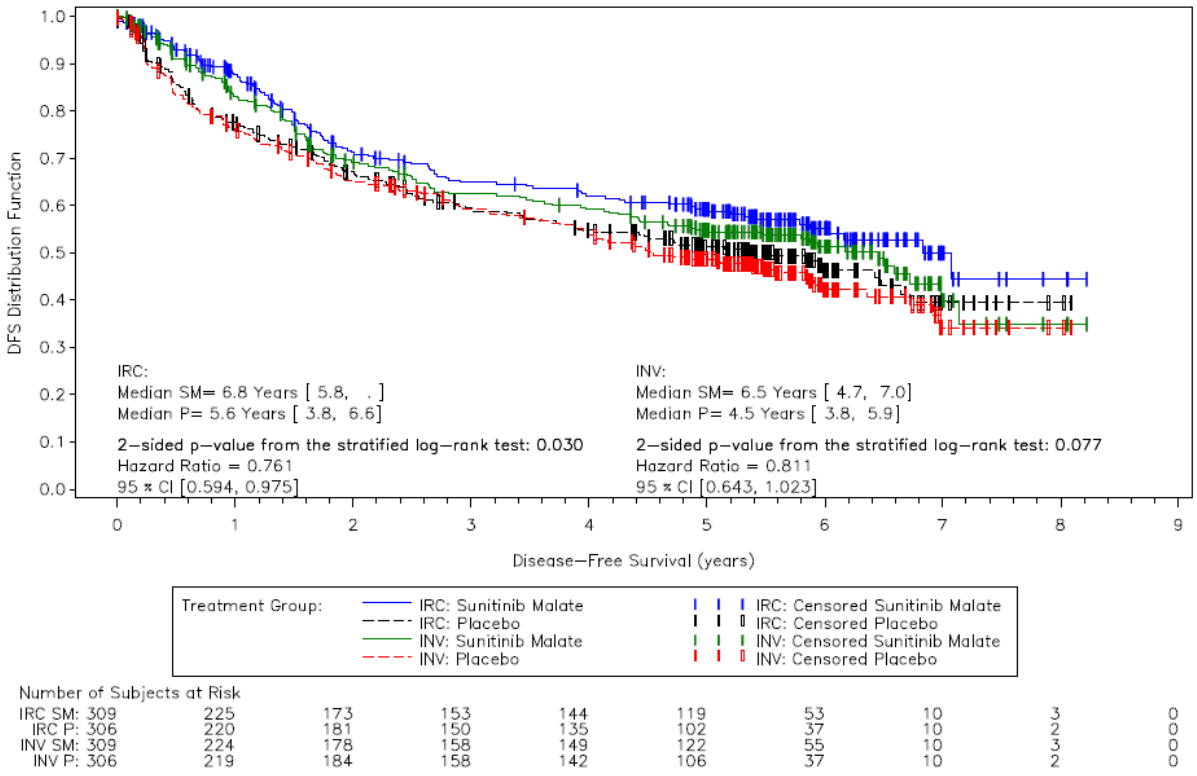


Figure 7: Kaplan-Meier of DFS by BICR and Investigator – study A6181109 – ITT population



Patients with disease at baseline are included in the events and their DFS time is 1 day

OS

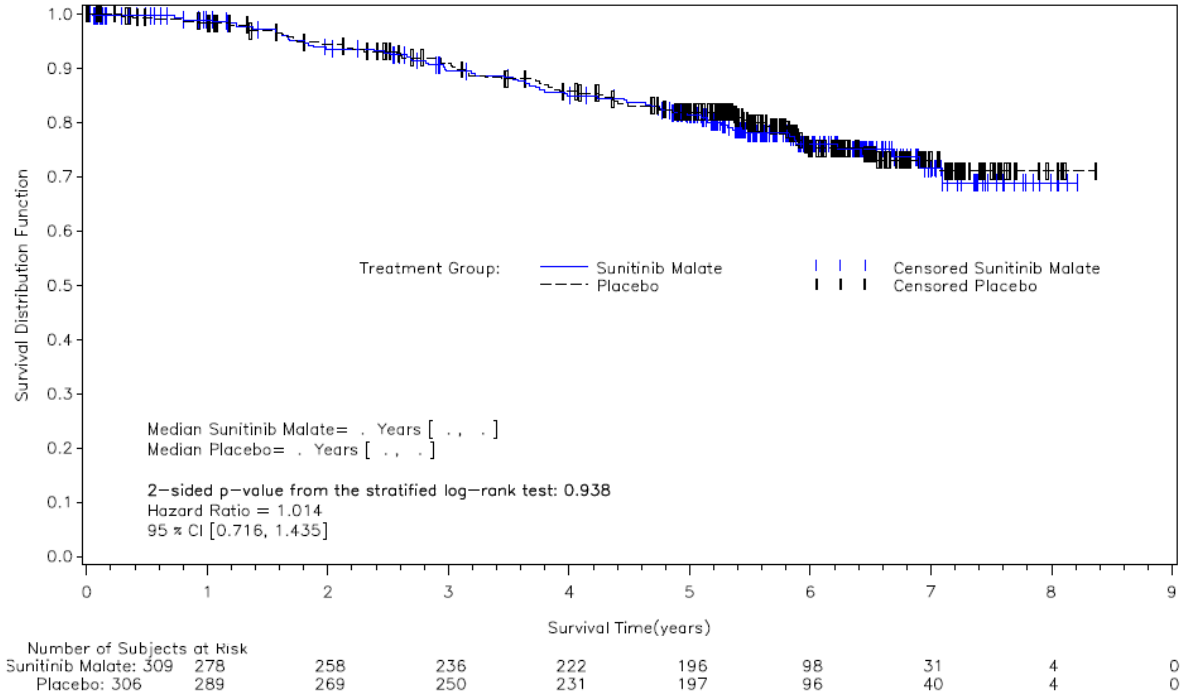
OS data are immature, with only approximately 20% of the death events within the enrolled population. Median OS was not reached.

Table 15: OS – study A6181109 – ITT population

	Sunitinib (N = 309)	Placebo (N = 306)
Number (%) of Deaths	64 (20.7)	64 (20.9)
Cause of Death, n (%)		
Disease Under Study	49 (15.9)	47 (15.4)
Study Treatment Toxicity	0	0
Unknown	8 (2.6)	7 (2.3)
Other	10 (3.2)	10 (3.3)
Number Censored, n (%)	245 (79.3)	242 (79.1)
Reason for Censorship, n (%)		
Alive	190 (61.5)	194 (63.4)
Patient No Longer Willing To Participate	26 (8.4)	25 (8.2)
Lost To Follow-up	16 (5.2)	15 (4.9)
Other	13 (4.2)	8 (2.6)
Probability of Being Event Free		
Year 2a (95% CI)	93.6 (90.0, 95.9)	94.5 (91.1, 96.6)
Year 5a (95% CI)	81.4 (76.2, 85.5)	81.9 (76.9, 86.0)
Kaplan-Meier Estimate of DFS (Year)		
50% Quartileb (95% CI)	-	-
Versus Placebo		
Hazard Ratioc (95% CI)	1.014 (0.716, 1.435)	
p-value	0.938	

a. Estimated from the Kaplan-Meier curve.
b. Calculated from Brookmeyer and Crowley method.
c. Based on the Cox Proportional Hazards model stratified by UISS High Risk Group.
d. 2-sided p-value from the log-rank test stratified by UISS High Risk Group.

Figure 8: Kaplan-Meier plot of OS – study A6181109 – ITT population



Updated OS (cut-off date 31 January 2017)

As of 31 January 2017, an additional 3 patients in the sunitinib arm and 10 patients in the placebo arm have died compared to the primary CRS cut-off date of 7 April 2016, for a total number of deaths of 67 (21.7%) and 74 (24.2%), respectively. The observed stratified HR was 0.918 (95% CI: 0.659, 1.279; 2-sided p-value = 0.612). The median OS was not reached for either treatment arm.

No deaths in either treatment arm were attributed to study treatment toxicity.

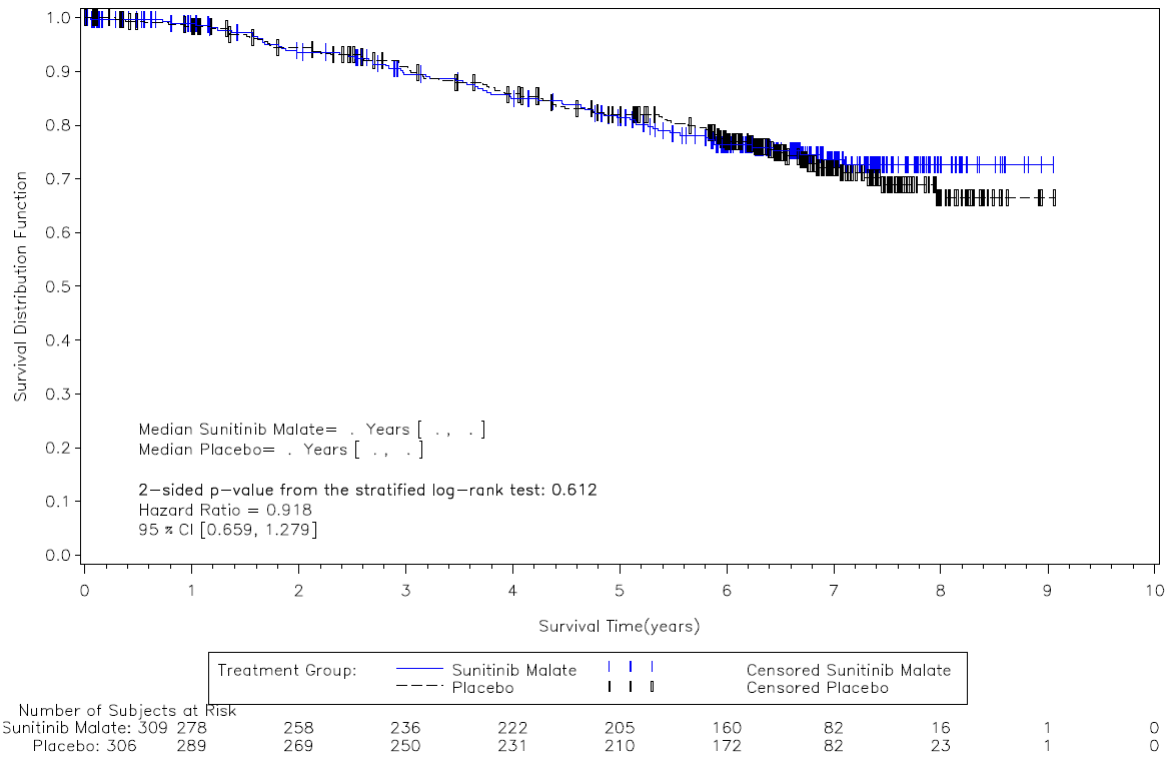
Table 16: OS – study A6181109 – ITT population (updated cut-off date 31 January 2017)

	Sunitinib (N = 309)	**Placebo (N = 306)**
Number (%) of Deaths	67 (21.7)	74 (24.2)
Cause of Death[a], n (%)		
Disease Under Study	50 (16.2)	50 (16.3)
Study Treatment Toxicity	0	0
Unknown	9 (2.9)	9 (2.9)
Other	11 (3.6)	16 (5.2)

Number Censored, n (%)	242 (78.3)	232 (75.8)
Reason for Censorship, n (%)		
Alive	178 (57.6)	174 (56.9)
Patient No Longer Willing to Participate	32 (10.4)	32 (10.5)
Lost to Follow-up	19 (6.1)	18 (5.9)
Other	13 (4.2)	8 (2.6)
Probability of Being Event Free		
Year 2[b] (95% CI)	93.6 (90.0, 95.9)	94.5 (91.1, 96.6)
Year 5[b] (95% CI)	81.4 (76.2, 85.6)	81.9 (76.9, 86.0)
Kaplan-Meier Estimate of OS (year)		
50% Quartile[c] (95% CI)	NR (NR, NR)	NR (NR, NR)
Versus Placebo		
Hazard Ratio[d] (95% CI)	0.918 (0.659, 1.279)	
p-value[e]		0.612

a A patient could have more than 1 cause of death.
b Estimated from the Kaplan-Meier curve.
c Calculated from Brookmeyer and Crowley method.
d Based on the Cox Proportional hazards model stratified by UISS High-Risk Group.
e 2-sided p-value from the log-rank test stratified by UISS High-Risk Group.

Figure 9: Kaplan-Meier of OS – study A6181109 – ITT (updated cut-off date 31.01.2017)



Patient Reported Outcomes

PROs were evaluated using EORTC QLQ-C30 and EQ-5D.

The questionnaires were to be completed on Day 1 and approximately every 6 weeks thereafter until

end of study treatment (i.e. up to 1 year).

For both questionnaires, over 90% of the eligible patients completed at least 1 question at each cycle visit, except at the EOT visit where the completion rate was over 80%. Completion rate was similar between the two arms.

Table 17: EORTC QLQ-C30: Global Health and Functional Scale Scores Between Treatment Comparison for Study A6181109 - ITT Population

Functional Scale	Sunitinib (N = 309)		Placebo (N = 306)		Sunitinib – Placebo		
	ESTD Mean	95% CI	ESTD Mean	95% CI	ESTD Mean	95% CI	p-value
Global health	69.07	(67.60,70.54)	73.84	(72.40, 75.27)	-4.76	(-6.82,−2.71)	<0.0001
Physical	83.54	(82.40, 84.68)	87.53	(86.42, 88.64)	−3.98	(−5.57, −2.39)	<0.0001
Role	78.94	(77.14, 80.74)	85.46	(83.70, 87.23)	−6.52	(−9.05, −4.00)	<0.0001
Emotional	80.92	(79.58, 82.27)	82.97	(81.66, 84.29)	−2.05	(−3.93, −0.17)	0.0326
Cognitive	85.50	(84.17, 86.83)	87.43	(86.13, 88.73)	−1.93	(−3.79, −0.07)	0.0415
Social	80.62	(79.04, 82.21)	87.99	(86.44, 89.53)	−7.36	(−9.58, −5.15)	<0.0001

Table 18: EORTC QLQ-C30: Symptom Scale Scores Between Treatment Comparison for Study A6181109 - ITT Population

Symptom Scale	Sunitinib (N = 309)		Placebo (N = 306)		Sunitinib - Placebo		
	ESTD Mean	95% CI	ESTD Mean	95% CI	ESTD Mean	95% CI	p-value
Fatigue	29.94	(28.33, 31.56)	21.74	(20.16, 23.31)	8.21	(5.95, 10.46)	<0.0001
Nausea and Vomiting	7.35	(6.38, 8.33)	3.46	(2.51, 4.41)	3.90	(2.53, 5.26)	<0.0001
Pain	21.81	(20.10, 23.52)	16.63	(14.96, 18.30)	5.18	(2.79, 7.57)	<0.0001
Dyspnoea	14.97	(13.38, 16.57)	11.89	(10.33, 13.45)	3.08	(0.85, 5.31)	0.0068
Insomnia	22.22	(20.26, 24.19)	20.73	(18.81, 22.65)	1.49	(−1.26, 4.24)	0.2876
Appetite Loss	14.66	(13.12, 16.21)	4.62	(3.11, 6.13)	10.04	(7.88, 12.20)	<0.0001
Constipation	11.24	(9.66, 12.82)	9.83	(8.29, 11.37)	1.41	(−0.80, 3.62)	0.2100
Diarrhoea	19.25	(17.54, 20.95)	7.25	(5.59, 8.91)	12.00	(9.62, 14.38)	<0.0001
Financial Difficulties	15.12	(13.42, 16.82)	13.92	(12.26, 15.59)	1.19	(−1.19, 3.57)	0.3255

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate, using method of restricted maximum likelihood and unstructured covariance matrix.
P-values not adjusted for multiplicity.
For symptom-oriented scales, higher scores represented more severe symptoms.
Abbreviations: CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; ESTD = estimated; N = number of patients in arm QLQ = Quality of Life Questionnaire.

EuroQoL EQ-5D: For both EQ-5D index and EQ-VAS, scores were comparable at baseline and numerically lower in the sunitinib group in subsequent cycles.

Based on the pre-specified repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate, sunitinib arm was shown to be significantly worse than placebo in EQ-5D (difference: −0.04, 95% CI: −0.06, −0.02, p-value: 0.0001); however, this

difference did not reach the published clinically important difference of 0.06 points for patients in the US or 0.08 points for patients in the UK.

Similarly the repeated measures comparison on EQ-VAS also showed that sunitinib was worse than placebo (diff: -3.80, 95% CI: −5.57, −2.04, p-value: <0.0001). This difference also did not reach the published clinically important difference of 7 to 12 points for the EuroQol EQ-VAS.

Figure 10: EORTC QLQ-C30 mean scores changes from baseline over time– Global Health Status/QoL– ITT population

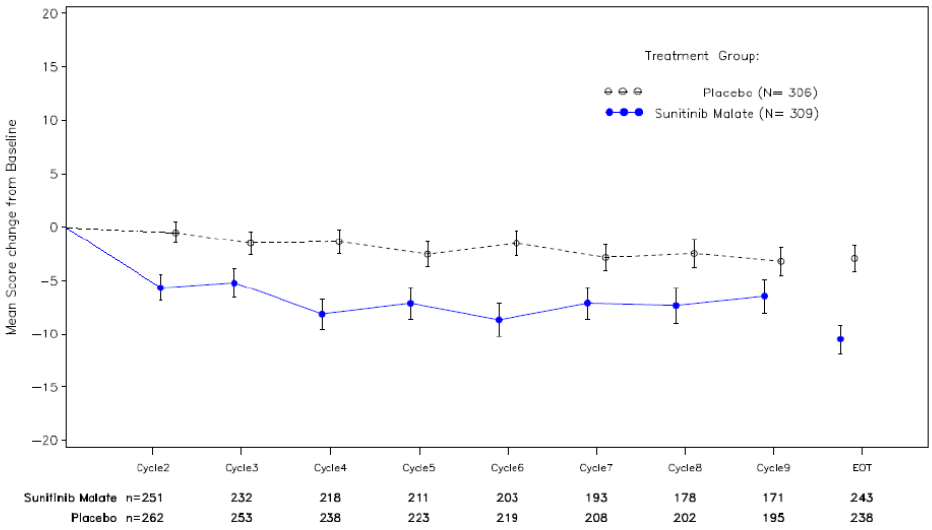
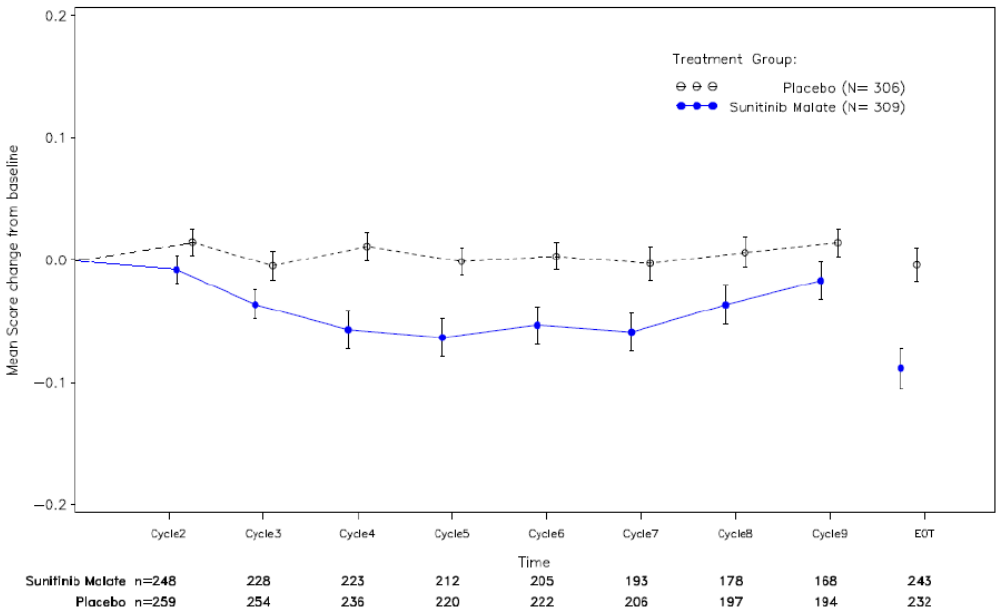


Figure 11: EuroQol EQ-5D mean score change from baseline over time –ITT population



Ancillary analyses

Discordance between BICR and Investigator Assessment

The discordance rates between assessments by BICR and investigator includes either disagreement in the occurrence or in the timing of radiologic progression. It was considered a disagreement in time a difference +/- 28 days.

Table 19: discordance between BICR and Investigator assessment of DFS in A6181109 (ITT)

Parameter and Disagreement Type	Sunitinib (N = 309)		Placebo (N = 306)		Difference (%)
	N	n (%)	N	n (%)	
Total Event Discordance Rate (c+b)/N	309	35 (11.3)	306	26 (8.5)	2.8
Early Disagreement Rate (b+a3)/(a1+a2+a3+b)	132	48 (36.4)	158	39 (24.7)	11.7
Late Disagreement Rate (c+a2)/(b+c+a2+a3)	86	38 (44.2)	85	46 (54.1)	−9.9
Overall Disagreement Rate (a2+a3+c+b)/N	309	86 (27.8)	306	85 (27.8)	0

a1: number of agreements on timing and occurrence of relapse by both BICR and investigator (within +/−28 days): both independent review and the investigator decided that the patient had an event, and the DFS values are within +/−28 days of each other.
a2: number of times investigator declared relapse later than BICR (>28 days): both independent review and the investigator decided that the patient had an event, and DFS value based on investigator minus DFS based on BICR assessment >28 days.
a3: number of times investigator declared relapse earlier than BICR (>28 days): both independent review and the investigator decided that the patient had an event, and DFS value based on investigator minus DFS based on BICR assessment ≤28 days.
b: number of times investigator declared relapse but BICR did not: Investigator called event, but BICR said no event.
c: number of times BICR declared relapse but investigator did not: BICR called event, investigator said no event.

Table 20: Table of Discordance in the First Year Between DFS Based on BICR Assessment and Investigator Assessment - Intent to Treat Global Cohort

Parameter and Disagreement Type	Sunitinib Malate (N=85)		Placebo (N=87)		Difference (%)
	N	n (%)	N	n (%)	
Total Event Discordance Rate (c+b)/N	85	15 (17.6)	87	9 (10.3)	7.3
Early Disagreement Rate (EDR) (b+a3)/(a1+a2+a3+b)	47	22 (46.8)	71	15 (21.1)	25.7
Late Disagreement Rate (LDR) (c+a2)/(b+c+a2+a3)	29	7 (24.1)	25	10 (40.0)	-15.9
Overall Disagreement Rate (a2+a3+c+b)/N	85	29 (34.1)	87	25 (28.7)	5.4

Reasons for early censoring

Table 21: reasons for early censoring (≤ 1 year) by BICR assessment –A6181109 (ITT)

Reasons for Early Censoring	Sunitinib (N = 309)	Placebo (N = 306)
	n (%)	
Patients with Early Censoring (≤1 year)	50 (16.2)	21 (6.9)
No Post Baseline Assessments	14 (4.5)	6 (2.0)
Discontinued Treatment due to AE but Still Listed as in Follow-up	0	1 (0.3)
Never Dosed & Withdrew Consent	3 (1.0)	0
Discontinued treatment due to AE & Withdrew Consent	4 (1.3)	0
Discontinued treatment due to reasons other than AE & Withdrew Consent	7 (2.3)	5 (1.6)
Withdrew Consent for Follow-up	13 (4.2)	6 (2.0)
Censored by INV - Completed Treatment	1 (0.3)	2 (0.7)
Censored by INV - Withdrew Treatment due to Toxicity	6 (1.9)	1 (0.3)
Censored by INV - Withdrew Treatment due to reasons other than Toxicity	4 (1.3)	3 (1.0)
Event by INV	2 (0.6)	0
Disease Relapse or death after ≥2 consecutive missed assessments	7 (2.3)	0
Event by INV	2 (0.6)	0
Censored by INV	5 (1.6)	0
Receiving further anticancer therapy prior to an event	7 (2.3)	7 (2.3)
Event by INV	6 (1.9)	7 (2.3)
Censored by INV - Discontinued Treatment due to AE	1 (0.3)	0
Censored by INV - Completed Treatment	0	0
Lost to Follow-up	4 (1.3)	0
Censored by INV - Withdrew Treatment due to Adverse Event	2 (0.6)	0
Censored by INV - Withdrew Treatment due to reasons other than Toxicity	1 (0.3)	0
Censored by INV - Completed Treatment	0	0
Event by INV	1 (0.3)	0
Listed as Still in Follow-up	5 (1.6)	2 (0.7)
Censored by INV - Withdrew from Treatment due to reasons other than AE	2 (0.6)	0
Censored by INV - Withdrew from Treatment due to AE	3 (1.0)	2 (0.7)
Censored by INV - Completed Treatment	0	0

Table 22: reasons for early censoring (>1 year and ≤2 years) by BICR –A618 1109 (ITT)

Reasons for Early Censoring	Sunitinib (N = 309)	Placebo (N = 306)
	n (%)	
Patients with Early Censoring (>1 year and ≤2 years)	11 (3.6)	10 (3.3)
No Post Baseline Assessments	0	0
Discontinued Treatment due to AE but Still Listed as in Follow-up	0	0
Never Dosed & Withdrew Consent	0	0
Discontinued treatment due to AE & Withdrew Consent	0	0
Discontinued treatment due to reasons other than AE & Withdrew Consent	0	0
Withdrew Consent for Follow-up	2 (0.6)	4 (1.3)
Censored by INV - Completed Treatment	1 (0.3)	4 (1.3)
Censored by INV - Withdrew Treatment due to Toxicity	1 (0.3)	0
Censored by INV - Withdrew Treatment due to reasons other than Toxicity	0	0
Event by INV	0	0
Disease Relapse or death after ≥2 consecutive missed assessments	3 (1.0)	3 (1.0)

Reasons for Early Censoring	Sunitinib (N = 309)	Placebo (N = 306)
Event by INV	3 (1.0)	2 (0.7)
Censored by INV	0	1 (0.3)
Receiving further anti-cancer therapy prior to an event	3 (1.0)	3 (1.0)
Event by INV	2 (0.6)	2 (0.7)
Censored by INV - Discontinued Treatment due to AE	0	0
Censored by INV - Completed Treatment	1 (0.3)	1 (0.3)
Lost to Follow-up	2 (0.6)	0
Censored by INV - Withdrew Treatment due to Adverse Event	1 (0.3)	0
Censored by INV - Withdrew Treatment due to reasons other than Toxicity	0	0
Censored by INV - Completed Treatment	1 (0.3)	0
Event by INV	0	0
Listed as Still in Follow-up	1 (0.3)	0
Censored by INV - Withdrew from Treatment due to reasons other than AE	0	0
Censored by INV - Withdrew from Treatment due to AE	0	0
Censored by INV - Completed Treatment	1 (0.3)	0

In the following interval period (between 1 and 2 years), the number of censoring is lower compared to ≤ 1 year period and it is similar between the two arms (11 [3.6%] and 10 [3.3%] patients in the sunitinib and placebo arm respectively). Two patients in the sunitinib arm vs. none in the placebo arm discontinued treatment due to AEs.

DFS sensitivity analyses

Sensitivity analysis according to both BICR and investigator assessment were carried out. These were:

1) considering all DFS events regardless of whether patients received new anticancer therapy or missed 2 or more consecutive disease assessment

2) using scheduled assessment dates to define censoring and event times

3) censoring deaths at the last assessment prior to death

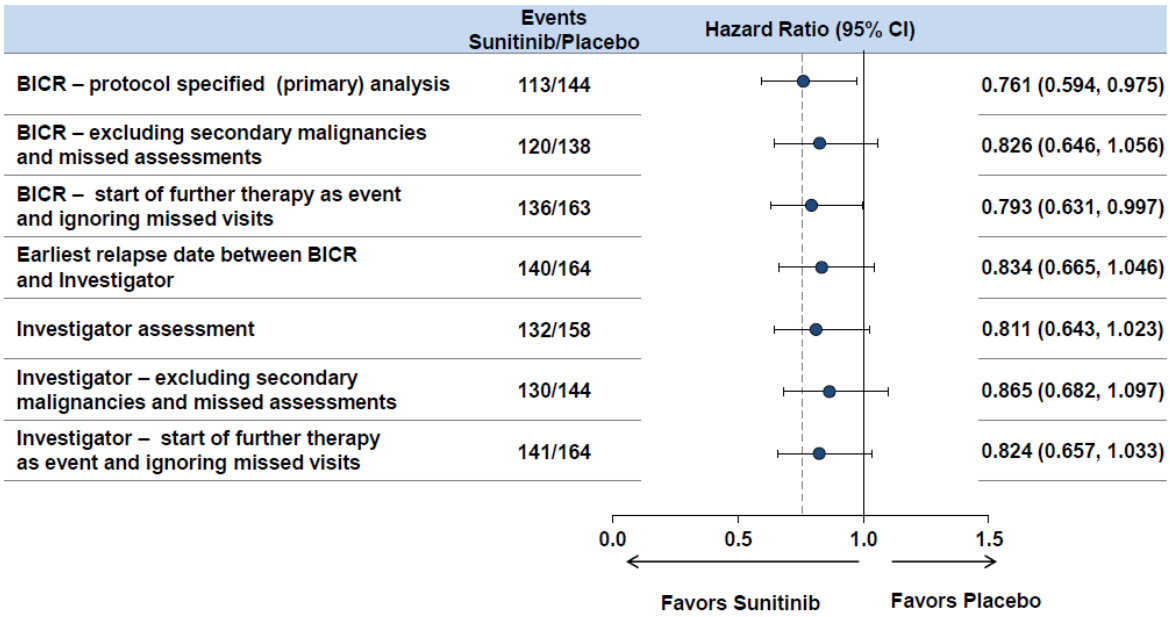
4) considering new anticancer therapy as an event at the time of initiation of therapy

The results of the sensitivity analyses are summarized in tables below:

Table 23: sensitivity analyses results of DFS by BICR and Investigator – Study A6181109 – ITT population

	p-value	HR (95% CI)	DFS (in years)	
			Sunitinib (N = 309)	Placebo (N = 306)
BICR Assessment				
DFS with all events regardless of new anti-cancer therapy or missed assessment	0.070	0.807 (0.640, 1.018)	5.9	4.7
DFS at scheduled assessment date	0.035	0.758 (0.589, 0.976)	7.0	5.5
DFS with deaths censored	0.015	0.730 (0.566, 0.941)	7.1	5.8
DFS with new anti-cancer therapy as an event	0.028	0.768 (0.607, 0.973)	6.2	4.5
Investigator Assessment				
DFS with all events regardless of new anti-cancer therapy or missed assessment	0.119	0.835 (0.666, 1.048)	5.9	4.5
DFS at scheduled assessment date	0.073	0.800 (0.630, 1.015)	6.5	5.0
DFS with deaths censored	0.058	0.795 (0.627, 1.008)	6.5	5.1
DFS with new anti-cancer therapy as an event	0.062	0.805 (0.641, 1.012)	6.2	4.5

Figure 12: DFS Analyses Performed (ITT Population)



DFS subgroup analyses

Subgroup analyses including the following baseline factors: UISS risk group, age, gender, ECOG PS, body mass index (BMI) and neutrophil-to-lymphocyte ratio (NLR), were pre-specified. A post-hoc analysis by Fuhrman's Grade was also performed. All subgroup analyses were considered exploratory and no adjustments for multiplicity were performed.

Figure 13: Forest Plot of DFS by BICR by subgroups – Study A6181109 – ITT population

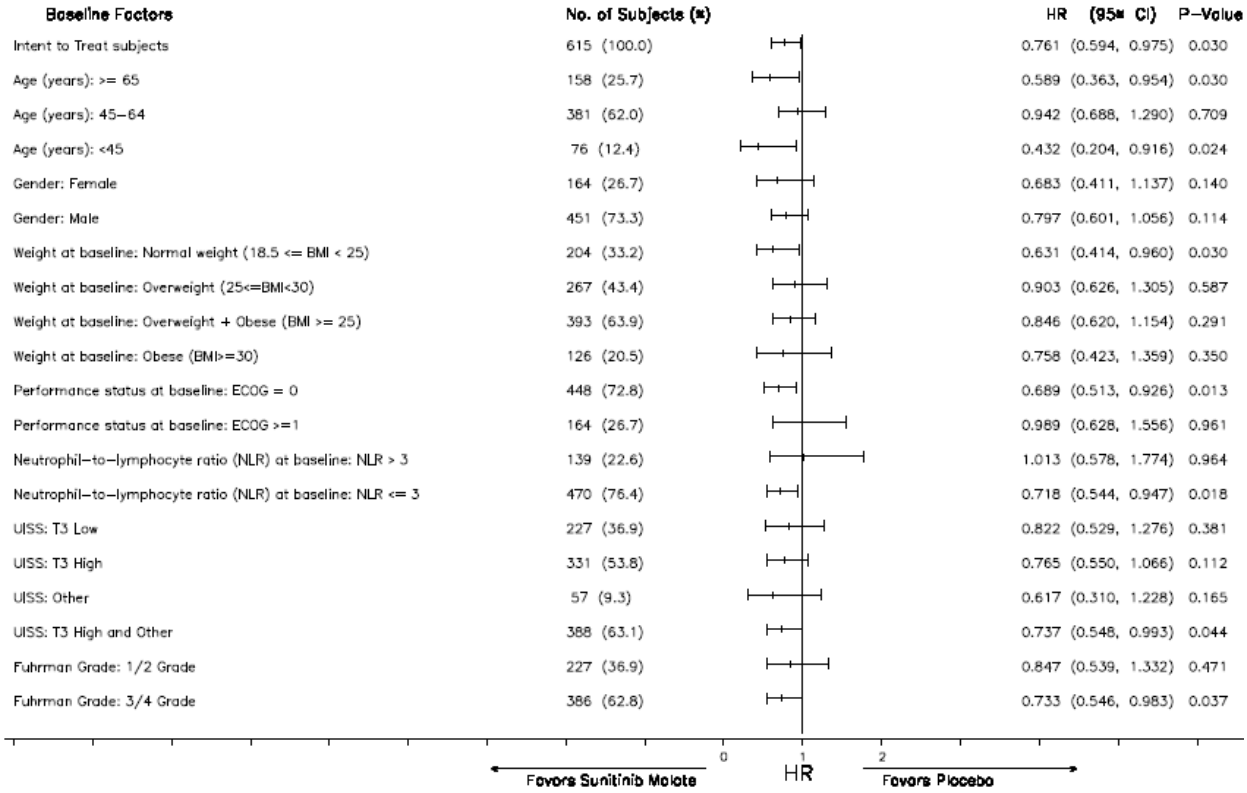


Table 24: supportive analysis on DFS by BICR by UISS subgroups – Study A6181109 (ITT)

UISS High Risk Group	Sunitinib	Placebo
T3 Low	**N = 115**	**N = 112**
Number (%) with Event	35 (30.4)	46 (41.1)
Kaplan-Meier Estimate of Time to Event (Year)		
50% Quartile (95% CI)	NR (5.2, NR)	6.4 (4.7, NR)
Vs Placebo		
Hazard Ratio (95% CI)	0.822 (0.529, 1.276)	
p-value	0.381	
T3 High	**N = 165**	**N = 166**
Number (%) with Event	63 (38.2)	79 (47.6)
Kaplan-Meier Estimate of Time to Event (Year)		
50% Quartile (95% CI)	6.8 (5.0, NR)	5.3 (2.9, NR)
Vs Placebo		
Hazard Ratio (95% CI)	0.765 (0.550, 1.066)	
p-value	0.112	
Other	**N = 29**	**N = 28**
Number (%) with Event	15 (51.7)	19 (67.9)
Kaplan-Meier Estimate of Time to Event (Year)		
50% Quartile (95% CI)	3.5 (1.2, NR)	1.7 (0.4, 3.0)
Vs Placebo		
Hazard Ratio (95% CI)	0.617 (0.310, 1.228)	
p-value	0.165	
T3 High and Other	**N = 194**	**N = 194**

Number (%) with Event	78 (40.2)	98 (50.5)
Kaplan-Meier Estimate of Time to Event (Year)		
50% Quartile (95% CI)	6.2 (4.9, NR)	4.0 (2.6, 6.0)
Vs Placebo		
Hazard Ratio (95% CI)	0.737 (0.548, 0.993)	
p-value	0.044	

Multivariate Cox Proportional Hazards Analysis of DFS

Multivariate Cox Proportional Hazards analysis of DFS by BICR and investigator assessment in the ITT population was performed. Baseline factors including treatment, UISS risk factor, age, gender, ECOG PS, BMI, and NLR were evaluated in the initial model using a stepwise procedure where factors could be entered into the model or removed from the model at each step. Factors with p-value < 0.1 were selected for the final model:

Table 25: Multivariate Stepwise Cox Proportional analysis of DFS by BICR – Study A6181109 – ITT population

Model	Hazard Ratio (95% CI)	p-value
Treatment (sunitinib vs placebo)	0.748 (0.582-0.961)	0.0231
UISS: T3 High vs T3 Low	1.137 (0.862-1.499)	0.3637
UISS: Other vs T3 Low	1.997 (1.310-3.043)	0.0013
NLR (>3 vs ≤3)	0.726 (0.530-0.995)	0.0467

Table 26: Multivariate Stepwise Cox Proportional analysis of DFS by Investigator – Study A6181109 – ITT population

Model	Hazard Ratio (95% CI)	p-value
Treatment (sunitinib vs placebo)	0.820 (0.648-1.037)	0.0980
UISS: T3 High vs T3 Low	1.050 (0.789-1.397)	0.7394
UISS: Other vs T3 Low	1.817 (1.209-2.730)	0.0041
Age (<65 vs ≥65), years	1.299 (1.002-1.684)	0.0484
NLR (>3 vs ≤3)	0.740 (0.551-0.993)	0.0448
Baseline ECOG (ECOG = 0 vs ECOG >0)	1.313 (0.997-1.728)	0.0523

The multivariate analyses confirm that the risk of a DFS event is almost twice higher in the UISS risk group “other” (T4 and N+ tumours) compared to the T3 low.

DFS based on exposure

Additional analyses of DFS according to BICR have been presented:

Table 27: DFS by IRC for subjects with dose reductions in treatment (regardless of time of reduced dose) – As treated

	Sunitinib Malate (N=140)		Placebo (N=15)	
	n	(%)	n	(%)
Number with event	54	(38.6)	6	(40.0)
Type of event				
Disease Recurrence or occurrence of a Secondary Malignancy	51	(36.4)	6	(40.0)
Death	3	(2.1)	0	
Number censored	86	(61.4)	9	(60.0)
Reason for censorship				
No post-baseline cancer event assessments	0		0	
No event at time of data cut-off	86	(61.4)	9	(60.0)
Withdrew consent for follow-up	7	(8.1)	1	(11.1)
Lost to follow-up	4	(4.7)	0	
Receiving further anti-cancer therapy prior to an event	7	(8.1)	2	(22.2)
Still in Disease Follow-up	63	(73.3)	6	(66.7)
Other	3	(3.5)	0	
Disease Relapse or death occurs after >= 2 consecutive missed assessments	2	(2.3)	0	
Probability of being event free at Year 2 [1] (95% CI)	76.4[68.2, 82.8]		68.4[35.7, 87.0]	
Probability of being event free at Year 5 [1] (95% CI)	63.0[53.9, 70.8]		49.9[20.0, 74.1]	
Kaplan-Meier estimates of Time to Event (Year)				
Quartiles (95% CI) [2]				
25%	2.1[1.5, 3.2]		1.6[0.1, 2.5]	
50%	6.8[5.4, .]		2.5[0.5, .]	
75%	. [7.1, .]		. [2.5, .]	
Versus Placebo				
Hazard Ratio[3]	0.714			
95% CI of Hazard Ratio	0.306-1.665			
P-value [4]	0.433			

[1] Estimated from the Kaplan-Meier curve.
[2] Calculated from Brookmeyer and Crowley Method.
[3] Based on the Cox Proportional hazards model.
[4] 2-sided p-value from the unstratified log-rank test.
CI = Confidence Interval

Table 28: DFS by IRC for subjects without any dose reductions (regardless of time on treatment) – As treated

	Sunitinib Malate (N=166)		Placebo (N=289)	
	n	(%)	n	(%)
Number with event	59	(35.5)	136	(47.1)
Type of event				
Disease Recurrence or occurrence of a Secondary Malignancy	54	(32.5)	132	(45.7)
Death	5	(3.0)	4	(1.4)
Number censored	107	(64.5)	153	(52.9)
Reason for censorship				
No post-baseline cancer event assessments	11	(6.6)	6	(2.1)
No event at time of data cut-off	96	(57.8)	147	(50.9)
Withdrew consent for follow-up	9	(9.4)	14	(9.5)
Lost to follow-up	5	(5.2)	6	(4.1)
Receiving further anti-cancer therapy prior to an event	5	(5.2)	11	(7.5)
Still in Disease Follow-up	61	(63.5)	106	(72.1)
Other	7	(7.3)	4	(2.7)
Disease Relapse or death occurs after >= 2 consecutive missed assessments	9	(9.4)	6	(4.1)
Probability of being event free at Year 2 [1] (95% CI)	65.8[56.8, 73.4]		67.6[61.7, 72.8]	
Probability of being event free at Year 5 [1] (95% CI)	55.3[46.0, 63.6]		51.7[45.3, 57.6]	
Kaplan-Meier estimates of Time to Event (Year)				
Quartiles (95% CI) [2]				
25%	1.5[1.3, 1.8]		1.2[0.7, 1.8]	
50%	6.2[4.0, .]		5.6[3.9, 6.6]	
75%	-		-	
Versus Placebo				
Hazard Ratio[3]	0.834			
95% CI of Hazard Ratio	0.614-1.132			
P-value [4]	0.243			

[1] Estimated from the Kaplan-Meier curve.
[2] Calculated from Brookmeyer and Crowley Method.
[3] Based on the Cox Proportional hazards model.
[4] 2-sided p-value from the unstratified log-rank test.
CI = Confidence Interval

Table 29: DFS by IRC for subjects without any dose reductions and completed 9 cycles of study treatment as planned – As treated

	Sunitinib Malate (N=86)		Placebo (N=203)	
	n	(%)	n	(%)
Number with event	34	(39.5)	76	(37.4)
Type of event				
Disease Recurrence or occurrence of a Secondary Malignancy	32	(37.2)	73	(36.0)
Death	2	(2.3)	3	(1.5)
Number censored	52	(60.5)	127	(62.6)
Reason for censorship				
No post-baseline cancer event assessments	0		0	
No event at time of data cut-off	52	(60.5)	127	(62.6)
Withdrew consent for follow-up	1	(1.9)	11	(8.7)
Lost to follow-up	2	(3.8)	5	(3.9)
Receiving further anti-cancer therapy prior to an event	2	(3.8)	6	(4.7)
Still in Disease Follow-up	44	(84.6)	98	(77.2)
Other	2	(3.8)	1	(<1.0)
Disease Relapse or death occurs after >= 2 consecutive missed assessments	1	(1.9)	6	(4.7)
Probability of being event free at Year 2 [1] (95% CI)	72.2[61.1, 80.6]		84.2[78.4, 88.7]	
Probability of being event free at Year 5 [1] (95% CI)	60.7[49.2, 70.4]		64.5[57.1, 71.0]	
Kaplan-Meier estimates of Time to Event (Year)				
Quartiles (95% CI) [2]				
25%	1.7[1.5, 4.1]		3.0[2.3, 4.0]	
50%	. [4.9, .]		6.7[6.0, .]	
75%	-		-	
Versus Placebo				
Hazard Ratio[3]	1.084			
95% CI of Hazard Ratio	0.723-1.625			
P-value [4]	0.695			

[1] Estimated from the Kaplan-Meier curve.
[2] Calculated from Brookmeyer and Crowley Method.
[3] Based on the Cox Proportional hazards model.
[4] 2-sided p-value from the unstratified log-rank test.
CI = Confidence Interval

Figure 14: DFS Analyses Comparing Defined Exposure-Related Subgroups Within the Sunitinib Arm – As-Treated Population

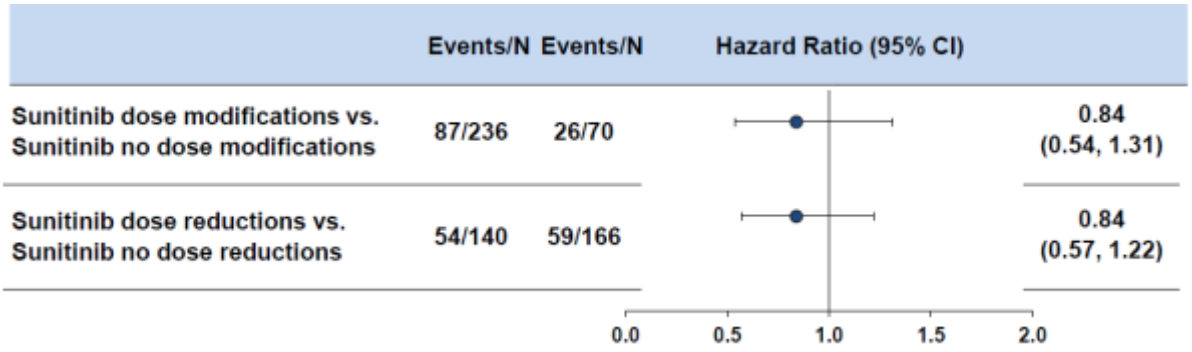
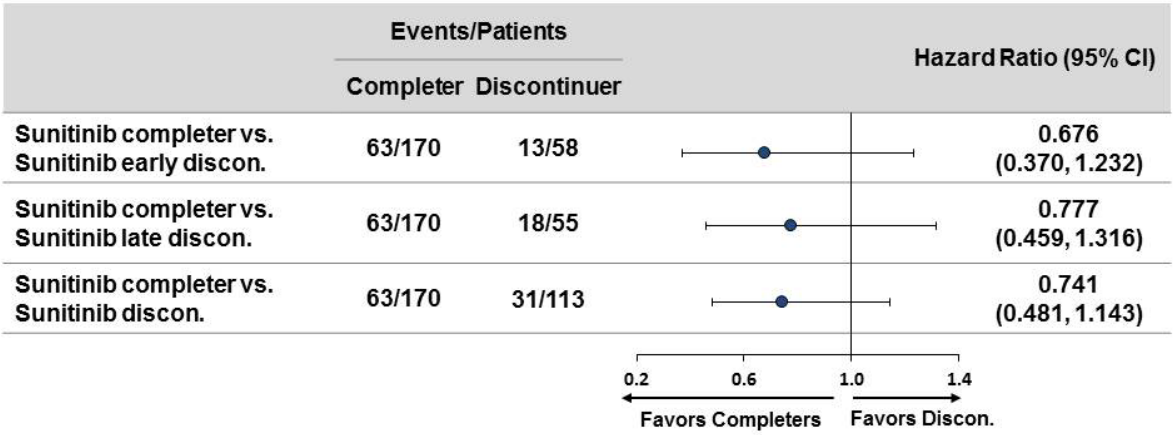


Figure 15: DFS by BICR Assessment Comparing Completers vs Early Discontinuations



Completer: patients who completed 9 cycles of therapy **Discontinuers**: patients who discontinued treatment prior to completing 9 cycles for reasons other than disease relapse or death. **Early Discontinuers**: Patients who discontinued within the first 3 cycles (on or prior to Week 18). **Late Discontinuers**: Patients who completed at least 3 cycles but fewer than 9 cycles.

Table 30: DFS (Based on the Assessments by Independent 3rd Party) Stratified by UISS High Risk Group - Subjects without vs. with dose reductions - As Treated

SU-011248 Protocol A6181109 (Date of data cut-off: 07Apr2016)
Disease Free Survival (Based on the Assessments by Independent 3rd Party) Stratified by UISS High Risk Group* - Subjects without vs. with dose reductions - As Treated
Global Cohort

	Sunitinib arm without any dose reductions (N=166)		Sunitinib arm with dose reductions (N=140)		Placebo (N=304)	
	n	(%)	n	(%)	n	(%)
Number with event	59	(35.5)	54	(38.6)	142	(46.7)
Type of event						
Disease Recurrence or occurrence of a Secondary Malignancy	54	(32.5)	51	(36.4)	138	(45.4)
Death	5	(3.0)	3	(2.1)	4	(1.3)
Number censored	107	(64.5)	86	(61.4)	162	(53.3)
Reason for censorship						
No post-baseline cancer event assessments	11	(6.6)	0		6	(2.0)
No event at time of data cut-off	96	(57.8)	86	(61.4)	156	(51.3)
Withdrew consent for follow-up	9	(9.4)	7	(8.1)	15	(9.6)
Lost to follow-up	5	(5.2)	4	(4.7)	6	(3.8)
Receiving further anti-cancer therapy prior to an event	5	(5.2)	7	(8.1)	13	(8.3)
Still in Disease Follow-up	61	(63.5)	63	(73.3)	112	(71.8)
Other	7	(7.3)	3	(3.5)	4	(2.6)
Disease Relapse or death occurs after >= 2 consecutive missed assessments	9	(9.4)	2	(2.3)	6	(3.8)
Probability of being event free at Year 2 [1] (95% CI)	65.8[56.8, 73.4]		76.4[68.2, 82.8]		67.6[61.8, 72.7]	
Probability of being event free at Year 3 [1] (95% CI)	61.5[52.3, 69.4]		68.2[59.3, 75.5]		59.9[53.9, 65.4]	
Probability of being event free at Year 5 [1] (95% CI)	55.3[46.0, 63.6]		63.0[53.9, 70.8]		51.6[45.4, 57.4]	
Kaplan-Meier estimates of Time to Event (Year)						
Quartiles (95% CI) [2]						
25%	1.5[1.3, 1.8]		2.1[1.5, 3.2]		1.2[0.7, 1.8]	
50%	6.2[4.0, .]		6.8[5.4, .]		5.6[3.9, 6.6]	
75%	-		. [7.1, .]		-	
Versus Sunitinib arm with dose reductions						
Hazard Ratio[3]	1.196					
95% CI of Hazard Ratio	0.820-1.742					
P-value [4]	0.353					
Versus Placebo						
Hazard Ratio[3]	0.848		0.707			
95% CI of Hazard Ratio	0.625-1.151		0.515-0.971			
P-value [4]	0.289		0.031			

[1] Estimated from the Kaplan-Meier curve. CI = Confidence Interval.
[2] Based on the Brookmeyer and Crowley Method.
[3] Based on the Cox Proportional hazards model stratified by UISS High Risk Group.
[4] 2-sided p-value from the log-rank test stratified by UISS High Risk Group.
*UISS High Risk Group:
T3 Low: T3 N0 or NX, M0, and any Fuhrman's grade, and ECOG =0, or T3 No or Nx, M0, Fuhrman's grade =1, and ECOG >=1.
T3 High: T3 N0 or NX, M0, Fuhrman's grade >=2, and ECOG >=1.
Other: T4 N0 or NX, M0, and Fuhrman's grade, and any ECOG status or any T, N1-2, M0 and Fuhrman's grade, and any ECOG status.
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 27JUN2016 Date of Table Generation: 12JUL2017 (23:51)

Analysis to further characterize relapse and recurrence

This analysis was restricted to patients who had DFS events in the primary DFS analysis after the censoring rules had been applied. This analysis was limited by data capture by investigators.

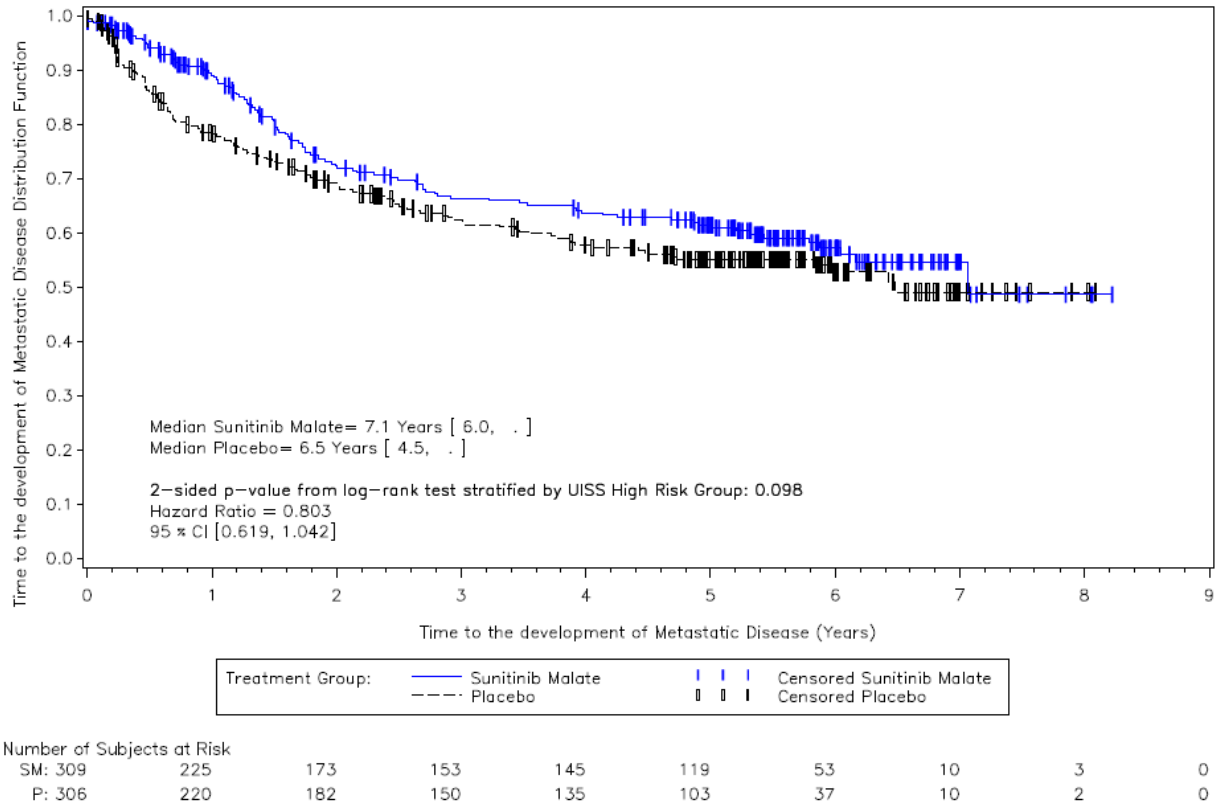
Based on BICR assessments, there were 105 and 140 patients in the sunitinib and placebo arm respectively who had disease recurrence. The majority of recurrences were distant recurrences (92.4% [97/105] of patients in the sunitinib arm and 87.1% [122/140] patients in the placebo arm). Most patients had one site of disease at the time of relapse (84 [27.2%] and 107 [35%] patients in sunitinib and placebo arm according to BICR). The lung was the most common site of distant relapse (40 [12.9%] and 49 [16.0%]), followed by lymph nodes, retroperitoneum and liver.

Difference in time from randomization to the development of metastatic disease or death due to any cause was not statistically significant.

Table 31: Time From Randomization to the Development of Metastatic Disease by BICR Assessment and Investigator Assessment - Study A6181109 – ITT population

	Sunitinib (N = 309)	**Placebo (N = 306)**
BICR Assessment		
Number (%) with Event	105 (34.0)	126 (41.2)
Probability of Being Event Free Year 3 (95% CI)	66.3 (60.1, 71.9)	62.3 (56.3, 67.8)
Kaplan-Meier estimates of DFS (Year) 50% Quartile (95% CI)	7.1 (6.0, NR)	6.5 (4.5, NR)
Versus Placebo Hazard Ratio (95% CI) p-value	0.803 (0.619, 1.042) 0.098	
Investigator Assessment		
Number (%) with Event	117 (37.9)	123 (40.2)
Probability of Being Event Free Year 3 (95% CI)	65.5 (59.4, 70.9)	65.4 (59.4,70.7)
Kaplan-Meier estimates of DFS (Year) 50% Quartile (95% CI)	6.7 (5.9, NR)	7.0 (4.9, NR)
Versus Placebo Hazard Ratio (95% CI) p-value	0.924 (0.717, 1.191) 0.541	

Figure 15: Kaplan-Meier Plot of Analysis of the Time From Randomization to the Development of Metastatic Disease by BICR Assessment - Study A6181109 – ITT population



Number of Subjects at Risk

SM: 309	225	173	153	145	119	53	10	3	0
P: 306	220	182	150	135	103	37	10	2	0

Post-studies anticancer therapy

Sixty-eight (22.0%) patients in the sunitinib arm and 87 (28.4%) patients in the placebo arm received at least 1 follow-up anticancer systemic treatment. The most common post-study treatment were everolimus and sunitinib in the sunitinib arm (18 [5.8%] patients each), while it was sunitinib in the placebo arm (55 [18%] patients). More patients in the placebo arm received subsequent anti-angiogenic therapy (40/68 [58.8%] patients in the sunitinib arm vs. 74/87 [85.1%] patients in the placebo arm).

As of 31 January 2017 (supplemental CSR data cutoff date), an additional 4 patients in the sunitinib arm and 2 patients in the placebo arm received anticancer follow-up treatment for a total of 72 (23.3%) and 89 (29.1%) patients, respectively (see table below).

Table 32: First-Line Anticancer and Anti-Angiogenic Therapies in Study A6181109- Intent-to-Treat Population – Global Cohort

First-Line Therapy	Number (%) of Patients	
	Sunitinib (N =	Placebo (N =
Everolimus	19 (6.1)	2 (0.7)
Sunitinib	19 (6.1)	57 (18.6)
Pazopanib	14 (4.5)	14 (4.6)
Interleukin-2	5 (1.6)	2 (0.7)
Sorafenib	5 (1.6)	1 (0.3)
Interferon	4 (1.3)	6 (2.0)
Bevacizumab	3 (1.0)	2 (0.7)
Temsirolimus	2 (0.6)	0
All Other Therapeutic Products	1 (0.3)	1 (0.3)
Axitinib	1 (0.3)	3 (1.0)
Cyclophosphamide	1 (0.3)	0
Ipilimumab	1 (0.3)	0
Nivolumab	1 (0.3)	0
AMG386	0	1 (0.3)
Atezolizumab	0	1 (0.3)
Carboplatin	0	1 (0.3)
Etoposide	0	1 (0.3)
Investigational Drug	0	2 (0.7)
Lenvatinib	0	1 (0.3)
Pembrolizumab	0	1 (0.3)
Total	**72**	**89**

Date of data cutoff: 31 January 2017.
AMG386 = trebananib; A patient can have 2 first-line therapies.

To evaluate whether or not adjuvant sunitinib adversely impacted the efficacy of follow-up anti-angiogenic therapy for mRCC, two retrospective exploratory analyses were performed:

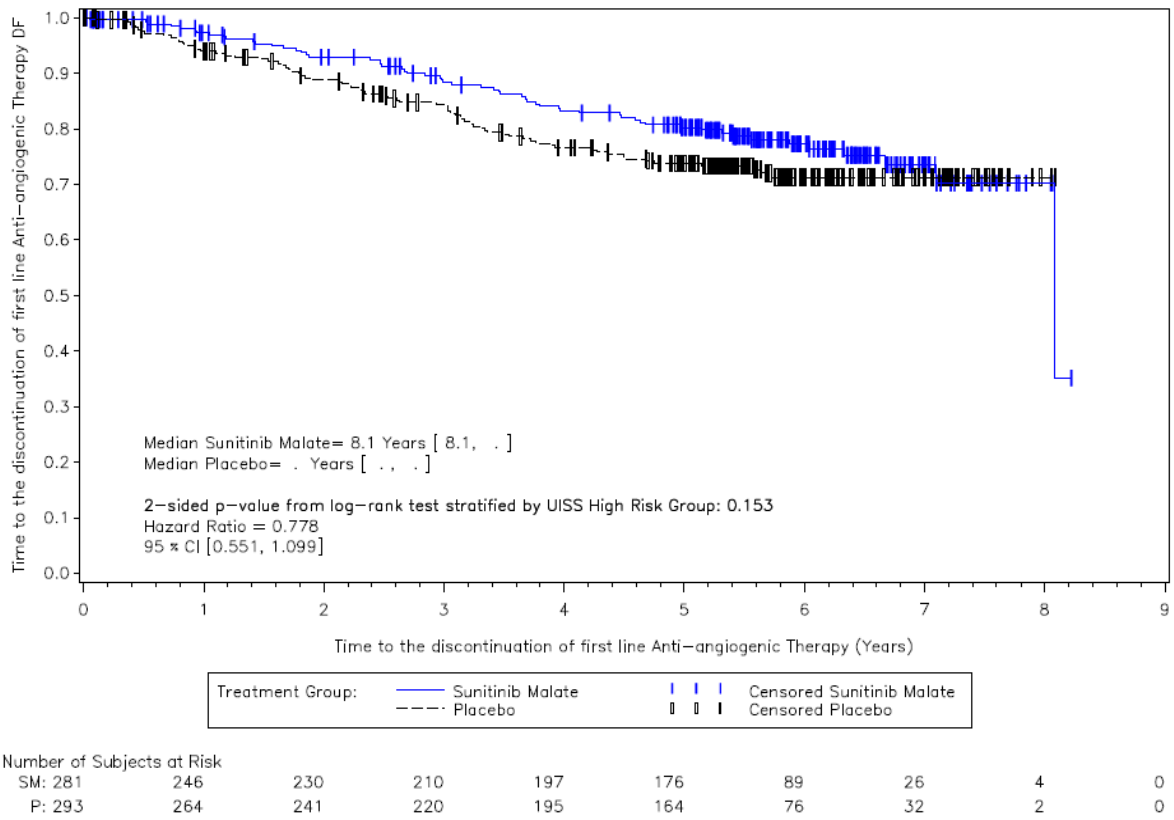
1) Time from randomization to permanent discontinuation of follow-up anti-angiogenic therapy or death. Consideration was given to the first therapy (or therapies if administered in combination) given subsequent to study treatment. Patients with non-anti-angiogenic follow-up therapy reported as the first subsequent therapy following study treatment were excluded from this analysis. Patients who did not have any follow-up therapies or who did not have a stop date for the follow-up anti-angiogenic therapy were censored at the last date the patient was known to be alive. Patients who either died or had a stop date reported for follow-up anti-angiogenic therapy, were considered to have had an event at the earlier of the 2 dates.

Table 33: Time From Randomization to the Discontinuation of Follow-Up Anti-Angiogenic Therapy in Study A6181109 – ITT Population

	Sunitinib (N = 281)	Placebo (N = 293)
Number (%) with Event	58 (20.6)	74 (25.3)
Type of Event, n (%)		
Discontinuation of the follow-up anti-angiogenic therapy	30 (10.7)	53 (18.1)
Death	28 (10.0)	21 (7.2)
Number Censored, n (%)	223 (79.4)	219 (74.7)
Reason for Censorship, n (%)		
Not received any therapy after study treatments	216 (76.9)	202 (68.9)
Follow-up anti angiogenic therapy without known stop date	7 (2.5)	17 (5.8)
Kaplan-Meier estimates of Time to Event (Year)		
50% Quartile (95% CI)a	8.1 (8.1, NR)	NR (NR, NR)
Versus Placebo		
Hazard Ratiob (95% CI)	0.778 (0.551, 1.099)	
p-valuec	0.153	

a. Based on the Brookmeyer and Crowley method.
b. Based on the Cox Proportional Hazards model.
c. 2-sided p-value from the unstratified log-rank test.

Figure 16: Kaplan-Meier Plot of Analysis of the Time from Randomization to the Discontinuation of Follow-Up Anti-Angiogenic Therapy in Study A6181109 ITT Population



2) Time interval from the date of relapse to the discontinuation of the follow-up anti-angiogenic therapy or death. As in the previous analysis, consideration was given to the first therapy (or therapies if administered in combination) given subsequent to study treatment. The analysis was restricted to

patients who had DFS events after the censoring rules had been applied. Patients without relapse or who had a non-anti-angiogenics as their first follow-up therapy were excluded from this analysis. Patients who did not have any follow-up therapies or who did not have a stop date for the follow-up anti-angiogenic therapy were censored at the last date the patient was known to be alive. Patients who either died or had a stop date reported for follow-up anti-angiogenic therapy, were considered to have had an event at the earlier of the 2 dates.

Table 34: Time From Relapse to the End of Follow-Up Anti-Angiogenic Therapy Based on BICR Assessment or Investigator Assessment in Study A6181109 – ITT Population

BICR Assessment		
	Sunitinib (N = 82)	**Placebo (N = 130)**
Number (%) with Event	36 (43.9)	59 (45.4)
Type of Event, n (%)		
Discontinuation of the follow-up anti-angiogenic therapy	22 (26.8)	46 (35.4)
Death	14 (17.1)	13 (10.0)
Number Censored, n (%)	46 (56.1)	71 (54.6)
Reason for Censorship, n (%)		
Not received any therapy after study treatments	39 (47.6)	58 (44.6)
Follow-up anti angiogenic therapy without known stop date	7 (8.5)	13 (10.0)
Kaplan-Meier estimates of Time to Event (Year)		
50% Quartile (95% CI)	3.6 (2.5, NR)	3.2 (2.1, NR)
Versus Placebo		
Hazard Ratio (95% CI)	0.898 (0.593, 1.360)	
p-value	0.612	
Investigator Assessment		
	Sunitinib (N = 99)	**Placebo (N = 143)**
Number (%) with Event	44 (44.4)	66 (46.2)
Type of Event, n (%)		
Discontinuation of the follow-up anti-angiogenic therapy	27 (27.3)	51 (35.7)
Death	17 (17.2)	15 (10.5)
Number Censored, n (%)	55 (55.6)	77 (53.8)
Reason for Censorship, n (%)		
Not received any therapy after study treatments	48 (48.5)	60 (42.0)
Follow-up anti angiogenic therapy without known stop date	7 (7.1)	17 (11.9)
Kaplan-Meier estimates of Time to Event (Year)		
50% Quartile (95% CI)	3.1 (2.1, NR)	2.6 (2.0, 4.0)
Versus Placebo		
Hazard Ratio (95% CI)	0.895 (0.611, 1.311)	
p-value	0.568	

Table 35: Disease Free Survival By BICR for subjects with T3 and Fuhrman's Grade >2 or T4 or Node Positive with any T *(i.e. patients at highest risk)*

	Sunitinib (N = 199)	Placebo (N = 199)
Number (%) with Event	81 (40.7)	105 (52.8)
Type of Event, n (%)		
Disease Recurrence or Occurrence of a Secondary Malignancy	73 (36.7)	103 (51.8)
Death	8 (4.0)	2 (1.0)
Number Censored, n (%)	118 (59.3)	94 (47.2)
Reason for Censorship, n (%)		
No Post-Baseline Cancer Event Assessments	10 (5.0)	3 (1.5)
No Event at Time of Data Cutoff	108 (54.3)	91 (45.7)
Withdrew Consent for Follow-Up	7 (6.5)	9 (9.9)
Lost to Follow-Up	5 (4.6)	3 (3.3)
Receiving Further Anti-Cancer Therapy Prior to an Event	8 (7.4)	10 (11.0)
Still in Disease Follow-up	75 (69.4)	62 (68.1)
Other	7 (6.5)	3 (3.3)
Disease Relapse or Death Occurred After ≥2 Consecutive Missed Assessments	6 (5.6)	4 (4.4)
Probability of Being Event Free		
Year 1[a] (95% CI)	85.3 (79.2, 89.8)	71.7 (64.7, 77.6)
Year 2[a] (95% CI)	68.0 (60.4, 74.5)	61.1 (53.6, 67.7)
Year 3[a] (95% CI)	61.5 (53.5, 68.4)	54.4 (46.9, 61.4)
Year 5[a] (95% CI)	54.7 (46.6, 62.0)	44.3 (36.7, 51.7)
Kaplan-Meier estimates of DFS (Year)		
50% Quartile (95% CI)[b]	6.0 (4.1, NR)	3.9 (2.5, 5.8)
Versus Placebo		
Hazard Ratio[c] (95% CI)	0.727 (0.544, 0.972)	
p-value[d]	0.0305	

Figure 17: Kaplan-Meier Plot of Disease Free Survival (By BICR) for subjects with T3 and Fuhrman's Grade >2 or T4 or Node Positive with any T *(i.e. patients at highest risk)*

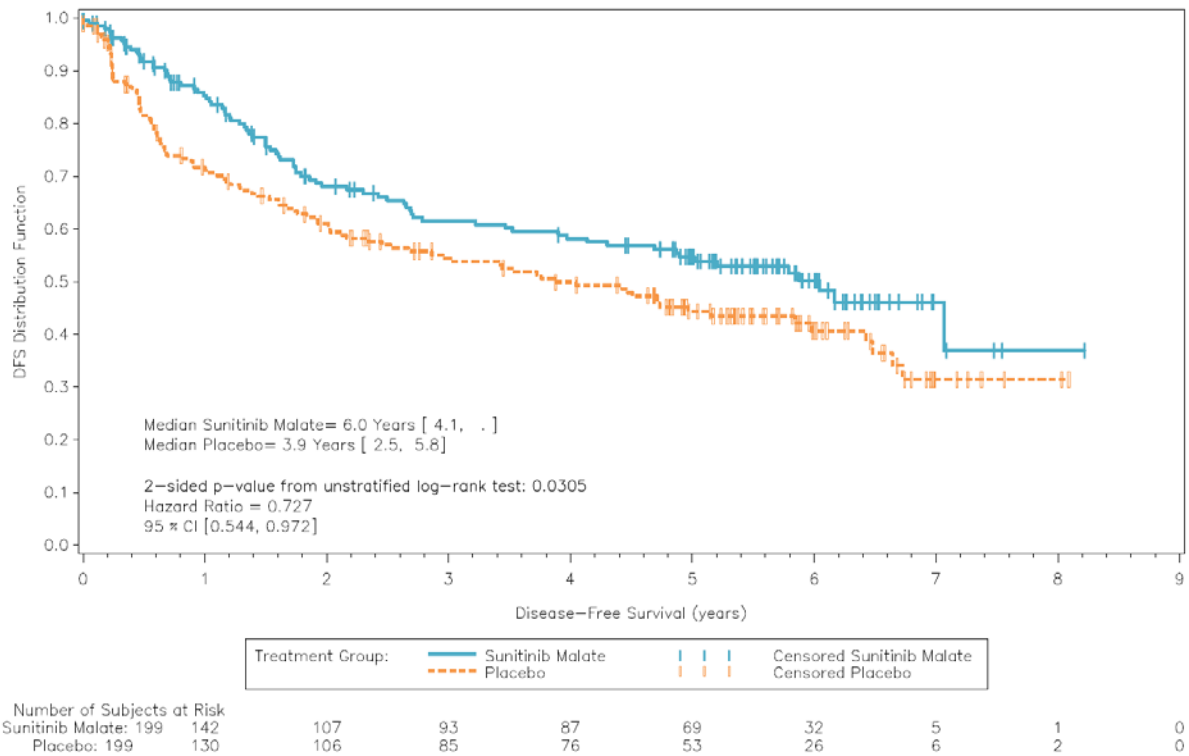
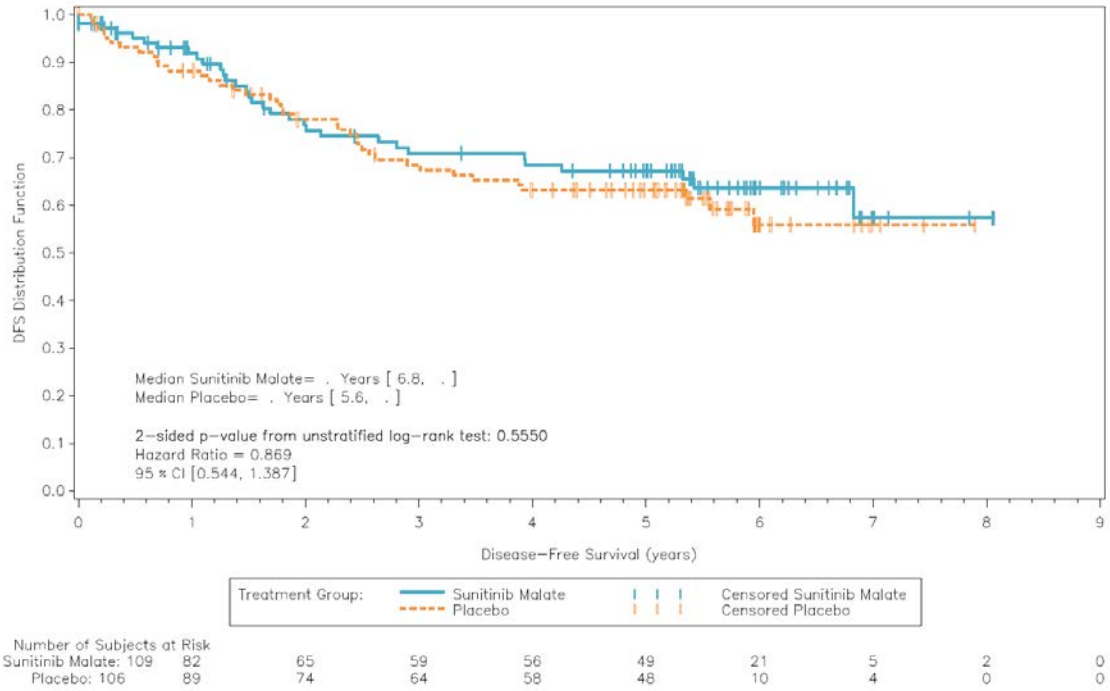


Table 36: DFS (By BICR) for subjects with T3 and Fuhrman's Grade 1 or 2 *(i.e. at lowest risk)*

	Sunitinib (N = 109)	Placebo (N = 106)
Number (%) with Event	32 (29.4)	39 (36.8)
Type of Event, n (%)		
Disease Recurrence or Occurrence of a Secondary Malignancy	32 (29.4)	37 (34.9)
Death	0 (0)	2 (1.9)
Number Censored, n (%)	77 (70.6)	67 (63.2)
Reason for Censorship, n (%)		
No Post-Baseline Cancer Event Assessments	4 (3.7)	3 (2.8)
No Event at Time of Data Cutoff	73 (67.0)	64 (60.4)
Withdrew Consent for Follow-Up	9 (12.3)	6 (9.4)
Lost to Follow-Up	4 (5.5)	3 (4.7)
Receiving Further Anti-Cancer Therapy Prior to an Event	4 (5.5)	3 (4.7)
Still in Disease Follow-up	48 (65.8)	49 (76.6)
Other	3 (4.1)	1 (1.6)
Disease Relapse or Death Occurred After ≥2 Consecutive Missed Assessments	5 (6.8)	2 (3.1)
Probability of Being Event Free		
Year 1[a] (95% CI)	91.9 (84.5, 95.9)	88.3 (80.2, 93.2)
Year 2[a] (95% CI)	76.9 (66.7, 84.3)	78.0 (68.6, 85.0)
Year 3[a] (95% CI)	70.9 (60.2, 79.2)	68.5 (58.3, 76.7)
Year 5[a] (95% CI)	67.2 (56.3, 76.0)	63.2 (52.7, 71.9)
Kaplan-Meier estimates of DFS (Year)		
50% Quartile (95% CI)[b]	NR (6.8, NR)	NR (5.6, NR)
Versus Placebo		
Hazard Ratio[c] (95% CI)	0.869 (0.544, 1.387)	
p-value[d]	0.5550	

a. Estimated from the Kaplan-Meier curve.
b. Based on the Brookmeyer and Crowley method.
c. Based on the Cox Proportional Hazards model
d. 2-sided p-value from the unstratified log-rank test.

Figure 18: Kaplan-Meier Plot of Disease Free Survival (By BICR) for subjects with T3 and Fuhrman's Grade 1 or 2 *(i.e. patients at lowest risk)*



Biomarker analysis

Exploratory biomarker analysis have been submitted to fulfill the post-approval commitment generated with the assessment of FUM 22.05 regarding the evaluation of biomarkers predicting safety and efficacy of sunitinib.

Genotyping

The objective of the genotyping analysis was to explore the potential association between genetic polymorphism in VEGF-A and VEGFR3 with DFS and OS.

Patients who had at least 1 genotype results available for exploratory genotype analysis were 286 patients (46.9% of the total population). Both treatment arms were well balanced with regard to patient's and risk group characteristics. However, there are significant differences between patients with or without genotype data in terms of age, race, and UISS high-risk group, therefore the population used in this genotyping analysis is not considered representative of the overall study population and conclusions derived from the analysis of the genotyped patients are not be extrapolated to the full study population.

The comparisons between genotyped and non-genotyped patients are exploratory in nature, and therefore, the p-value is considered descriptive and rather than confirmatory. It should be noted that some genotypes were represented by fewer than 10 patients.

The main conclusions of the genotype analyses were:

- The genotypes 'C/C' for VEGFR1 rs9554320, 'T/T' for VEGFR2 rs2071559, and 'T/T' for eNOS rs2070744 were associated with a longer DFS in the sunitinib arm versus the placebo arm.
- The common genotypes 'C/C' of VEGFR1 rs9582036, 'A/A' of VEGFR1 rs9554320 showed trends toward longer DFS versus the heterozygous and rare homozygous genotypes in the sunitinib arm,

in the placebo arm and in the combined treatment arms.

- Most of these tests were not considered statistically significant after p-value adjustment (p-value >0.0045), reinforcing the need for additional validation of those exploratory findings.

Immunohistochemistry Biomarker

Archival tumour tissue was evaluated for tumour-infiltrating and/or myeloid-derived suppressor cell population by IHC analysis of biomarkers CD4, CD8, CD68 and PD-L1 and for potential association with DFS and OS.

191 patients (101 in the Sunitinib arm and 90 in the placebo arm) had at least a baseline biomarker result for at least 1 biomarker, corresponding to about 31% of the total enrolled population.

No significant difference was seen between the IHC-analyzed and non-analyzed subpopulations, and thus the subpopulation used in this study is considered representative of the study population as a whole, extrapolation to the overall study population is limited due to the small sample size as only approximately 31% patients were included in the IHC analyses.

In general, the analyses showed that staining for immune-related cells was rather low. A very low level of expression of PD-L1 was found in the analyzed samples.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37: Summary of Efficacy for trial A6181109 (S-TRAC)

Title: Sunitinib Treatment of Renal Adjuvant Cancer (S-TRAC): A Randomized Double Blind Phase 3 Study of Adjuvant Sunitinib vs. Placebo in Subjects at High Risk of Recurrent Renal Cell Carcinoma (RCC)			
Study identifier	EudraCT number: 2006-004024-37		
Design	Multicenter, international, randomized 1:1, double-blind, placebo-controlled phase III trial of adjuvant sunitinib 50 mg on schedule 4/2 vs. placebo in adult patients with high risk of recurrent RCC following nephrectomy.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		not applicable not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Sunitinib		50 mg orally once daily schedule 4/2 (4 weeks on 2 weeks off) for maximum 9 cycles (approximately 1 year) or until disease recurrence, occurrence of a secondary malignancy, significant toxicity, or withdrawal of consent. 309 patients randomized, 306 treated
	Placebo		Blinded matching placebo 306 patients randomized, 304 treated
Endpoints and definitions	Primary endpoint	DFS (by BICR)	time from randomization to recurrence or occurrence of a secondary malignancy or death, based on BICR assessment

	Secondary endpoint	DFS (by investigator)	time from randomization to recurrence or occurrence of a secondary malignancy or death, based on investigator assessment
	Secondary endpoint	OS	time from randomization to death due to any cause
	Secondary endpoint	PROs	Assessed with EORTC-QLQ-C30 and EQ-5D questionnaires
Data cut off date	7 April 2016		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and effect estimate per comparison	Treatment group	Sunitinib 50 mg OD orally 4/2 for 9 cycles (1 year)	Placebo
	Number of subject	309	306
	Primary endpoint		
	DFS (BICR) N. with events (%)	113 (36.6)	144 (47.1)
	Median DFS years (95% CI)	6.8 (5.8, NR)	5.6 (3.8, 6.6)
	HR Sunitinib vs. placebo (95% CI)	0.761 (0.594, 0.975)	
	p-value (2 sided log-rank test stratified by UISS groups)	0.030	
	Secondary endpoints		
	DFS (Investigator) N. with events (%)	132 (42.7)	158 (51.6)
	Median DFS years (95% CI)	6.5 (4.7, 7.0)	4.5 (3.8, 5.9)
	HR Sunitinib vs. placebo (95% CI)	0.811 (0.643, 1.023)	
	p-value (2 sided log-rank test stratified by UISS groups)	0.077	
	OS N. with events (%)	64 (20.7)	64 (20.9)
	Median OS years (95% CI)	NR	NR
	HR Sunitinib vs. placebo (95% CI)	1.014 (0.761, 1.435)	
	p-value (one sided)	0.938	
Notes	Updated OS (cut-off date 31st January 2017): HR = 0.918 (95% CI: 0.659, 1.279; 2-sided p-value = 0.612, stratified). Median OS not reached for either treatment arm.		

Analysis performed across trials (pooled analyses and meta-analysis)

In response to CHMP request, the MAH has pooled data from the highest risk patients in ASSURE (described later on) and S-TRAC (see table below). Meta-analyses should be interpreted with caution given multiple limitations.

For these analyses, highest risk was defined as:

- T3 High: T3 N0 or Nx, M0, Fuhrman's Grade ≥2, ECOG PS ≥1;
- T4: T4 N0 or Nx, M0, any Fuhrman's grade, any ECOG PS; or
- Node Positive: Any T, N1 2, M0, any Fuhrman's grade, any ECOG PS.
- Clear cell >25% and patients who started on 50 mg and did not have their dose reduced below 37.5 mg.

Table 38. Meta-Analysis of Disease-Free Survival in Patients at Highest Risk of Recurrent Renal Cell Carcinoma from S-TRAC and ASSURE

Analysis	Number of Patients/ Number of Events		Median (95% CI)		Hazard Ratio (95% CI)	p-value
	Sunitinib	Placebo	Sunitinib	Placebo		
S-TRAC BICR	194/ 78	194/ 98	6.2 (4.9, NR)	4.0 (2.6, 6.0)	0.737 (0.548, 0.993)	0.044
S-TRAC INV	194/ 90	194/ 109	5.9 (4.4, 7.0)	3.9 (2.8, 5.6)	0.763 (0.577, 1.009)	0.056
ASSURE INV[a]	39/ 21	62/ 40	3.0 (1.7, 6.1)	2.1 (1.1, 6.7)	0.852 (0.501, 1.447)	0.551
Meta-Analysis INV[a]	**233/ 111**	**256/ 149**	**5.8 (3.5, 6.6)**	**3.3 (2.3, 4.5)**	**0.772 (0.604, 0.987)**	**0.039**

a. Includes clear cell >25% and patients who started on 50 mg and did not have their dose reduced below 37.5 mg

Clinical studies in special populations

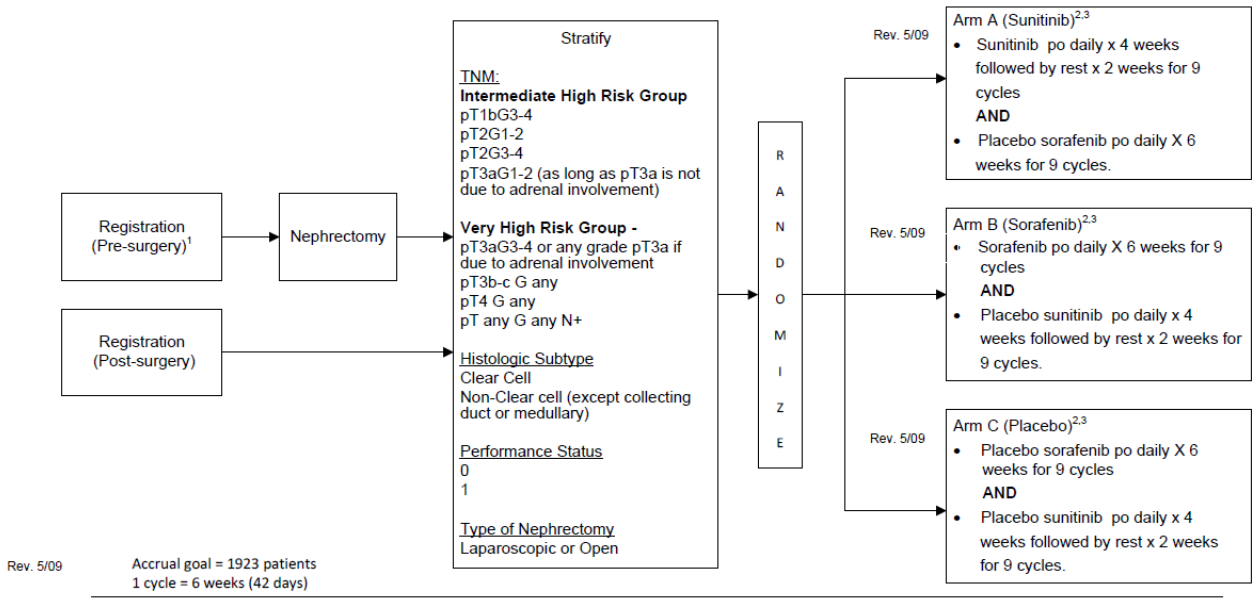
Not performed.

Study E2805/ASSURE

ASSURE: Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma

ASSURE (E2805) is a randomized, double-blind, placebo controlled phase III study led by the European Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN), ClinicalTrials.gov Identifier NCT00326898, investigating adjuvant treatment with sunitinib or sorafenib vs. placebo in previously untreated patients with resected RCC.

Figure 19: study design ASSURE trial



Rev. 5/09 Accrual goal = 1923 patients
1 cycle = 6 weeks (42 days)

1. All patients must be registered either pre- or post-surgery. Physicians are strongly urged to register patients prior to radical or partial nephrectomy so that fresh tissue can be procured for correlative endpoints at the time of surgery; however, patients may participate in this Phase III trial even if they are registered following surgery.

Rev. 7/09 2. Biopsy at recurrence.

Rev. 5/09 Rev. 7/09 Rev. 7/09 3. Patients should start sunitinib / placebo at 37.5mg (3 x 12.5mg) orally once daily and sorafenib / placebo at 400mg (2 x 200mg) orally once daily with subsequent **mandatory escalation** to sunitinib / placebo at **50mg** (4 x 12.5mg) orally once daily and sorafenib / placebo at 400mg (2 x 200mg) orally **twice** daily at the beginning of cycle 2 or 3 if ONLY grade 1 or lower toxicity has occurred in the preceding cycle. In addition, dose escalation at the beginning of cycle 2 or 3 is allowed if the most severe grade of toxicity in the preceding cycle is grade 2.

Rev. 4/07, 9/08 NOTE: Patients with cT1b-T4N0 or any fully resectable (N1-2)M0 disease should be included in pre-operative registration.

Rev. 9/08 NOTE: Please see Section 3.2.3 for post-operative staging requirements.

Differences between the ASSURE study and S-TRAC (A6181109) study

The main differences between ASSURE and S-TRAC studies are summarized in the table below:

Table 39: Key Study Design Differences Between the ASSURE Study and Study A6181109

	ASSURE Study	Study A6181109
Patient Population	• 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.	• T3 N0 or NX, M0; • T4 N0 or NX, M0; • Any T, N1-2, M0.
Central Review conducted to confirm lack of metastasis prior to randomization	No	Yes
Histology	Clear cell and non-clear cell RCC	Preponderant (defined as >50%) clear cell RCC
Starting Dose (sunitinib arm)	Approximately one-third of patients received a starting sunitinib dose of 37.5 mg once daily and two-thirds received 50 mg once daily	50 mg once daily for all patients
Dose Reductions (sunitinib arm)	2 dose reduction levels (37.5 mg and 25 mg)	1 dose reduction level (37.5 mg)
Assessment Schedule of recurrence or occurrence of a secondary malignancy	Every 3 cycles (approximately every 4 months) during treatment, then every 6 months for 2 years, and then once a year for 10 years during follow-up	Every 12 weeks during the first 3 years and every 6 months thereafter
Definition of DFS	Event: • Recurrence • Death • Secondary malignancy (excluding localized breast or prostate, non-melanoma skin) Censoring: • Relapse after start of non-protocol therapy considered an event • Patients without follow-up disease evaluations were censored at the date of last contact • No censoring due to time without adequate assessment	Event: • Recurrence • Death • All secondary malignancy Censoring: • Relapse after start of non-protocol therapy censored at last assessment prior to start of therapy • Patients without follow-up disease evaluations were censored at date of randomization • Patients with 2 or more missed assessments prior to relapse/death were censored at last assessment prior to the missed visits

Table 40: summary of patients in the ASSURE study who met the recruitment/dosing criteria from study A6181109 – as treated population

	Sunitinib (N=166)	Placebo (N=228)	Total (N=394)
Any T, N1-2, M0, any Fuhrman's Grade, any ECOG PS	10 (6.0)	28 (12.3)	38 (9.6)
T3 N0 or NX, M0, Fuhrman's Grade ≥2, ECOG PS missing	2 (1.2)	3 (1.3)	5 (1.3)
T3 N0 or NX, M0, Fuhrman's Grade ≥2, ECOG PS >=1	27 (16.3)	30 (13.2)	57 (14.5)
T3 N0 or NX, M0, any Fuhrman's Grade ECOG PS 0 or Fuhrman's Grade =1 ECOG PS ≥1	126 (75.9)	167 (73.2)	293 (74.4)
T4 N0 or NX, M0, any Fuhrman's Grade, any ECOG PS	1 (0.6)	0	1 (0.3)

N = number of patients meeting one of the above criteria who have clear cell RCC and were prescribed sunitinib 50 mg at Cycle 1 and either 50 mg or 37.5 mg in subsequent cycles in each treatment arm. Missing N stage was considered NX.

Methods

Study participants

In the ASSURE study, eligible patients must have been 18 years of age or older, had histologically proven, completely resected (clear margins), clear or non-clear cell RCC. Patients were treatment-naïve for kidney cancer, had ECOG PS 0 or 1, normal organ function, and completed surgery between 4-12 weeks prior starting treatment. TNM stage (AJCC 6th edition, 2002) included:

- pT1b G3-4 N0 (or pNX where clinically N0) M0
- pT2 - pT4 G(any) N0 (or pNX where clinically N0) M0
- T(any) G(any) N+(fully resected) M0

Main exclusion criteria were collecting duct or medullary carcinoma, evidence of residual or mRCC (as assessed by investigator) or history of distant metastases, prior anti-cancer treatments including metastasectomy or radiation therapy. Patients should have LVEF ≥ 50%, QTc < 500 msec, adequate organ function and no serious intercurrent illness.

Treatments

In ARM A, sunitinib was administered orally OD for 4 weeks on/2 weeks off of each 6-week cycle, for 9 cycles (i.e. about 1 year). When the study began, the starting dose of sunitinib/placebo was 50 mg OD. After observing a high rate of treatment discontinuation due to adverse events or patient refusal, each drug's starting dose was reduced and then individually titrated. The starting dose of sunitinib was decreased to 37.5 mg OD. If the patient experienced no toxicities of grade 2 or higher, then the dose was escalated to 50 mg at the beginning of cycle 2 or 3. Starting dose of sorafenib was reduced as well.

As a result, among the 647 patients randomized to sunitinib arm, 438 (69.6%) were in the full starting dose group, and 191 (30.4%) at a reduced starting dose. Data is unknown/ missing for 18 patients.

Objectives

Primary objective: To demonstrate an improvement in DFS in locally advanced renal cell carcinoma patients randomly assigned to adjuvant sunitinib (Arm A) or sorafenib (Arm B) versus placebo (Arm C) after radical or partial nephrectomy.

Secondary objective: OS, toxicity.

Other secondary objectives (non-assessed in the CRS provided): molecular analyses, QoL

Outcomes/endpoints

Primary endpoint: DFS, defined as time from randomization to recurrence, development of second primary cancer (other than localized breast cancer, localized prostate cancer, or non-melanoma skin cancer), or death from any cause.

No central imaging review was performed. DFS is based on investigator's assessment.

Censoring rules:

- Patients alive without recurrence: censored at the date of last disease evaluation.
- Patients with no follow-up after randomization: censored at the date of randomization.
- Patients with no follow-up disease evaluation: censored at the date of last contact.

Patients determined to be ineligible due to the presence of disease at baseline will be considered to have recurred on day 1.

Secondary endpoint: OS, defined as the time from study entry to death from any cause.

Patients alive at the time of analysis will be censored at the date last known alive. Patients for whom no follow-up survival data are available will be censored at baseline.

Sample size

Original design

The study was designed to demonstrate a 25% reduction in the hazard rate of DFS events among patients treated with either agent compared to placebo, corresponding to an improvement in median DFS from 5.8 to 7.7 years. In the original design, planned full information was 498 events in the two arms for that comparison, which would have provided 80% power, allowing for interim analyses, the first of which was scheduled to occur at approximately 34% of information.

Revised Design

Because of higher than expected rates of treatment discontinuation on the experimental arms due to adverse events and patient refusal, an amendment to expand accrual to 1923 patients was activated in July, 2009. The revised design proposed to enroll these patients over 4 years and follow them for 6.6 additional years. Full information would exist when 842 DFS events were observed on the arms being compared. This revised design provided 81% power to test the original hypothesis of 25% reduction in the hazard rate, assuming the discontinuation rate on the experimental arms was 23.4%. Yearly interim analyses were planned beginning at approximately 33% of full information (275 events on the 2 arms being compared). The first interim analysis was not to occur before accrual was complete.

Table 41: overview of original and revised design

	Original	Revised
Sample size	444 per arm (1332)	641 per arm (1923)
% Intermediate High Risk	69% (5-yr RFR 61·8%)	50% (5-yr DFS61·8%)
% Very High Risk	31% (5-yr RFR 39·7%)	50% (5-yr DFS 39·7%)
Median disease-free survival	5·8 to 7·7 years (25% hazard reduction)	4·9 to 6·5 years (25% hazard reduction)
Median OS	7·4 to 10 years (26% hazard reduction)	6·6 to 8·08 years (26% hazard reduction)
DFS Events for Full Information	498/pair of arms	842/pair of arms
Power	80%	80%
Type I Error	2·5%	2·5%
Accrual rate	333 patients/year	480 patients/year

RFR: Recurrence-free rate
DFS: Disease-free survival

From Haas NB et al. Lancet 2016

Randomization

Randomization was 1:1:1. Treatments were assigned using permuted blocks within strata with dynamic balancing within main institutions and their affiliate networks. Stratification factors were:

1) TNM:

Intermediate High Risk Group vs.

pT1b G 3-4 N0(or pNX where clinically N0) M0

pT2 G 1-2 N0(or pNX where clinically N0) M0

pT2 G 3-4 N0(or pNX where clinically N0) M0

pT3a G1-2 (as long as pT3a is not due to adrenal involvement) N0 (or pNX where clinically N0) M0

Patients with microvascular invasion of the renal vein of pT1a-pT3a (as long as pT3a is not due to adrenal involvement and grade 1-2) N0(or pNX where clinically N0) M0

Very High Risk Group

pT3a G3-4 (or any grade pT3a if due to adrenal involvement) N0 (or pNX where clinically N0) M0

pT3b-c G any N0(or pNX where clinically N0) M0 or

pT4 G N0(or pNX where clinically N0) M0 any or

pT any G any N+

Patients with microvascular invasion of the renal vein with above other characteristics

2) Histologic Subtype: Clear Cell vs. Non-Clear Cell

3) Performance Status: 0 vs. 1

4) Type of Nephrectomy: Laparoscopic vs. Open

Blinding

The study was double-blind.

Statistical methods

The primary analysis population included all patients as randomized (ITT population).

Accrual was expanded to 1923 because of higher than expected rates of treatment discontinuation on the experimental arms due to adverse events and patient refusal. The revised design proposed to enroll these patients over 4 years and follow them for 6.6 additional years. Full information would exist when 842 DFS events were observed on the arms being compared. This revised design provided 81% power to test the original hypothesis of 25% reduction in the hazard rate, assuming the discontinuation rate on the experimental arms was 23.4%. Yearly interim analyses were planned beginning at approximately 33% of full information (275 events on the 2 arms being compared). The first interim analysis was not to occur before accrual was complete.

Significance levels at each analysis were determined using a truncated O'Brien-Fleming error spending rate function. Boundaries for analyses prior to an information proportion of 50% were truncated at 0.00025, with the significance levels at subsequent analyses adjusted to preserve the overall type I error rate. At each analysis (interim and final), one-sided p-values comparing each of the two agents to placebo were calculated using a stratified log-rank test. Each of the two p-values was then compared to the nominal significance level corresponding to an overall significance level of 0.0125. If either p-value was smaller than the corresponding nominal significance level, the other p-value would have been compared to the nominal significance level corresponding to an overall significance level of 0.025. At each interim analysis, a nominal (1-2α) 100% confidence interval was computed. If the confidence interval did not contain the alternative of interest (adjusted hazard ratio of 1.25), then the Data Safety Monitoring Committee could have considered stopping the study early for lack of effect.

DFS among patients with clear cell histology will be included in a secondary efficacy analysis. The analysis should occur when 794 DFS events have been observed among patients with clear cell histology in 2 arms being compared - expected to occur about 13 years after the start of the study (about 2 years after the primary efficacy analysis).

The study was designed to have 80% to detect a 20.6% reduction in the survival hazard rate, corresponding to an improvement in median overall survival from 6.4 to 8.08 years, assuming an exponential distribution. Power for this comparison using a one-sided 1.25% log rank test was expected to be available when 719 deaths had occurred.

Results

Participant flow

Figure 20:

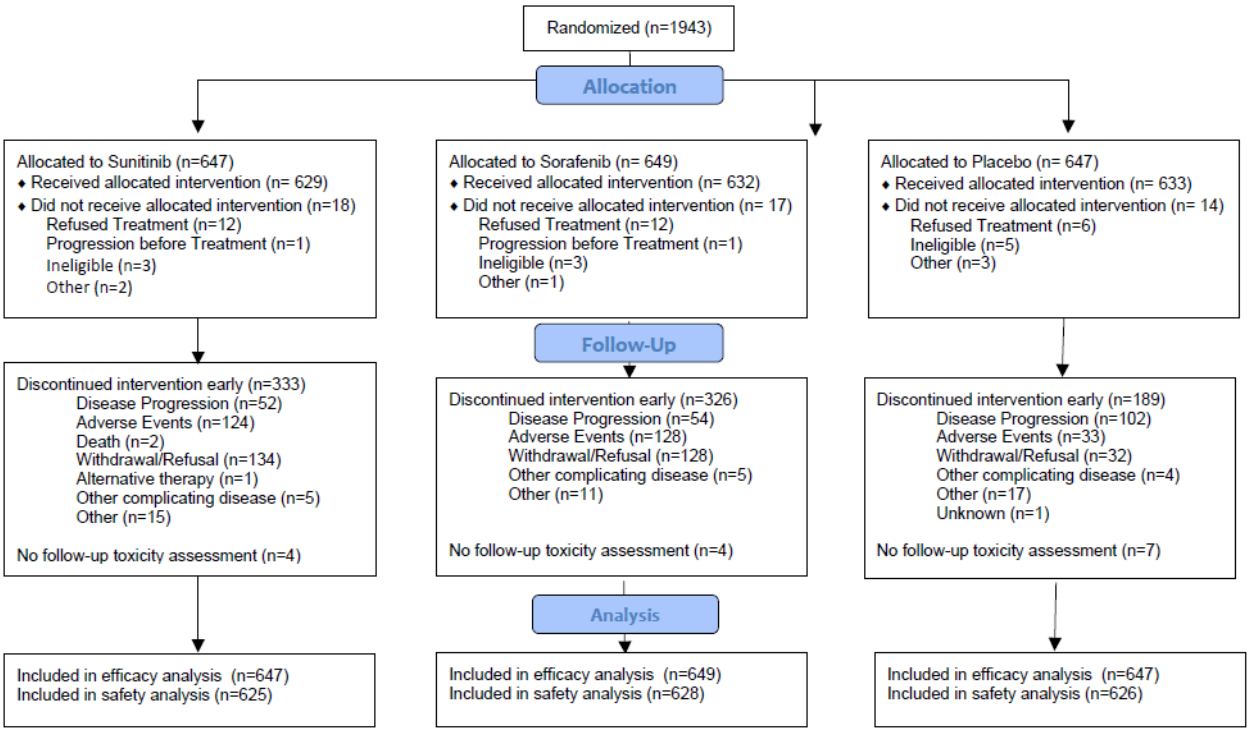


Table 42: patient disposition in the ASSURE study

	Number (%) of Patients	
Population Group	**Sunitinib N (%)**	**Placebo N (%)**
Intent-to-Treat	647	647
As-Treated	629	633
Not Treated	18	14
Discontinued from Treatment	333 (51.5)	189 (29.2)

Recruitment

Recruitment was from April 2006 to September 2010 across 226 study centers in USA and Canada.

Data cut-off for the report was 27th August 2015. Median follow-up as of this date is 69.7 months.

Conduct of the study

There were 5 updates and 14 addenda to the original protocol of April 2006.

Because of higher than expected rates of treatment discontinuation on the experimental arms due to adverse events and patient refusal, the protocol was amended in 2009 (when recruitment was ongoing) to reduce drugs starting dose for the first 1-2 cycles and escalated to full dose based on side effects, and to expand accrual to 1923 patients.

Baseline data

Table 43: selected baseline patients characteristics –ASSURE study – ITT population

	Sunitinib (N = 647)	Placebo (N = 647)
Age (years):		
≤48	157 (24.3)	155 (24.0)
49-56	172 (26.6)	167 (25.8)
57-64	160 (24.7)	178 (27.5)
≥65	158 (24.4)	147 (22.7)
Gender, n (%)		
Male	429 (66.3)	443 (68.5)
Female	218 (33.7)	204 (31.5)
Race, n (%)		
White	598 (93.6)	585 (92.0)
African-American	27 (4.2)	31 (4.9)
Asian	11 (1.7)	15 (2.4)
Hawaiian/Pacific Island	1 (0.2)	0
Native American	2 (0.3)	5 (0.8)
Other	0	0
Unknown/Missing	8	11
Ethnicity, n (%)		
Hispanic	30 (5.0)	41 (6.8)
Non-Hispanic	576 (95.0)	560 (93.2)
Unknown/Missing	41	46
ECOG Performance Status, as stratified, n (%)		
0	510 (78.8)	508 (78.5)
1	137 (21.2)	139 (21.5)

N = number of patients in arm; n = number of patients with observations.

Table 44: selected baseline disease characteristics –ASSURE study – ITT population

	Sunitinib (N = 647)	Placebo (N = 647)
Primary Diagnosis, n (%)		
Renal Cell Carcinoma	647 (100.0)	647 (100.0)
Disease of Body Site at Diagnosis, n (%)		
Right Kidney	316 (48.8)	312 (48.3)
Left Kidney	330 (51.0)	334 (51.7)
Both Kidneys	1 (0.2)	0 (0.0)
Histological Classification at Screening, n (%)		
Clear Cell Carcinoma	512 (79.1)	509 (78.8)
Clinical Tumour Stage (confirmed), n (%)		
T1A	9 (1.4)	8 (1.2)
T1B	73 (11.4)	78 (12.1)
T2	197 (30.8)	197 (30.7)
T3A	197 (30.8)	171 (26.6)
T3B	153 (23.9)	174 (27.1)
T3C	4 (0.6)	6 (0.9)
T4	6 (0.9)	6 (0.9)
TX	0 (0.0)	2 (0.3)
UCLA Risk Stratification, n (%)		
Intermediate High	323 (49.9)	326 (50.4)
Very High	324 (50.1)	321 (49.6)
Fuhrman's Grade		
1	12 (1.9)	17 (2.7)
2	210 (32.9)	192 (30.0)
3	296 (46.3)	301 (47.1)
4	121 (18.9)	129 (20.2)
Unknown/Missing	8 (1.2)	8 (1.2)
AJCC Stage, n (%)		
I	57 (8.8)	64 (9.9)
II	159 (24.6)	154 (23.8)
III	422 (65.2)	425 (65.8)
IV	9 (1.4)	3 (0.5)

Numbers analyzed

The primary analysis population included all patients as randomized (ITT population). Overall, 1943 patients were randomized; 647 were assigned to the sunitinib arm and 647 to placebo.

Outcomes and estimation

Primary endpoint

DFS

There was no statistically significant difference in DFS for sunitinib vs. placebo, based on the stratified log-rank test (HR 1.02, 97.5%CI 0.85-1.23, p = 0.80).

Table 45: DFS –ASSURE trial – ITT population

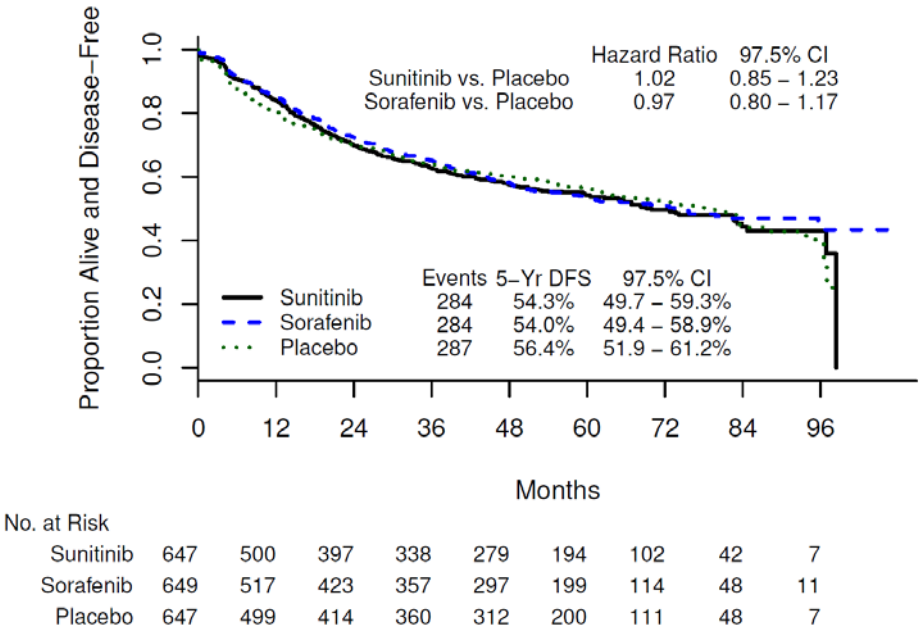
Table 44: DFS Summary

	Sunitinib	Sorafenib	Placebo
Patients	647	649	647
Events	284	284	287
5-Yr DFS	54.3%	54.0%	56.4%
97.5% CI	49.7 - 59.3%	49.4 - 58.9%	51.9 - 61.2%
Median DFS (yrs)	5.8	6.1	6.6
97.5% CI (yrs)	5.0 - NR	4.8 - NR	5.3 - 7.8

Table 45: DFS Differences

	Sunitinib vs. Placebo	Sorafenib vs. Placebo
Stratified Logrank P	0.80	0.72
Hazard Ratio	1.02	0.97
97.5% CI	0.85 - 1.23	0.80 - 1.17

Figure 21: DFS –ASSURE trial – ITT population



No. at Risk

Sunitinib	647	500	397	338	279	194	102	42	7
Sorafenib	649	517	423	357	297	199	114	48	11
Placebo	647	499	414	360	312	200	111	48	7

Secondary endpoints

OS

At the time of analysis, 435 deaths have occurred (about 60% of the original planned information).

The OS for Sunitinib vs. placebo was 5 years OS 77.9% (97.5%CI 74.1%-81.9%) vs. 80.3% (97.5%CI 76.8%-84.0%), HR 1.12, 97.5%CI 0.90-1.52, p=0.1762). Difference in OS was not statistically significant.

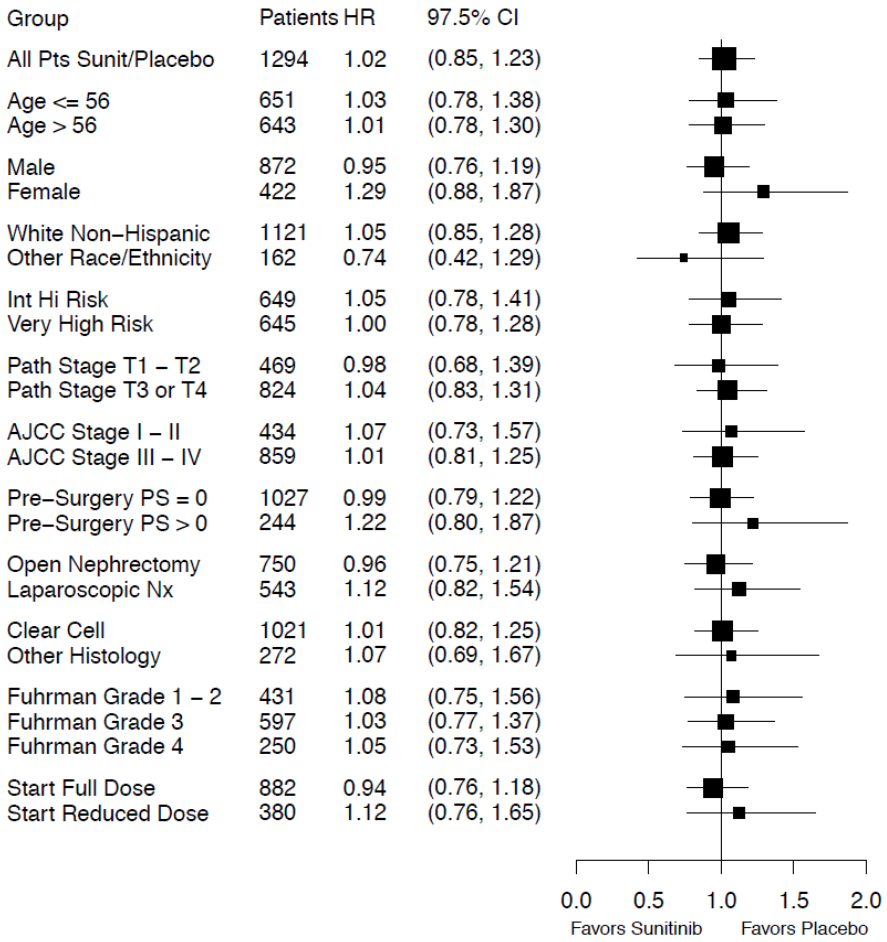
Ancillary analyses

Subgroups analyses showed no statistically significant difference between subgroups.

According to a planned subset analysis, patients with clear cell histology had DFS outcome similar to those with other histologies, with no statistically significant difference between sunitinib vs. placebo arms.

Starting patients at a lower dose and individually titrating them to a higher dose if tolerated reduced the probability of discontinuing treatment due to adverse events or patient's refusal and did not adversely affect the total dose administered. Post-hoc analysis showed no statistically significant difference in DFS by starting dose groups, either overall (p= 0.28) or stratified by arms (p=0.11).

Figure 22: forest plot for DFS – sunitinib vs. placebo – ASSURE study



2.4.3. Discussion on clinical efficacy

This is an extension of indication for Sutent (sunitinib) in the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy supported by the results from the pivotal phase III Study A6181109 (S-TRAC = Sunitinib Treatment of Renal Adjuvant Cancer) of sunitinib vs. placebo. Given the recent publication of the negative phase III trial E2805/ASSURE evaluating sorafenib or sunitinib vs. placebo as adjuvant treatment for RCC (Haas NB et al. Lancet 2016), additional data on this study have been provided and discussed by the MAH.

Design and conduct of clinical studies

S-TRAC is an international, multicenter, randomized, double-blind, Phase III study of adjuvant sunitinib 50 mg once daily 4 weeks on/ 2 weeks off (Schedule 4/2) for 9 cycles (i.e. 1 year) vs. placebo in patients with loco-regional RCC at high risk of recurrence following nephrectomy. The dose of sunitinib used is the same approved for the metastatic RCC indication. Given the low tolerance of sunitinib and high rate of dose reductions/discontinuations observed in both S-TRAC and ASSURE studies in the adjuvant RCC setting, moreover coupled with a small magnitude/absence of the treatment effect, an alternative dose/schedule would have been of interest. However, based on available data, even considering the reduced starting dose adopted for the last 30% of patients enrolled in the ASSURE trial, it is not possible to make any recommendation on reduced starting dose in the SmPC.

The inclusion criteria are in overall reflective of a population with clear RCC at higher risk of recurrence after nephrectomy according to UISS score. Only 6% of patients had a partial nephrectomy, and these patients were balanced between the two treatment arms. Given the very low (<8%) probability of positive surgical margins with partial nephrectomy, it is acknowledged that it is considered unlikely that these patients could have had an impact on the results. Although ECOG PS 0-2 was allowed, only one patient with ECOG 2 was enrolled. Median age was 58 years, however the usual age at diagnosis of RCC is approximately 64 years (SEER and NCI data). Thus, the included patients are considered younger and more fit than the average patient in the clinical setting - however consistent with the median age published in recent adjuvant clinical trials in RCC, considering representing the patients that are willing to accept adjuvant treatment to delay or prevent recurrence of the disease.

Since there are currently no approved adjuvant treatments for RCC, the placebo-controlled design appears appropriate. However, although the trial was double blind, the toxicity profile of sunitinib makes the active treatment easily recognizable compared to the placebo.

The primary endpoint was disease free survival (DFS), defined as the time interval from randomization to the first date of recurrence (including relapse of the primary tumour in-situ or at metastatic site) or the occurrence of secondary malignancies or death, as assessed by an independent central review (BICR). DFS assessed by investigator, OS and PROs were secondary endpoints. DFS according to BICR review is an acceptable primary endpoint considering the adjuvant treatment setting, with OS as secondary endpoint. It is noted that censoring rules for the primary DFS analysis are not in line with EMA scientific guidelines, and do not follow the “ITT principle”.

The ITT population consisted of 615 patients randomized 1:1 to sunitinib (309 patients) or placebo (306 patients), stratified according UISS high-risk group, ECOG and country using dynamic allocation. Result of re-randomization test has been provided as requested, showing a robust estimate of the treatment effect. Only UISS high-risk group has been used as stratification variable for the efficacy analyses, which is acceptable based on the justification provided.

Several amendments to protocol and SAP have been performed. Due to the slow accrual and high screening failure rate observed at the beginning of the study conduction, eligibility criteria were modified: in particular, while initially the accrual of subjects with T3 N0 or NX, M0, tumours was limited to Fuhrman’s grade ≥2, ECOG ≥1, with amendment 6 eligibility was extended to T3 N0 or NX, M0 subjects with any Fuhrman’s grade, and any ECOG status. The sample size was increased accordingly from 236 patients (101 DFS events) to 500 patients (320 DFS events), and this appears adequately justified due to the inclusion of patients with a slightly lower risk of recurrence compared to the population initially eligible (the patients newly added correspond to the “T3 low” sub-population of the efficacy analyses) in order to overcome the observed high rate of screening failures. Sample size was further expanded to 600 patients (320 DFS events) before the IA1, as the target of DFS event for the IA1 was not reached. This subsequent modification to the sample size raises more concerns; even though it appears that this increase in the sample size was not driven by an unblinded analysis, it is noted that this expansion was recommended by the external Data Monitoring Committee, who had access to unblinded patient treatment assignment information. There was no re-estimation of the number of DFS events for interim analysis and the DMC had no access to DFS analysis. Therefore the method outlined by Cui to control the type I error was not applied, which is considered acceptable in this context.

Finally, due to lower than expected DFS rate observed during the study, time of the final DFS analysis was changed to at 5 years after LSFV, or when approximately 258 DFS events are observed, whichever later, for approximately an 84% power to detect the statistical significance for the HR of 0.69 at 2-sided significance level of 0.05. Conducting the analysis when all patients have been observed for at least 5 years is reasonable, even though ideally the final DFS analysis should be performed at the time

in which the DFS curve reach a plateau and most patients with no DFS events are presumably “cured”. In addition, statistical evidence was considerably stronger than the conventional $p<0.05$ ($p<0.025$ one-sided) usually required for a pivotal (CPMP/EWP/2330/99).

The statistical methods used for time to events endpoints proposed are considered adequate. There were two interim analyses to allow early stopping of the study for futility, to assess safety and to allow for sample size re-estimation. The O’Brien-Fleming approach to allocate Type I error rate across interim analyses is appropriate as well. The multiple trial changes, probably partly justified by the limited historical data, and by the choice to revise the eligibility criteria, have heavily modified the statistical component of the study design and therefore have influenced the conduct of the study, having implications for the clinical interpretation of the results. The study seems to be planned as an adaptive design involving modification based on the results of the interim analyses (re-estimation of expected number of DFS events and time to event for the DFS) and the rate of DFS events during the study.

Efficacy data and additional analyses

Data cut-off for the final analysis was 7th April 2016. Median follow-up was 5.4 years. Efficacy analyses were performed on the ITT population.

Baseline patients and disease characteristics appeared overall balanced between the two arms. According to UISS high risk group, patients were classified in “T3 Low” (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): 37.2% vs. 36.6%; “T3 High” (T3 N0 or NX, M0, Fuhrman’s Grade ≥ 2, ECOG PS ≥ 1): 53.4% vs. 54.2%; T4: 1.3% vs. 1.3%; N+: 8.1% vs. 7.8% in sunitinib and placebo arm respectively. T4 and N+ were grouped together as “Other” in the efficacy analyses.

Sunitinib showed statistically significant advantage over placebo in DFS according to BICR evaluation [median DFS 6.8 (95%CI: 5.8, NR) vs. 5.6 years (95%CI: 3.8, 6.6), HR 0.761 (95%CI: 0.594, 0.975), p = 0.030 (2-sided p-value from the log-rank test stratified by UISS High Risk Group)]. It is noted the overlapping of confidence intervals and that the observed HR of 0.761 is higher than the pre-specified efficacy HR of 0.69.

Probability of being event free at year 1 was 87.7% vs. 77.6% for sunitinib and placebo. The smallest differences in DFS rate were at 2 and 3 years. Probability of being event free at year 5 was 59.3% vs. 51.3%, although a high number of censoring around year 5 is noted.

A high rate of censoring is observed in the first portion (≤1 year) of the DFS curve according to BICR, occurring mainly in the sunitinib arm (50 [16.2%] vs. 21 [6.9%] patients). Among them, the censored patients who discontinued/withdrew treatment due to AEs were 16 vs. 4.

A sensitivity analysis was performed by the MAH regarding the impact of potential informative censoring in the first year. Even accepting a method that assumes as worst case scenario that dropouts in the experimental arm perform as those in the placebo arm (i.e. excluding a priori the option of a detrimental effect), in most of instances statistical significance is not reached, thus further questioning the robustness of DFS results.

It is noted that the censoring rules set for the primary analysis are not in line with EMA scientific guidelines (EMA/CHMP/27994/2008/Rev.1), and do not follow the “ITT principle”. A number of sensitivity analyses have been provided, most of them not supporting the primary analysis. In particular, DFS sensitivity analyses (by both BICR or Investigators) with all DFS events regardless of new anti-cancer therapy or missed assessment - more in line with relevant guidelines- are not supportive of the results observed in the primary analysis. The sensitivity analyses requested by CHMP which are considered closer to the ITT principle (i.e. including further therapy as event and regardless

missed assessment [HR=0.793], regardless of the start of new anticancer therapy or missed assessment [HR=0.807]), or more correctly capturing the effect on the prevention of recurrence (i.e. not considering second primary cancers as events and regardless of missed assessment, [HR=0.826]), all showed lower magnitude of benefit of sunitinib over placebo compared to the primary analysis (HR=0.761).

When DFS was assessed by Investigator, although results are numerically in favor of sunitinib arm, statistical significance is not reached (HR 0.811, 95%CI: 0.643, 1.023, p= 0.077 2-sided from the log-rank test stratified by UISS High Risk Group), unlike DFS by BICR.

The type of discordance (early vs. late) and the discordance rate between assessments by BICR and investigator, was unevenly distributed between arms. Indeed, in the sunitinib arm, the early disagreement rate (meaning that the investigator declared relapse earlier than BICR or declared relapse when the BICR did not) was higher compared to the placebo arm. Conversely, investigator tended to call relapse later then BICR more frequently in the placebo arm compared to the sunitinib arm. Such differential discordance is more pronounced during year 1, i.e. during active treatment and there appears to be a bias favouring the placebo arm in the first year (i.e. during treatment); the most plausible explanation being the poor tolerability of the experimental drug. The analysis by BICR is the most relevant but on the other hand, the observation of this behaviour of Investigators reinforces the concerns on the compliance that might be observed in clinical practice due to tolerability. The difference in DFS results according to BICR and investigator, along with the discordance in radiological assessments, raise the question whether the efficacy of sunitinib seen in the trial per BICR will be reflective of the real practice use and results in clinical setting. The external validity of the trial is thus questioned.

Secondary primary malignancies were included as events for DFS. A lower number of second primary cancers was found in the sunitinib arm compared to placebo. Whether this could be reflective of a "protective" effect of sunitinib or, more likely, just a chance finding is unknown; in order to explore this issue, and disentangle the effect of treatment on new primaries and on renal cancer recurrence, a sensitivity analysis, based on BICR which excludes secondary malignancies and regardless missed assessments, showed that the magnitude of the benefit of sunitinib over placebo was lower compared to the primary DFS analysis (HR 0.826 [95% CI: 0.646, 1.056], 2-sided p value=0.126). The MAH argues that not censoring for 2 or more missed assessment potentially overestimates DFS time for patients with missed assessment; however, no data are provided to show that the results of the requested sensitivity are influenced by missed assessment rather than by exclusion of secondary malignancies. It is not self-evident that patients with secondary malignancies have missed assessment; instead, they might have even received more frequent assessments. Further, the overall rate of missed assessments appears to be higher in the experimental arm. A sensitivity analysis on Time to Recurrence by BICR, demonstrated consistent results (HR: 0.778 [95% CI: 0.601, 1.009]) with those from the primary analysis, however, that this latter sensitivity analysis excluded deaths considered non-disease related, an approach that is questioned since an influence of treatment of these deaths cannot be ruled out. In conclusion, the primary analysis has demonstrated a borderline beneficial effect. The requested sensitivity analysis not considering second primary cancers as events and regardless missing assessment show a lower effect with no statistical significance, raising further doubts on the ability of adjuvant sunitinib treatment in preventing kidney cancer recurrence and death in the overall population.

In the DFS by BICR subgroup analysis, a trend toward higher benefit of sunitinib vs. placebo is seen in higher UISS risk groups: T3 low HR 0.822; T3 high HR 0.765, Other [T4, N+] 0.617, although none of them reached statistical significance. When the groups at higher risk (corresponding to the initially planned population) are combined (T3 high + Other), HR is 0.737 (95%CI: 0.548, 0.993), p= 0.044.

These results are suggesting of a higher benefit from the use of adjuvant sunitinib in RCC with the higher risk of recurrence. A pooled analysis of the highest risk RCC subset of patients from S-TRAC and ASSURE populations was performed showing similar HR (HR = 0.772) to the highest risk subgroup. The low number of patients matching the above criteria and the limitations of this analysis are acknowledged.

PRO analyses (EORTC QLQ-C30 and EuroQol EQ-5D) showed a negative impact of sunitinib on the quality of life of patients throughout the treatment. PRO endpoints were statistically significantly worse for sunitinib compared to placebo, although the difference in most of the scales did not reach the clinically important difference in points published in the literature (with the exception of diarrhoea and appetite loss). The MAH's arguement that 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 (King MT et al, 1996; Osoba D et al, 1998) is acknowledged. However it is noted that the 10 points cut-off for clinically meaningful change in QoL was derived from a population of advanced patients in whom the acceptability of AEs of treatment might be different, as indirectly supported by the high rate of permanent discontinuations due grade 1-2 AEs, that has been also emphasized by the MAH. Applying a more conservative 8-point threshold, a clinically meaningful deterioration was also seen in fatigue.

No statistically significant difference in OS between arms in observed (HR 1.014), although current data are immature (approximately 20% of events). Updated OS (additional 9 months of observation) showed an observed stratified HR of 0.918, with median OS nor reached for either treatment arm (about 23% of population had an OS event). There is no indication of a detrimental effect at present. However data are still immature. The MAH is not planning to collect further OS data, and the final OS analysis will be the one with data cut-off date of 31st Jan 2017, which is considered quite immature at 23% of OS events. Although the difficulties in later assessment of OS underlined by the MAH are acknowledged, data currently available are highly immature and a possible overestimation of the effect cannot be excluded at this time. Given the uncertainties regarding the beneficial effect of Sutent in the adjuvant setting, the lack of long-term OS data is considered a major drawback as no further support can be provided. No relevant differences in the pattern of recurrence can be highlighted between arms.

In patients that received adjuvant sunitinib in the trial, the use of anti-angiogenic therapy as subsequent treatment decreased compared to placebo arm. In the latter, sunitinib was instead by far the most commonly used treatment at relapse. Retrospective exploratory analyses provided are inconclusive as to whether adjuvant sunitinib adversely affected the efficacy of subsequent follow-up anti-angiogenic therapy. In the metastatic RCC setting published data showed a treatment benefit of VEGFR-inhibitor-VEGFR-inhibitor sequence. However, the magnitude of efficacy of a TKI after a prior exposure to another TKI compared to no drug treatment in the adjuvant setting cannot be evaluated. Based on an observational study (RESUME) sunitinib rechallenge showed potential clinical benefit in the metastatic setting and PD with first-line sunitinib not associated with persistent resistance to therapy. Such information would be crucial as no further support from more mature OS data can be available.

Only 55.6% of patients were able to complete the planned treatment with sunitinib (compared to 69.4% in placebo arm). About 25% of the patients discontinued treatment due to drug-related AEs in the sunitinib arm (see Clinical Safety). The higher rate of discontinuation of sunitinib due to AEs underlines the overall limited tolerance of the sunitinib regimen. For patients treated without dose reduction and who completed 9 cycles as planned, HR point estimate was in favour of placebo (HR 1.084, 95% CI 0.723-1.625, p= 0.695), further questioning the benefit of sunitinib treatment in the claimed indication. The MAH further evaluated DFS in patients with or without dose modifications (i.e. dose reduction, dosing interruption, or delay in a cycle start), as well as patients with or without only

dose reductions to evaluate the impact of dosing in treatment outcomes. According to this analysis, DFS is not adversely impacted. It is noted that these analyses do not assess the impact of permanent discontinuations due to treatment-related AEs that was much higher in the sunitinib arm compared to placebo (25.2% vs. 4.3%). New analyses were performed, showing that patients who completed 9 cycles of sunitinib may derive more benefit compared to patients who discontinued treatment prior to completing 9 cycles for reasons other than disease relapse or death, in particular compared with patients who discontinued earlier. These analyses may suggest that the maintenance of a full dose for all 9 cycles could be of importance for the overall sunitinib activity.

Exploratory biomarker analyses have been submitted to fulfill the post-approval commitment generated with the assessment of FUM 22.05. No clear prognostic/predictive biomarkers have been identified based on the genotyping data. IHC biomarker results were limited mainly by the low number of patients analysed.

The recently published results of a three-arm randomized double blind placebo controlled phase III trial E2805/ASSURE, conducted in US and Canada by cooperative group ECOG-ACRIN (partly founded by the MAH) evaluating adjuvant RCC treatment with sorafenib or sunitinib vs. placebo have been discussed, to put the S-TRAC trial in the context of the available evidence of sunitinib in the adjuvant setting. The main differences among the two studies pertained to study population (ASSURE enrolled 1/3 of patients with lower risk of recurrence (pT1b G3-4, pT2 N0) and 20% of non-clear cell), lack of radiological independent review and starting dose (30% of patients received 37.5 mg OD, to be increased if no side effects). 647 patients were enrolled in the sunitinib arm and 647 in the placebo arm.

ASSURE was a negative trial. An advantage in DFS with the use of sunitinib in the adjuvant RCC setting compared to placebo was not demonstrated (HR 1.02, 97.5%CI 0.85-1.23, stratified Logrank p = 0.80). No advantage in DFS was seen according to subgroup analyses for sunitinib in pT3-pT4 disease, clear cell histology, nor for patients started at full dose, to compare with the S-TRAC study. A published retrospective post-hoc analysis of ASSURE including high-risk patients with pT3, pT4, or N+ and clear cell (histologically>25%) only histology (Haas N et al. JAMA Oncol 2017) to “match” the main disease characteristics in S-TRAC did not find statistically significant differences in DFS, also by dose quartile. No difference in OS was seen. Overall, patients treated in the ASSURE who met the recruitment and dosing criteria of S-TRAC study were 30.4% (394). The imbalance in UISS risk group composition compared to S-TRAC is acknowledged.

The definition of T3 high and T3 low in the trial included both objective (T stage and Fuhrman’s Grade) and subjective (ECOG performance status) prognostic parameters. In order to delineate the patient population purely based on objective parameters, an additional analysis was performed classifying patients into highest risk, defined as T3 and Fuhrman’s Grade >2 or T4 or Node Positive with any T, and patients into lower risk, defined as T3 and Fuhrman’s Grade 1 or 2. According to this classification the S-TRAC trial had 398 (65%) patients at highest risk and 215 (35%) patients at lower risk; two patients could not be classified due to missing Fuhrman’s Grade data. The DFS by BICR for sunitinib vs. placebo in the highest risk population showed a HR of 0.727 (95% CI: 0.544 -0.972, p-value 0.031) compared to those with lower risk of recurrence (HR 0.869, 95% CI: 0.544, 1.387, p-value 0.555). This remains consistent with the hazard ratios for DFS in the T3 high (HR 0.737, 95% CI: 0.548, 0.993; p-value: 0.044) and T3 low (HR 0.822 95% CI: 0.529, 1.276; p-value: 0.381) groups, respectively, as in the S-TRAC clinical study report.

2.4.4. Conclusions on the clinical efficacy

As the uncertainties discussed above have not been resolved, the clinical efficacy of adjuvant treatment with Sutent in patients at high risk for recurrent RCC following nephrectomy has not been adequately demonstrated.

2.5. Clinical safety

Introduction

The most common adverse reactions of any grade associated with sunitinib treatment (experienced by patients in metastatic RCC, GIST, and pNET registrational trials) included fatigue, decreased appetite, taste disturbance, hypertension, gastrointestinal disorders (i.e. diarrhoea, nausea, stomatitis, dyspepsia and vomiting), skin discolouration, palmar-plantar erythrodysaesthesia (PPE) syndrome. Hypothyroidism may commonly develop during treatment. The most important serious adverse reactions were pulmonary embolism, thrombocytopenia, tumour hemorrhage, febrile neutropenia, and hypertension.

Safety analyses supporting sunitinib application in adjuvant RCC are based on data from the pivotal Phase 3 Study A6181109. Overall, 610 patients (306 in the sunitinib arm and 304 in the placebo arm) who received at least one dose of study medication are included in the As-Treated population analysed for safety. Patients received oral sunitinib 50 mg OD on Schedule 4 weeks on/2 weeks off for 9 cycles (approximately 1 year) or placebo. The cut-off date for safety data from study A6181109 was 7th April 2016.

In addition, additional safety information in the adjuvant setting are provided by the ASSURE study (629 patients received sunitinib and 633 placebo). The cut-off date used in ASSURE CSR was 27th August 2015. Safety data collected in the ASSURE study were limited to Grade 3 to Grade 5 non-hematologic and infection AEs and Grade 4 or Grade 5 hematologic events. AEs were not coded using MedDRA but they were reported using CTCAE preferred terms, while AEs in S-TRAC study were reported using MedDRA V19.0. Due to the difference in collection and reporting of safety data between S-TRAC and ASSURE studies, pooling of safety data was not done but where possible, Grade 3-5 events have been compared.

Patient exposure

Patient exposure and dose intensity

Patients exposure and dose intensity in the pivotal S-TRAC study are summarized in the tables below:

Table 46: Duration of Treatment in Study A6181109 - As-Treated Population

	Sunitinib (N=306)	**Placebo (N=304)**
Duration of Treatment (months)		
Median	12.4	12.4
Mean	9.5	10.3
SD	4.4	3.7
Range	0.13 - 14.9	0.03 - 13.7

The Duration of treatment was the time period starting from the date of first dose and ending at the earlier of the termination date or 2 weeks after the last dose.

Table 47: dose intensity - S-TRAC study, As treated population

	Sunitinib (N = 306)	Placebo (N = 304)
Actual Cumulative Dose (mg)		
Median	9637.5	12600.0
Mean	8403.2	10388.4
SD	4144.8	3789.9
Range	100.0 - 13800.0	50.0 - 13350.0
Relative Dose Intensity (%)		
Median	88.4	99.7
Mean	84.6	96.6
SD	17.1	12.3
Range	15.0 - 106.2	10.0 - 105.7
Average Daily Dose (mg) as Administered (excluding 2 weeks off)		
Median	45.9	50.0
Mean	43.2	48.8
SD	8.0	4.4
Range	8.9 - 52.6	6.7 - 52.8

ASSURE study: Patients exposure and dose intensity in the ASSURE study are summarized in tables below. The dose of sunitinib was changed when the trial was ongoing; indeed, after having observed an high rate of treatment discontinuation due to adverse events or patient refusal, the starting dose of sunitinib/placebo was reduced from the initial 50 mg to 37.5 mg OD, and then escalated in patients who experienced no grade ≥ 2 toxicities. Patients started at full and reduced sunitinib dose were 69.6% and 30.4% respectively.

Table 48: patients started at FULL or REDUCED dose - ASSURE study

Factor	Level	Sunitinib	Sorafenib	Placebo	Total	Test
Total		647	649	647	1943	–
Starting Dose Group	Full Dose	438(69.6)	441(70.0)	444(70.1)	1323(69.9)	0.980
	Reduced Dose	191(30.4)	189(30.0)	189(29.9)	569(30.1)	
	Unk/Miss	18	19	14	51	

Table 49: Duration of Treatment - ASSURE study

	Sunitinib (N=629)	Placebo (N=633)
Duration of Treatment (months)		
Median	11.1	12.4
Mean	8.4	10.6
SD	4.8	3.6
Range	0.07 - 15.2	0.10 – 15.9

Table 50: relative dose intensity (%) – ASSURE study

	Sunitinib (N=629)	Placebo (N=633)
Relative dose intensity (%)		
n	551	537
Median	77.72	96.23
Mean	78.50	93.65
Std. Dev.	22.30	10.72
Range	10.00-150.00	10.89-150.00

N= number of patients who received at least one dose
n= the number of patients for whom relative dose in calculated
Relative Dose Intensity is defined as Actual Dose Intensity (per week)/Intended Dose Intensity (per week)*100% where the intended dose intensity is based on 50 mg per day.
RDI (%) >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.

The median cumulative dose was lower in the sunitinib treatment arm than in the placebo treatment arm: 6.8 g or 6,800 mg (range: 2,600 mg to 9,900 mg) for sunitinib versus 11.9 g or 11,900 mg (range: 8,400 mg to 12,400 mg) for placebo.

Table 51: summary of key differences between patient exposure to sunitinib in ASSURE and A6181109 study

	ASSURE Study Sunitinib	Study A6181109 Sunitinib
Median Relative Dose Intensity (%)	77.7	88.4
Median Cumulative Dose (mg)	6800	9637.5
Median Duration of Treatment (months)	11.1	12.4
Completed 9 cycles (approximately 1 year) of Treatment (%)	49	55.6
Permanent Discontinuation due to AE or patient refusal for patients who started on 50 mg dose (%)	44	32

In the ASSURE study, patients started at reduced dose could escalate if they experienced no grade ≥ 2 toxicities. In addition, 2 dose reduction levels (37.5 mg and 25 mg) were allowed, while in S-TRAC study it was not possible to reduce the dose below 37.5 mg.

Adverse events

The investigators used the CTCAE (version 3.0) for grading the severity of AEs. All AEs and SAEs in Study A6181109 are reported using MedDRA terms Version 19.0 and are summarized by system organ class (SOC) and preferred term (PT).

Table 52: Summary of All-Causality, Treatment-Emergent Adverse Events in Study[a] A6181109- As-Treated Population

Category	Sunitinib n (%)	Placebo n (%)
Number (%) of patients:		
Subjects evaluable for adverse events	306	304
Number of adverse events	4068	1777
Subjects with adverse events	305 (99.7)	269 (88.5)
Subjects with serious adverse events	67 (21.9)	52 (17.1)
Subjects with Grade 3 or 4 adverse events	189 (61.8)	61 (20.1)
Subjects with Grade 5 adverse events	5 (1.6)	5 (1.6)
Subjects discontinued due to adverse events	86 (28.1)	17 (5.6)
Subjects with dose reduced due to adverse events	105 (34.3)	6 (2.0)
Subjects with temporary discontinuations due to adverse events	142 (46.4)	40 (13.2)

Treatment Emergent Adverse Events (TEAEs)

All-causality TEAE in ≥ 10% of patients are presented in the table below:

Table 53. All-Causality, TEAEs by PT Experienced by ≥10% of Patients - As-Treated Population

MedDRA Preferred Term	Sunitinib (N=306) n (%)						Placebo (N=304) n (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Any AE	**17 (5.6)**	**98 (32.0)**	**148 (48.4)**	**37 (12.1)**	**5 (1.6)**	**305 (99.7)**	**91 (29.9)**	**114 (37.5)**	**48 (15.8)**	**11 (3.6)**	**5 (1.6)**	**269 (88.5)**

Table 53. All-Causality, TEAEs by PT Experienced by ≥10% of Patients - As-Treated Population

MedDRA Preferred Term	Sunitinib (N=306) n (%)						Placebo (N=304) n (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Diarrhoea	86 (28.1)	76 (24.8)	12 (3.9)	0	0	174 (56.9)	56 (18.4)	8 (2.6)	1 (0.3)	0	0	65 (21.4)
Palmar-plantar erythrodysaesthesia syndrome	45 (14.7)	60 (19.6)	46 (15.0)	3 (1.0)	0	154 (50.3)	22 (7.2)	8 (2.6)	1 (0.3)	0	0	31 (10.2)
Hypertension	28 (9.2)	61 (19.9)	24 (7.8)	0	0	113 (36.9)	18 (5.9)	14 (4.6)	3 (1.0)	1 (0.3)	0	36 (11.8)
Fatigue	57 (18.6)	40 (13.1)	13 (4.2)	2 (0.7)	0	112 (36.6)	52 (17.1)	18 (5.9)	4 (1.3)	0	0	74 (24.3)
Nausea	70 (22.9)	29 (9.5)	6 (2.0)	0	0	105 (34.3)	36 (11.8)	6 (2.0)	0	0	0	42 (13.8)
Mucosal inflammation	50 (16.3)	39 (12.7)	14 (4.6)	0	0	103 (33.7)	25 (8.2)	0	0	0	0	25 (8.2)
Dysgeusia	77 (25.2)	26 (8.5)	0	0	0	103 (33.7)	15 (4.9)	3 (1.0)	0	0	0	18 (5.9)
Dyspepsia	46 (15.0)	32 (10.5)	4 (1.3)	0	0	82 (26.8)	17 (5.6)	2 (0.7)	0	0	0	19 (6.3)
Stomatitis	45 (14.7)	29 (9.5)	5 (1.6)	2 (0.7)	0	81 (26.5)	11 (3.6)	2 (0.7)	0	0	0	13 (4.3)
Neutropenia	12 (3.9)	34 (11.1)	23 (7.5)	3 (1.0)	0	72 (23.5)	2 (0.7)	0	0	0	0	2 (0.7)
Asthenia	26 (8.5)	32 (10.5)	11 (3.6)	0	0	69 (22.5)	21 (6.9)	13 (4.3)	2 (0.7)	1 (0.3)	0	37 (12.2)
Hair colour changes	62 (20.3)	6 (2.0)	0	0	0	68 (22.2)	6 (2.0)	1 (0.3)	0	0	0	7 (2.3)
Thrombocytopenia	31 (10.1)	14 (4.6)	15 (4.9)	4 (1.3)	0	64 (20.9)	3 (1.0)	1 (0.3)	1 (0.3)	0	0	5 (1.6)
Rash	43 (14.1)	14 (4.6)	2 (0.7)	0	0	59 (19.3)	24 (7.9)	5 (1.6)	0	0	0	29 (9.5)
Decreased appetite	48 (15.7)	9 (2.9)	2 (0.7)	0	0	59 (19.3)	14 (4.6)	2 (0.7)	0	0	0	16 (5.3)
Vomiting	34 (11.1)	17 (5.6)	7 (2.3)	0	0	58 (19.0)	16 (5.3)	4 (1.3)	0	0	0	20 (6.6)
Headache	43 (14.1)	12 (3.9)	2 (0.7)	0	0	57 (18.6)	29 (9.5)	7 (2.3)	0	0	0	36 (11.8)
Hypothyroidism	17 (5.6)	39 (12.7)	0	0	0	56 (18.3)	2 (0.7)	2 (0.7)	0	0	0	4 (1.3)
Epistaxis	45 (14.7)	10 (3.3)	0	0	0	55 (18.0)	8 (2.6)	1 (0.3)	0	0	0	9 (3.0)
Leukopenia	19 (6.2)	22 (7.2)	3 (1.0)	1 (0.3)	0	45 (14.7)	2 (0.7)	0	0	0	0	2 (0.7)
Pain in extremity	31 (10.1)	13 (4.2)	1 (0.3)	0	0	45 (14.7)	15 (4.9)	5 (1.6)	0	0	0	20 (6.6)
Dry skin	37 (12.1)	6 (2.0)	0	0	0	43 (14.1)	16 (5.3)	1 (0.3)	0	0	0	17 (5.6)
Abdominal pain	24 (7.8)	13 (4.2)	4 (1.3)	1 (0.3)	0	42 (13.7)	14 (4.6)	1 (0.3)	1 (0.3)	0	0	16 (5.3)
Abdominal pain upper	25 (8.2)	14 (4.6)	0	0	0	39 (12.7)	12 (3.9)	1 (0.3)	0	0	0	13 (4.3)
Pyrexia	25 (8.2)	10 (3.3)	0	1 (0.3)	0	36 (11.8)	15 (4.9)	2 (0.7)	0	0	0	17 (5.6)
Constipation	30 (9.8)	6 (2.0)	0	0	0	36 (11.8)	27 (8.9)	5 (1.6)	0	0	0	32 (10.5)
Arthralgia	21 (6.9)	13 (4.2)	1 (0.3)	0	0	35 (11.4)	25 (8.2)	4 (1.3)	0	0	0	29 (9.5)
Anaemia	19 (6.2)	9 (2.9)	4 (1.3)	1 (0.3)	0	33 (10.8)	6 (2.0)	1 (0.3)	0	0	0	7 (2.3)
Yellow skin	31 (10.1)	1 (0.3)	0	0	0	32 (10.5)	2 (0.7)	0	0	0	0	2 (0.7)

The 3 SOCs with the highest frequencies of all-causality TEAEs in the sunitinib arm were: Gastrointestinal disorders (262 [85.6%] patients), Skin and subcutaneous tissue disorders (235 [76.8%] patients), and General disorders and administration site conditions (227 [74.2%] patients).

The most common (>25% of patients in either treatment arm) 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), Fatigue (36.6% vs. 24.3% in the placebo arm), Nausea (34.3% vs. 13.8% in the placebo arm), Dysgeusia (33.7% vs 5.9% in the placebo arm), Mucosal inflammation (33.7% vs. 8.2% in the placebo arm), Dyspepsia (26.8% vs 6.3% in the placebo arm), and Stomatitis (26.5% vs. 4.3% in the placebo arm).

Grade 3-5 TEAEs

All-causality Grade ≥ 3 TEAE in ≥ 1% of patients are presented in the table below:

Table 54. Summary of All-Causality, Treatment-Emergent Adverse Events (All Grades and Grade 3 and Grade 4) Experienced by ≥10% of Patients in Study A6181109 - As-Treated Population

MedDRA Preferred Term	Sunitinib (N=306) n (%)			Placebo (N=304) n (%)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any AEs	305 (99.7)	148 (48.4)	37 (12.1)	269 (88.5)	48 (15.8)	11 (3.6)
Diarrhoea	174 (56.9)	12 (3.9)	0	65 (21.4)	1 (0.3)	0
Palmar-plantar erythrodysaesthesia syndrome	154 (50.3)	46 (15.0)	3 (1.0)	31 (10.2)	1 (0.3)	0
Hypertension	113 (36.9)	24 (7.8)	0	36 (11.8)	3 (1.0)	1 (0.3)
Fatigue	112 (36.6)	13 (4.2)	2 (0.7)	74 (24.3)	4 (1.3)	0
Nausea	105 (34.3)	6 (2.0)	0	42 (13.8)	0	0
Dysgeusia	103 (33.7)	0	0	18 (5.9)	0	0
Mucosal inflammation	103 (33.7)	14 (4.6)	0	25 (8.2)	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
Neutropenia	72 (23.5)	23 (7.5)	3 (1.0)	2 (0.7)	0	0
Asthenia	69 (22.5)	11 (3.6)	0	37 (12.2)	2 (0.7)	1 (0.3)
Hair colour changes	68 (22.2)	0	0	7 (2.3)	0	0
Thrombocytopenia	64 (20.9)	15 (4.9)	4 (1.3)	5 (1.6)	1 (0.3)	0
Decreased appetite	59 (19.3)	2 (0.7)	0	16 (5.3)	0	0
Rash	59 (19.3)	2 (0.7)	0	29 (9.5)	0	0
Vomiting	58 (19.0)	7 (2.3)	0	20 (6.6)	0	0
Headache	57 (18.6)	2 (0.7)	0	36 (11.8)	0	0
Hypothyroidism	56 (18.3)	0	0	4 (1.3)	0	0
Epistaxis	55 (18.0)	0	0	9 (3.0)	0	0
Leukopenia	45 (14.7)	3 (1.0)	1 (0.3)	2 (0.7)	0	0
Pain in extremity	45 (14.7)	1 (0.3)	0	20 (6.6)	0	0
Dry skin	43 (14.1)	0	0	17 (5.6)	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
Pyrexia	36 (11.8)	0	1 (0.3)	17 (5.6)	0	0
Arthralgia	35 (11.4)	1 (0.3)	0	29 (9.5)	0	0
Anaemia	33 (10.8)	4 (1.3)	1 (0.3)	7 (2.3)	0	0
Yellow skin	32 (10.5)	0	0	2 (0.7)	0	0

The majority of all causality TEAEs were Grade 2 or Grade 3 in severity.

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.

Most common Grade ≥3 TEAEs in the sunitinib arm were: PPE syndrome (16% 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), Thrombocytopenia (6.2% vs 0.3% in the placebo arm), Fatigue (4.9% vs 1.3% in the placebo arm), Mucosal inflammation (4.6% vs 0% in the placebo arm), and Diarrhoea (3.9% vs 0.3% in the placebo arm).

The proportion of patients who experienced Grade 4 AEs was higher in the sunitinib arm (12.1%) than in the placebo arm (3.6%). The most common Grade 4 AEs in the sunitinib arm were Thrombocytopenia (1.3%) and Pulmonary embolism (1.3%).

The median time to onset of Grade 3/4 AEs was variable and ranged from 15-672 days in the sunitinib arm and 7-322 days in the placebo arm.

In the sunitinib arm 84% of all Grade 3/4 AEs were resolved at last reported outcome and 74% were reported as resolved in the placebo arm (see table below):

Table 55: Resolution Status for TEAEs for any 3/4 CTCAE Grade - As Treated

	Sunitinib Malate (N=306) n (%)	Placebo (N=304) n (%)
Any Grade 3/4		
n	189	61
Resolved	158 (83.6)	45 (73.8)
Still Ongoing	29 (15.3)	15 (24.6)
Unknown	2 (0.8)	1 (0.4)

Five (1.6%) Grade 5 AEs were reported in the sunitinib arm (PTs: Cardiac arrest, Death, Disease progression, Injury, Vena cava thrombosis) and 5 (1.6%) in the placebo arm (PTs: Cardiac arrest, Multiple organ dysfunction syndrome, Metastases to lung, Cerebral haematoma, Haemoptysis). None of these Grade 5 events were considered treatment-related.

A summary of TEAE by time of reporting (occurring between 0 to <3 months, 3 to <6 months, 6 to <9 months, 9 to <12 months, and ≥12 months from randomization) and severity is reported below:

Table 56. Summary of Treatment-Emergent Adverse Events by Time and Maximum CTCAE Grade in the Sunitinib Arm of Study A6181109 - As-Treated Population

Time period from first dose	N	Sunitinib n (%)					
		Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
0 to <3 months	306	41 (13.4)	146 (47.7)	93 (30.4)	17 (5.6)	1 (0.3)	298 (97.4)
3 to <6 months	257	56 (21.8)	109 (42.4)	52 (20.2)	9 (3.5)	0	226 (87.9)
6 to <9 months	228	54 (23.7)	88 (38.6)	45 (19.7)	6 (2.6)	0	193 (84.6)
9 to <12 months	203	42 (20.7)	71 (35.0)	47 (23.2)	4 (2.0)	1 (0.5)	165 (81.3)
≥12 months	73	14 (19.2)	16 (21.9)	8 (11.0)	2 (2.7)	0	40 (54.8)

Evaluation by time and severity has been provided for the adverse events of special interest in the sunitinib arm. Figures representing the trend in the frequency of some of the TEAEs during the 9 cycles of treatment are showed below (most common: diarrhea, fatigue and asthenia, PPE, hypertension):

Figure 23: plot of relative frequency of TEAEs Diarrhoea by maximum CTCAE grade and cycle in the sunitinib arm of Study A6181109 - As-Treated Population

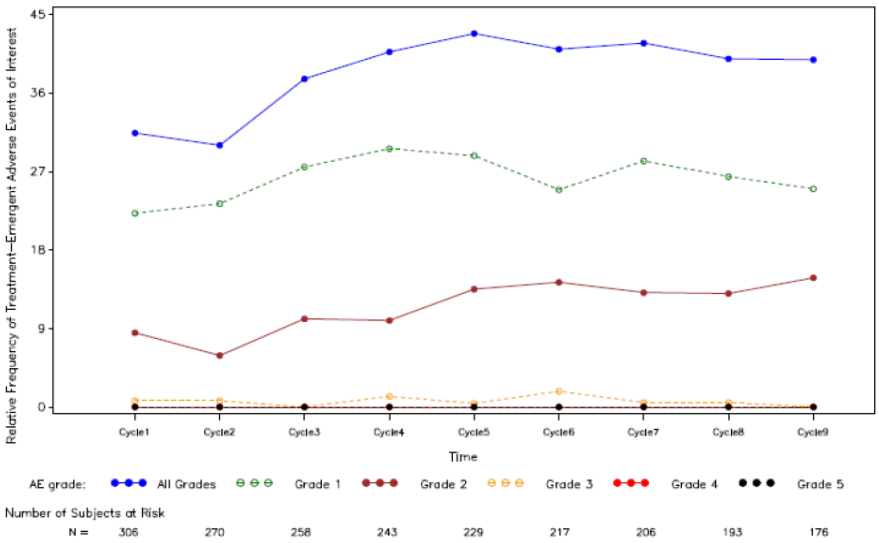


Figure 24: plot of relative frequency of TEAEs PPE syndrome by maximum CTCAE grade and cycle in the sunitinib arm of Study A6181109 - As-Treated Population

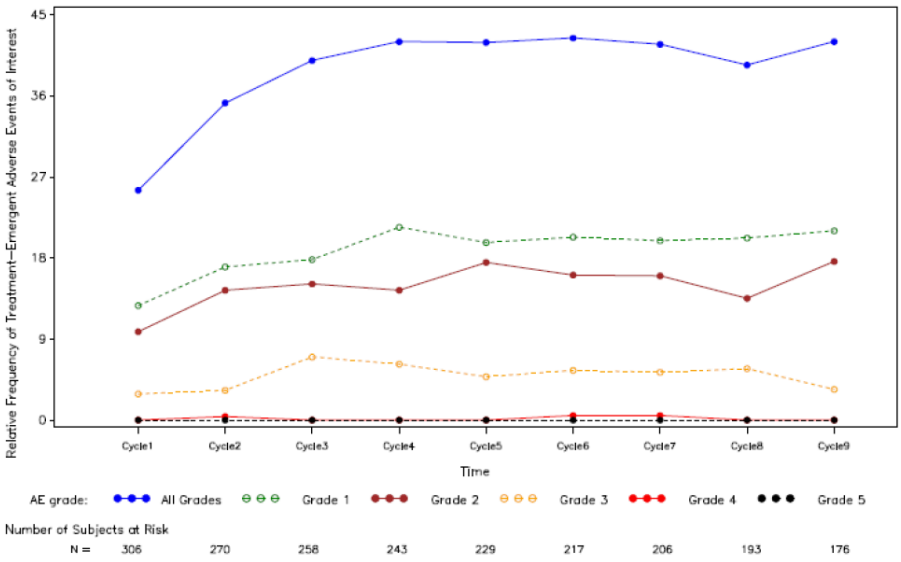


Figure 25: plot of relative frequency of TEAEs Fatigue by maximum CTCAE grade and cycle in the sunitinib arm of Study A6181109 - As-Treated Population

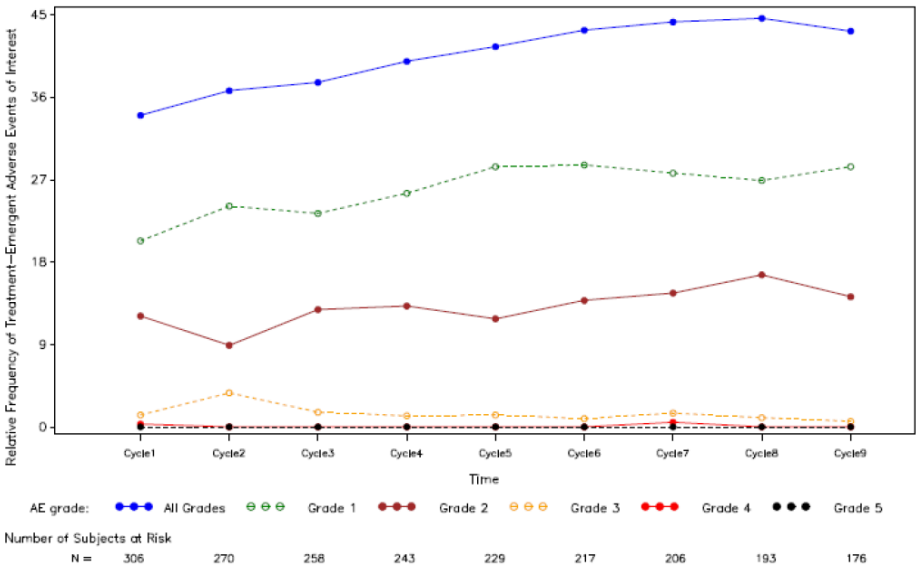
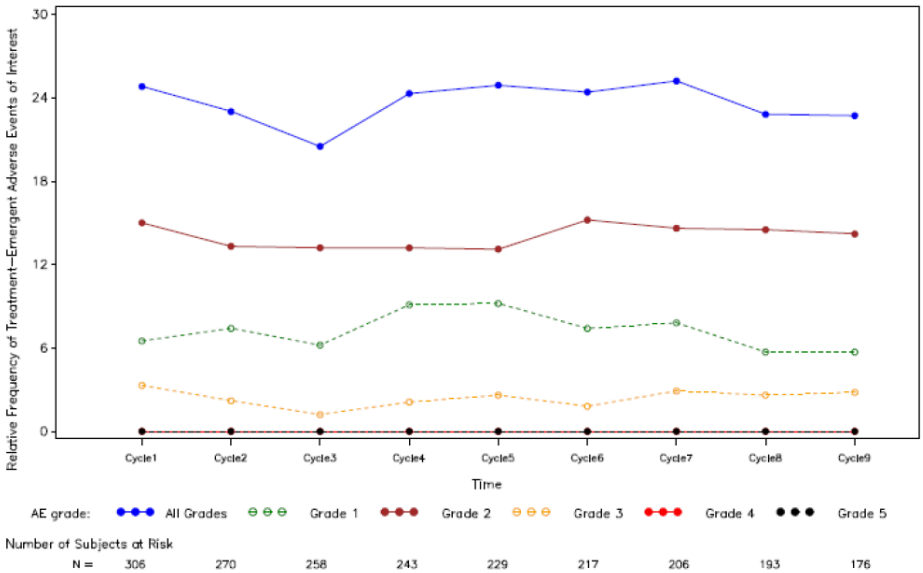


Figure 26: plot of relative frequency of TEAEs Hypertension by maximum CTCAE grade and cycle in the sunitinib arm of Study A6181109 - As-Treated Population



S-TRAC vs. ASSURE: due to the difference in collection and reporting of safety data between the two studies, only Grade 3-5 events have been compared, when possible. See table below:

Table 57: 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 Study A6181109 and ASSURE

Preferred Term	Study A6181109 (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

Table 57: 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 Study A6181109 and ASSURE

Preferred Term	Study A6181109 (N=306) n (%)			Adverse Event Term	ASSURE Study (N=625) n (%)		
	Grade 3	Grade 4	Grade 5		Grade 3	Grade 4	Grade 5
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
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

Adverse events in the follow-up period: Late adverse events reported after sunitinib was

permanently discontinued were reviewed. Although any AE reported during the follow up period was captured in the safety database, it should be noted that, during the follow-up period, investigators were only required to report treatment-related SAEs.

Table 58. Summary of Treatment-Emergent Adverse Events After the Last Dose of by Time and Maximum CTCAE Grade in Study A6181109 - As-Treated Population

Onset Date	**Sunitinib (N = 306) n (%)**					
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
After last dose day + 28 days	22 (7.2)	9 (2.9)	14 (4.6)	7 (2.3)	2 (0.7)	54 (17.6)
Last dose + 28 days to <3 months after last dose	21 (6.9)	8 (2.6)	4 (1.3)	1 (0.3)	0	34 (11.1)
3 to <6 months after last dose	1 (0.3)	0	0	0	0	1 (0.3)
6 to <12 months after last dose	2 (0.7)	1 (0.3)	0	0	0	3 (1.0)
≥12 months after last dose	2 (0.7)	1 (0.3)	10 (3.3)	7 (2.3)	2 (0.7)	22 (7.2)
	Placebo (N = 304) n (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
After last dose day + 28 days	15 (4.9)	10 (3.3)	13 (4.3)	4 (1.3)	5 (1.6)	47 (15.5)
Last dose + 28 days to <3 months after last dose	9 (3.0)	5 (1.6)	0	0	0	14 (4.6)
3 to <6 months after last dose	3 (1.0)	1 (0.3)	1 (0.3)	0	0	5 (1.6)
6 to <12 months after last dose	0	0	0	1 (0.3)	0	1 (0.3)
≥12 months after last dose	5 (1.6)	5 (1.6)	12 (3.9)	3 (1.0)	5 (1.6)	30 (9.9)

The frequency of Grade 3 and Grade 4 in the period ≥12 months after the last dose of study drug was: 10 AEs (3.3%) and 7 AEs (2.3%) in the sunitinib arm, and 12 AEs (3.9%) and 3 AEs (1%) in the placebo arm. In the sunitinib arm, the highest frequencies of Grade 3 AEs in the period ≥12 months after the last dose were in the Cardiac disorders SOC (3 AEs, preferred terms: Acute coronary syndrome, Atrial fibrillation, Myocardial infarction) and Infections and infestations SOC (3 AEs, preferred terms: Cellulitis, Pneumonia, and Urinary tract infection), whereas the majority of Grade 4 AEs during this period were in the Neoplasms benign, malignant and unspecified SOC (5 AEs, preferred terms: Acute myeloid leukaemia, Colon cancer, Endometrial adenocarcinoma, Hepatocellular carcinoma, and Prostate cancer). In the placebo arm, the highest frequency of Grade 3 AEs in the period ≥12 months after the last dose was in the Neoplasms benign, malignant and unspecified SOC (4 AEs, preferred terms: Acute promyelocytic leukaemia, Basal cell carcinoma, Carcinoid tumour of the gastrointestinal tract, Lung neoplasm malignant). The highest frequency of Grade 4 AEs in the placebo arm during this period was in the Cardiac disorders SOC (2 AEs, PTs: Bradycardia, Myocardial infarction).

Treatment-related TEAEs

The following table shows the number and percentage of subjects with treatment-related TEAEs experienced by ≥10% of patients in either treatment arm (i.e. considered by the Investigator to be possibly, probably, or definitely related to study drug):

Table 59. Summary of Treatment-Related, Treatment-Emergent Adverse Events (All Cycles) Experienced by ≥10% of Patients Receiving Sunitinib or Placebo in Study A6181109 - As-Treated Population

MedDRA Preferred Term	Sunitinib (N=306) n (%)			Placebo (N=304) n (%)		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Any AEs	**301 (98.4)**	**147 (48.0)**	**28 (9.2)**	**230 (75.7)**	**21 (6.9)**	**4 (1.3)**
Diarrhoea	171 (55.9)	12 (3.9)	0	55 (18.1)	1 (0.3)	0
PPE syndrome	154 (50.3)	46 (15.0)	3 (1.0)	31 (10.2)	1 (0.3)	0
Fatigue	112 (36.6)	13 (4.2)	2 (0.7)	60 (19.7)	4 (1.3)	0
Hypertension	110 (35.9)	24 (7.8)	0	29 (9.5)	2 (0.7)	0
Dysgeusia	103 (33.7)	0	0	16 (5.3)	0	0
Mucosal inflammation	103 (33.7)	14 (4.6)	0	25 (8.2)	0	0
Nausea	102 (33.3)	6 (2.0)	0	36 (11.8)	0	0
Stomatitis	80 (26.1)	5 (1.6)	2 (0.7)	11 (3.6)	0	0
Dyspepsia	78 (25.5)	4 (1.3)	0	17 (5.6)	0	0
Neutropenia	72 (23.5)	23 (7.5)	3 (1.0)	2 (0.7)	0	0
Asthenia	68 (22.2)	11 (3.6)	0	31 (10.2)	2 (0.7)	0
Hair colour change	67 (21.9)	0	0	7 (2.3)	0	0
Thrombocytopenia	63 (20.6)	15 (4.9)	4 (1.3)	4 (1.3)	0	0
Decreased appetite	56 (18.3)	2 (0.7)	0	13 (4.3)	0	0
Vomiting	56 (18.3)	7 (2.3)	0	14 (4.6)	0	0
Hypothyroidism	55 (18.0)	0	0	4 (1.3)	0	0
Rash	54 (17.6)	2 (0.7)	0	29 (9.5)	0	0
Epistaxis	52 (17.0)	0	0	7 (2.3)	0	0
Headache	47 (15.4)	1 (0.3)	0	29 (9.5)	0	0
Leukopenia	45 (14.7)	3 (1.0)	1 (0.3)	2 (0.7)	0	0
Dry skin	43 (14.1)	0	0	17 (5.6)	0	0
Pain in extremity	41 (13.4)	1 (0.3)	0	7 (2.3)	0	0
Abdominal pain upper	37 (12.1)	0	0	9 (3.0)	0	0
Abdominal pain	37 (12.1)	4 (1.3)	1 (0.3)	11 (3.6)	0	0
Constipation	33 (10.8)	0	0	22 (7.2)	0	0
Yellow skin	32 (10.5)	0	0	2 (0.7)	0	0

A total of 301 (98.4%) and 230 (75.7%) treatment-related TEAEs were reported for patients in the sunitinib and placebo treatment arms, respectively.

The most common treatment-related TEAEs according to SOC in the sunitinib arm were gastrointestinal disorders (83%), skin and subcutaneous tissue disorders (75.2%), General disorders and administration site conditions (71.6%) and nervous system disorders (50.7%).

The most common (≥ 25%) treatment-related TEAEs in the sunitinib arm were Diarrhoea (55.9%), PPE (50.3%), Fatigue (36.6%), Hypertension (35.9%), Dysgeusia (33.7%), Mucosal inflammation (33.7%), Nausea (33.3%), Stomatitis (26.1%), and Dyspepsia (25.5%).

The most common (≥5%) Grade ≥3 treatment-related TEAEs reported 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 0.7% in the placebo arm), and Thrombocytopenia (6.2% vs 0% in the placebo arm). No Grade 5 treatment-related TEAEs were reported in either treatment arm.

TEAEs of special interest

TEAEs of special interest for sunitinib include thyroid disorders and cardiovascular events.

Thyroid disorders are presented below:

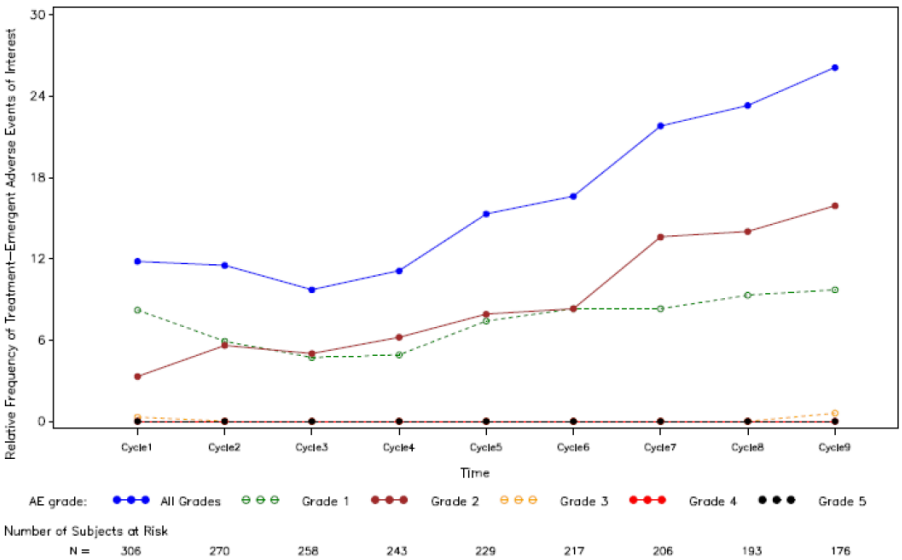
Table 60 Descriptive Summary of Duration of Treatment-Emergent Adverse Events for MedDRA Preferred Terms of Thyroid Disorders (All Causalities, All Cycles) in Study A6181109 - As-Treated Population

MedDRA Preferred Term	Sunitinib (N=306) Duration (Weeks) n	Mean (SD)	Min - Max	Placebo (N=304) Duration (Weeks)[Error! Reference source not found.] n	Mean (SD)	Min - Max
Patients with any Thyroid Disorder AE	63	46.4 (71.43)	0.1 - 312.4	11	103.9 (122.79)	7.1 - 374.3
Benign Neoplasm of Thyroid Gland	0			1	35.1 (N/A)	35.1 - 35.1
Goitre	0			2	305.6 (97.08)	237.0 - 374.3
Hyperthyroidism	12	23.2 (25.95)	2.1 - 77.7	2	110.8 (146.57)	7.1 - 214.4
Hypothyroidism	56	46.9 (75.30)	0.1 - 312.4	4	58.0 (62.06)	12.1 - 149.4
Papillary Thyroid Cancer	0			1	22.1 (N/A)	22.1 - 22.1
Thyroid Disorder	1	19.0 (N/A)	19.0 - 19.0	0		
Thyroid Mass	0			1	20.4 (N/A)	20.4 - 20.4

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 and very low frequencies of Grade 3 AEs of thyroid dysfunction were observed (1 AE in Cycle 1 and Cycle 9). One patient permanently discontinued and 2 patients temporarily discontinued due to the AE hypothyroidism in the sunitinib arm. No data are available regarding resolution of thyroid dysfunction.

The frequency of thyroid dysfunction AEs steadily increased from Cycle 4 through Cycle 9 (see figure below):

Figure 28: plot of relative frequency of TEAEs thyroid dysfunction by maximum CTCAE grade and cycle in the sunitinib arm of Study A6181109 - As-Treated Population



Cardiovascular events (defined as PT that fall under the "High Level Group Terms (HLGTs)"

cardiac arrhythmia, coronary artery disorder, heart failure, embolism and thrombosis and central nervous system vascular disorder) (hypertension is not included) are presented below:

Table 61: Summary of Treatment Emergent Cardiovascular Adverse Events (including Follow up period) - As Treated, Global Cohort

System Organ Class and MedDRA Preferred Term	Sunitinib Malate (N=306) n (%)	Placebo (N=304) n (%)
Number (%) of Subjects with Treatment Emergent Cardiovascular Adverse Events	30 (9.8)	27 (8.9)
Cardiac disorders	25 (8.2)	23 (7.6)

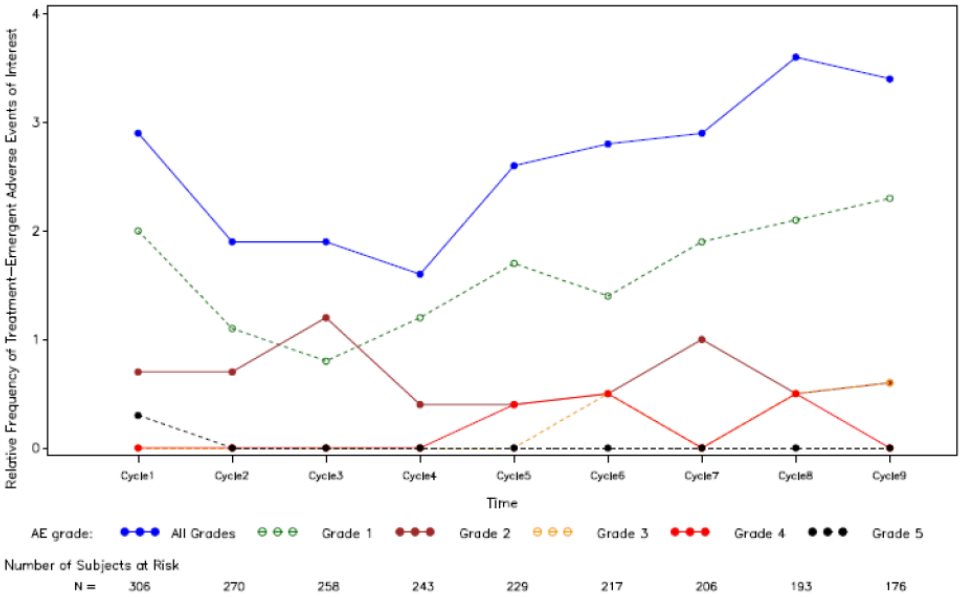
Table 61: Summary of Treatment Emergent Cardiovascular Adverse Events (including Follow up period) - As Treated, Global Cohort

System Organ Class and MedDRA Preferred Term	Sunitinib Malate (N=306) n (%)	Placebo (N=304) n (%)
Angina pectoris	5 (1.6)	2 (0.7)
Atrial fibrillation	3 (1.0)	5 (1.6)
Myocardial infarction	3 (1.0)	1 (0.3)
Acute myocardial infarction	2 (0.7)	1 (0.3)
Arrhythmia	2 (0.7)	5 (1.6)
Sinus bradycardia	2 (0.7)	2 (0.7)
Acute coronary syndrome	1 (0.3)	0
Atrial flutter	1 (0.3)	0
Bradycardia	1 (0.3)	2 (0.7)
Bundle branch block left	1 (0.3)	0
Cardiac arrest	1 (0.3)	1 (0.3)
Conduction disorder	1 (0.3)	0
Extrasystoles	1 (0.3)	0
Myocardial ischaemia	1 (0.3)	0
Supraventricular extrasystoles	1 (0.3)	2 (0.7)
Tachycardia	1 (0.3)	0
Ventricular extrasystoles	1 (0.3)	1 (0.3)
Angina unstable	0	2 (0.7)
Arrhythmia supraventricular	0	1 (0.3)
Atrioventricular block	0	1 (0.3)
Cardiac failure	0	2 (0.7)
Sinus tachycardia	0	1 (0.3)
Nervous system disorders	3 (1.0)	4 (1.3)
Transient ischaemic attack	2 (0.7)	1 (0.3)
Carotid arteriosclerosis	1 (0.3)	0
Cerebrovascular accident	1 (0.3)	2 (0.7)
Carotid artery stenosis	0	1 (0.3)
Cerebral haematoma	0	1 (0.3)
Cerebral infarction	0	1 (0.3)
Vascular disorders	3 (1.0)	2 (0.7)
Deep vein thrombosis	1 (0.3)	1 (0.3)
Embolism venous	1 (0.3)	0
Vena cava thrombosis	1 (0.3)	0
Venous thrombosis limb	0	1 (0.3)

In the sunitinib arm, subjects experiencing cardiovascular events were younger compared to the placebo arm (mean age: 56 vs 63 years; subjects <65 years were 87% vs 56%).

The severity of cardiovascular events was overall similar in both arms: G1/2 60% vs 52%, G3 17% vs 26%, G4 17% vs 15%, G5 7% vs 7%). In the sunitinib and in the placebo arm respectively, 10 and 11 patients experienced G3/4 events. There were 2 Grade 5 events cardiovascular events in the sunitinib arm: a cardiac arrest and a vena cava thrombus. Two Grade 5 events were reported also in the placebo arm. The frequency of cardiovascular events in the sunitinib arm was slightly increased from Cycle 5 through 8, as shown in figure below:

Figure 29: plot of relative frequency of TEAEs Cardiovascular Adverse Events by maximum CTCAE grade and cycle in the sunitinib arm of Study A6181109 - As-Treated Population



20% of the cardiovascular events occurred in the follow-up period (i.e. after stopping treatment), 6 in the sunitinib arm, all but one reported as resolved.

About 40% of the cardiovascular events in both arms were SAE. Drug was discontinued if ongoing. These events are mostly reported as resolving/resolved.

When considering the TEAEs belonging to the SOC "cardiac disorder", all causality TEAEs were experienced by 38 (12.4%) patients in the sunitinib arm vs. 30 (9.9%) patients in the placebo arm, which were G≥3 TEAE in 3.3% vs. 1.6%. Frequency of Treatment-related TEAEs within this SOC was 8.2% vs 4.6%, treatment-related SAEs within this SOC was 1.6% vs 0.7%. Patients experiencing treatment-related TEAEs belonging to the SOC Cardiac disorders leading to permanent treatment discontinuation were 7 (2.3%) vs 2 (0.7%) (sunitinib: left ventricular dysfunction [2], acute myocardial infarction [2], myocardial infarction, myocarditis, atrial fibrillation; placebo: angina unstable, left ventricular dysfunction).

Updated cardiovascular toxicity analyses

Table 62: Summary of Treatment-Emergent Cardiovascular Adverse Events (Including the Follow-up Period) by MedDRA SOC, PT, and Maximum CTCAE Grade (All Causalities) - As Treated, Global Cohort

	Sunitinib (N=306) n (%)						Placebo (N=304) n (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
AnyAEs	24 (7.8)	12 (3.9)	14 (4.6)	7 (2.3)	2 (0.7)	59 (19.3)	22 (7.2)	10 (3.3)	8 (2.6)	5 (1.6)	2 (0.7)	47 (15.5)

Mean age of patients experiencing CV events was 56 vs 60 years in sunitinib vs placebo arm, with 20.8% vs 13.1% of patients < 65 years experienced a CV AEs in Sutent and placebo arm respectively.

Serious adverse event / deaths / other significant events

Serious adverse event (SAE)

All-causality treatment-emergent SAEs were reported in 67 (21.9%) and 52 (17.1%) patients in the sunitinib and placebo treatment arms, 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).

Table 63. Summary of All-Causality, Treatment-Emergent Serious Adverse Events (All Cycles) Experienced by ≥2 Patients Receiving Sunitinib or Placebo in Study A6181109 - As-Treated Population

MedDRA Preferred Term	Sunitinib (N=306) n (%)	Placebo (N=304) n (%)
Any SAE	67 (21.9)	52 (17.1)
Hypertension	8 (2.6)	2 (0.7)
Thrombocytopenia	7 (2.3)	1 (0.3)
Pulmonary embolism	5 (1.6)	1 (0.3)
Pyrexia	5 (1.6)	0
Abdominal pain	3 (1.0)	1 (0.3)
Myocardial infarction	3 (1.0)	1 (0.3)
Vomiting	3 (1.0)	0
Acute kidney injury	2 (0.7)	0
Acute myocardial infarction	2 (0.7)	1 (0.3)
Atrial fibrillation	2 (0.7)	1 (0.3)
Chest pain	2 (0.7)	1 (0.3)
Cholelithiasis	2 (0.7)	1 (0.3)
Dehydration	2 (0.7)	0
Diarrhoea	2 (0.7)	1 (0.3)
Hepatitis acute	2 (0.7)	0
Leukopenia	2 (0.7)	0
Mucosal inflammation	2 (0.7)	0
Nausea	2 (0.7)	0
Neutropenia	2 (0.7)	0
Renal failure	2 (0.7)	0
Transient ischaemic attack	2 (0.7)	1 (0.3)
Upper gastrointestinal haemorrhage	2 (0.7)	1 (0.3)

Drug-related SAE

SAEs considered to be related to treatment were reported in 13.1% of patients in the sunitinib arm and 2.3% of patients in the placebo arm, most common being thrombocytopenia (n=7) and hypertension (n=7). The majority of treatment-related SAEs were Grade ≥3 in severity and there were no Grade 5.

SAEs in the follow-up period (i.e. after discontinuation of study drug + 28 days): there were 19 patients experiencing SAEs in the sunitinib arm and the majority of SAEs were Grade 3 in severity (11/19).

Two SAEs were considered related to sunitinib treatment by the investigator: PT Gastritis haemorrhagic and Tympanic membrane perforation, both reported during the interval 0 + 28 Days-<3 months. No SAEs were reported after 3 months post study treatment.

In the sunitinib arm, the SOCs containing more than 2 SAEs were *Cardiac disorders* (5 SAEs), which reported the PTs Acute coronary syndrome, Atrial fibrillation, Cardiac arrest, and Myocardial infarction (reported for 2 patients), *Infections and investigations* (4 SAEs), which reported the preferred terms Cellulitis, Pneumonia, Pneumonia legionella, Sepsis, and Urinary tract infection; and *Neoplasms benign, malignant, and unspecified* (5 SAEs), which reported the preferred terms Acute myeloid

leukaemia, Colon cancer, Endometrial adenocarcinoma, Hepatocellular carcinoma, and Prostate cancer. One Grade 5 SAE (Cardiac arrest) was reported after the last dose +28 days of sunitinib.

In the placebo arm, 24 SAEs were reported during this period, the majority were Grade 3 in severity (13/24). The only SOCs containing more than 2 SAEs were *Neoplasms benign, malignant, and unspecified* (8 SAEs), which reported the preferred terms Acute promyelocytic leukaemia, Basal cell carcinoma, Carcinoid tumour of the gastrointestinal tract, Intraductal proliferative breast lesion, Lung neoplasm malignant, Metastases to lung, Papillary thyroid cancer, and Prostate cancer*; Cardiac disorders* (5 SAEs), which reported the preferred terms Angina pectoris, Atrioventricular block, Bradycardia, Cardiac arrest, and Myocardial infarction; and *Infections and infestations* (4 SAEs), which reported the preferred terms Pneumonia, Respiratory tract infection, and Urinary tract infection (2 SAEs). Five (5) Grade 5 SAEs (Cardiac arrest, Multiple organ dysfunction syndrome, Metastases to lung, Cerebral haematoma, Haemoptysis) were reported after the last dose +28 days of placebo. None of the Grade 5 AEs were considered related to treatment by the investigator.

Deaths

No deaths in either group were attributed to study treatment toxicity. The most common cause of death in both arms was the disease under study. There were 2 patients in the sunitinib arm and none in the placebo arm who died on study treatment or within 28 days after the last dose. In the follow-up period, defined as after 28 days of last dose of study drug, a total of 61 (19.9%) patients in the sunitinib arm and 64 (21.1%) patients in the placebo arm died.

Table 64. Summary of Deaths in Study A6181109 - As-Treated Population

	Sunitinib (N=306) n (%)	**Placebo (N=304) n (%)**
Number (%) of subjects:		
Deaths	63 (20.6)	64 (21.1)
Subjects who died while on treatment[a]	2 (0.7)	0
Disease under study	2 (0.7)	0
Study treatment toxicity	0	0
Unknown	0	0
Other	1 (0.3)	0
Subjects who died during follow-up[b]	61 (19.9)	64 (21.1)
Disease under study	46 (15.0)	47 (15.5)
Study treatment toxicity	0	0
Unknown	8 (2.6)	7 (2.3)
Other	9 (2.9)	10 (3.3)

a. On-treatment deaths are those that occurred after the first dose of study drug and within 28 days of last dose.
b. Follow-up deaths are those that occurred >28 days after the last dose.

Other significant events: Second primary malignancies

Second primary malignancies were reported as part of the disease assessment for the primary efficacy endpoint of disease-free survival. There were 9 (2.9%) patients in the sunitinib arm and 20 (6.6%) patients in the placebo arm experiencing second primary malignancies (table X). The time to onset ranged from 0.9 - 6.6 years and from 1.3 - 6.7 years in the sunitinib arm and placebo arm, respectively.

Table 65. Summary of Second Primary Malignancies in Study A6181109 Based on Efficacy Assessments - As-Treated Population

Treatment Arm Diagnosis (Preferred Term)	Time to Onset (Years)
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

To identify second primary malignancies in patients who may have had an event after their efficacy endpoint was reached, a search of AEs reported as second primary malignancies was conducted: 5 patients in the sunitinib arm and 11 patients in the placebo arm with second primary malignancies were identified (see table below). The onset ranged from 1.5 - 4.2 years and from 0.4 years - 6.7 years in the sunitinib and placebo arm, respectively. None of the second primary malignancies in the sunitinib arm were attributed to study drug.

Table 66. Summary of Second Primary Malignancies in Study[a] A6181109 Based on Adverse Events - As-Treated Population

Treatment Arm Adverse Event (Preferred Term)	Day of Onset of Adverse Event[b]
Sunitinib	
Endometrial adenocarcinoma	550
Colon cancer	[784][c]
Prostate cancer	966
Acute myeloid leukaemia	1444
Hepatocellular carcinoma	1539
Placebo	
Malignant melanoma	135
Brain cancer metastatic	179
Lung adenocarcinoma	195
Prostate cancer	648
Intraductal proliferative breast lesion	1029
Lung neoplasm malignant	1052
Basal cell carcinoma	1434
Papillary thyroid cancer	1647
Metastases to lung	1997
Carcinoid tumour of the gastrointestinal tract	2004
Acute promyelocytic leukaemia	2457

a. Includes data from the active treatment and follow-up periods in Study A6181109.
b. Day relative to start of study treatment. First day of treatment = Day 1.
c. Values in brackets are imputed from incomplete dates and times.

A higher number of secondary primary malignancies have been reported in the placebo arm compared to the sunitinib arm. Whether this could be reflective of a possible "protective" effect of sunitinib from malignancy or just a chance finding is unknown.

No trends in the type and primary of second malignancies reported are noted.

Laboratory findings

Haematology: In the sunitinib arm, the most common shifts from Grade ≤ 2 to Grade 3 or 4 severity were for absolute neutrophils (12.7% [38 patients] and 0.7%, respectively) and platelets (3.3% and 1.3%, respectively). Overall, the incidence of shifts in haematological parameter were higher in the sunitinib compared to the placebo arm.

Reduction in neutrophils was the most common grade 3 laboratory abnormality observed in S-TRAC study. Neutropenia was the third most common cause of temporary discontinuation in the sunitinib arm (5.2% vs. 0% of patients in sunitinib vs placebo). No cases of neutropenia/neutropenic infections were reported and no cases of neutropenia required hospitalization. Grade 4 neutropenia was reported in 3 (1%) patients in the sunitinib arm.

Clinical chemistry: Overall, the frequency of Grade 3 liver tests was higher in the sunitinib arm compared with the placebo arm. In the sunitinib arm, the most common shifts from Grade ≤ 2 to Grade 3 severity were for ALT (2.3% versus 0.7% in the placebo arm). The only Grade 4 LFTs reported were for AST in 2 (0.7%) patients in the sunitinib arm. There were no patients in either treatment arm who met the criteria for a potential Hy's Law case.

Higher frequencies of elevated liver tests TEAEs were reported in the sunitinib arm compared with the placebo arm, with 16 (5.2%) and 2 (0.7%) of patients experiencing AST increased, respectively, and 15 (4.9%) and 2 (0.7%) of patients experiencing ALT increased, respectively. TEAEs of Hepatotoxicity and Jaundice were reported at incidences of 0.3% and 6.5% of patients in the sunitinib arm, respectively, and at 0.3% and 0% of patients in the placebo arm, respectively. Two SAEs of ALT increased and AST increased, both considered related to treatment by the investigator, were reported in the sunitinib arm.

Shifts from Grade ≤ 2 to Grade 3 or 4 severity in the remaining chemistry parameters were similar in the two arms.

QTcF: A total of 11 (3.6%) patients in the sunitinib arm and 7 (2.3%) patients in the placebo arm experienced QTcF≥501 milliseconds (ms), irrespective of baseline value. Shifts in QTcF interval from Grade 0 at baseline to Grade ≥3 (QTc ≥501 ms) post-baseline was 7 (2.3%) patients in the sunitinib arm versus 3 (1.0%) patients in the placebo arm; from Grade 1 (QTc 451 – 470 ms) at baseline to Grade ≥3 (QTc ≥501 ms) post-baseline was 1 (0.3%) patient in the sunitinib arm versus 2 (0.7%) patients in the placebo arm; and Grade 2 (QTc 471 – 500 ms) at baseline to Grade ≥3 (QTc ≥ 501 ms) post-baseline was 3 (1.0%) patients in the sunitinib arm versus 1 (0.3%) patient in the placebo arm.

The TEAE of Electrocardiogram QT prolonged was reported for 4 (1.3%) patients in the sunitinib arm and for 1(0.3%) patient in the placebo arm. No TEAEs of torsades de pointes, Sudden death, Ventricular tachycardia, Ventricular fibrillation, or Ventricular flutter were reported in Study A6181109. One (1 [0.3%]) TEAE of Seizure (Grade 2 in severity) was reported in the follow-up period in the sunitinib arm of Study A6181109. Two (2 [0.7%]) TEAEs of Syncope (1 Grade 1 and 1 Grade 3 in severity) were reported in the sunitinib arm of Study A6181109, however, there was no indication that an arrhythmia was the aetiology for syncope in these cases.

LVEF: Mean LVEF measurements during (Cycles 2, 4, and 8) and at the end of treatment were similar between the 2 treatment arms. All-causality Ejection fraction decreased was reported for 4 patients (1.3%) in the sunitinib arm and for 6 patients (2.0%) in the placebo arm.

Safety in special populations

Age

The majority of patients were <65 years of age (75.5% in the sunitinib arm and 73% in the placebo group). TEAEs in the sunitinib arm reported in a higher proportion (>10% difference) of <65 years compared with ≥65 years included Diarrhoea (60.2% vs 46.7%) and PPE syndrome (54.1% vs 38.7%).

TEAEs in the sunitinib arm reported in a higher proportion (>10% difference) of patients aged ≥65 years of age compared with <65 years included Thrombocytopenia (32.0% vs 17.3%) and Nausea (42.7% vs 31.6%).

Gender

The majority of patients were male (71.9% in the sunitinib arm and 74.7% in the placebo group).

TEAEs in the sunitinib treatment arm were reported in a higher proportion (>10% difference) with female compared to male included: thrombocytopenia (36.0% vs 15.0%), Hypothyroidism (30.2% vs 13.6%), Alopecia (19.8% vs 4.1%), Vomiting (29.1% vs 15.0%), Nausea (44.2% vs 30.5%), and Hypertension (45.3% vs 33.6%).

Race

The majority of patients in the sunitinib arm (82.0%) and placebo arm (85.6%) were white, therefore, a meaningful review of safety by race is not possible because of the small number of non-white patients.

Geographical Region

The majority of patients in the Global cohort were in Europe with 235 patients in both the sunitinib arm (76.8%) and placebo arm (77.3%) located in this region. Patients from Asia were 45 (14.7%) in the sunitinib arm and 41 (13.5%) in the placebo arm.

TEAEs in the sunitinib arm reported in a higher proportion (>15% difference) of patients across geographical regions include PPE syndrome (Asia 82.2%, North America 59.1%, Europe 43.8%), Nausea (North America 54.5%, Europe 34.5%, Asia 20.0%), Dyspepsia (North America 50.0%, Europe 28.1%, Asia 6.7%), dysgeusia (North America 45.5%, Europe 35.7%, Asia 13.3%), Fatigue (North America 68.2%, Europe 34.9%, Asia 31.1%), Neutropenia (Asia 35.6%, Europe 21.3%, North America 18.2%), Stomatitis (America 45.5%, Asia 42.2%, Europe 22.1%), Mucosal inflammation (Europe 37.4%, North America 36.4%, Asia 15.6%), Rash (North America 36.4%, Asia 22.2%, Europe 17.4%), and Asthenia (Europe 26.0%, Asia 11.1%, North America 9.1%).

The majority of PPE syndrome AEs reported in Asia were Grade 1 or 2 in severity and no Grade 4 or 5 PPE syndrome AEs were reported in this subpopulation

Safety related to drug-drug interactions and other interactions

There were no new drug-drug interactions identified in Study A6181109.

Discontinuation due to adverse events

Treatment discontinuation

Subjects in the sunitinib arm of the S-TRAC study permanently discontinued treatment more frequently than in the placebo arm (44.4% vs. 30.6% respectively). The most common reason for permanent discontinuation was treatment-related AEs in the sunitinib arm (25.2% vs. 4.3% with sunitinib and placebo respectively), while it was objective progression or relapse in the placebo arm (7.2% vs. 19.4% with sunitinib and placebo respectively).

Table 67. Patient Discontinuations from the Treatment Phase in Study A6181109 – As-Treated Population

	Number (%) of Patients	
	Sunitinib (N = 306)	**Placebo (N = 304)**
Patient Died	1 (0.3)	1* (0.3)
Relation to Study Drug not Defined	51 (16.7)	76 (25.0)
Global deterioration of health status	1 (0.3)	0
Lost to follow-up	1 (0.3)	1 (0.3)
Objective progression or relapse	22 (7.2)	59 (19.4)
Other	12 (3.9)	7 (2.3)
Protocol violation	1 (0.3)	1 (0.3)
Patient refused continued treatment for reason other than adverse event	14 (4.6)	8 (2.6)
Related to Study Drug	77 (25.2)	13 (4.3)
Adverse event	77 (25.2)	13 (4.3)
Not Related to Study Drug	7 (2.3)	3 (1.0)
Adverse event	7 (2.3)	3 (1.0)
Total	136 (44.4)	93 (30.6)

ASSURE study

Table 68: discontinuations from treatment– patients starting at FULL DOSE - ASSURE study

Reason	Sunitinib	Sorafenib	Placebo	Total	p
	438	441	444	1323	–
Complete per Protocol	199(45.4)	203(46.0)	299(67.5)	701(53.0)	0.000
Disease Progression	31(7.1)	30(6.8)	81(18.3)	142(10.7)	
Adverse Events	97(22.1)	102(23.1)	23(5.2)	222(16.8)	
Death	1(0.2)	0(0.0)	0(0.0)	1(0.1)	
Patient Withdrawal/Refusal	96(21.9)	97(22.0)	24(5.4)	217(16.4)	
Alternative Therapy	1(0.2)	0(0.0)	0(0.0)	1(0.1)	
Other Complicating Disease	3(0.7)	3(0.7)	2(0.5)	8(0.6)	
Other	10(2.3)	6(1.4)	14(3.2)	30(2.3)	
Unk/Miss	0	0	1	1	

Table 69: discontinuations from treatment– patients starting at REDUCED DOSE - ASSURE

Reason	Sunitinib	Sorafenib	Placebo	Total	p
	191	189	189	569	–
Complete per Protocol	97(50.8)	103(54.5)	145(76.7)	345(60.6)	0.000
Disease Progression	21(11.0)	24(12.7)	21(11.1)	66(11.6)	
Adverse Events	27(14.1)	26(13.8)	10(5.3)	63(11.1)	
Death	1(0.5)	0(0.0)	0(0.0)	1(0.2)	
Patient Withdrawal/Refusal	38(19.9)	30(15.9)	8(4.2)	76(13.4)	
Other Complicating Disease	2(1.0)	2(1.1)	2(1.1)	6(1.1)	
Other	5(2.6)	4(2.1)	3(1.6)	12(2.1)	
Unk/Miss	0	0	0	0	

In S-TRAC study, AEs leading to permanent discontinuation in >1% of patients in the sunitinib arm were PPE syndrome (4.2%), Hypertension (2.0%) and Asthenia (1.3%). Summary of discontinuations due to AE experienced by ≥ 1% of patients is presented in the table below:

Table 70. Summary of Permanent Discontinuations Due to Adverse Events Experienced by ≥1% of Patients in Study A6181109 by Preferred Term - As-Treated Population

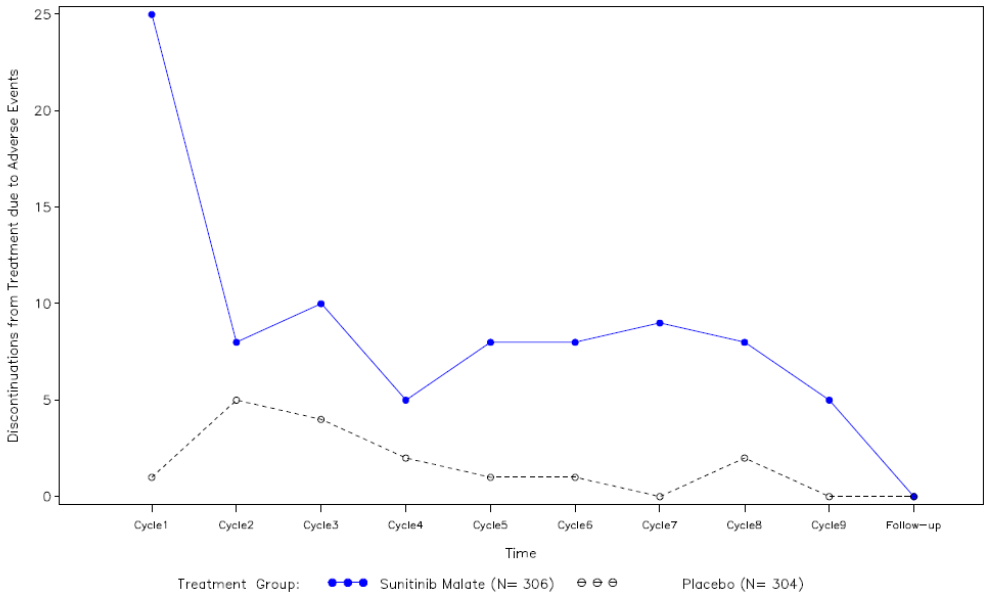
MedDRA Preferred Term	**Number (%) of Patients**	
	Sunitinib (N=306)	**Placebo (N=304)**
Permanent Discontinuations Due to Adverse Events	86 (28.1)	18 (5.9)
PPE syndrome	13 (4.2)	0
Hypertension	6 (2.0)	0
Asthenia	4 (1.3)	0
Fatigue	3 (1.0)	1 (0.3)
Pulmonary embolism	3 (1.0)	1 (0.3)
Gastrooesophageal reflux disease	3 (1.0)	0

In the sunitinib arm, more patients discontinued due to AEs during Cycle 1 (8.2%) and fewer patients overall discontinued due to AEs in later cycles (range 2.1%-4.4%). The AEs reported as the cause of discontinuation in Cycle 1 in > 1 patient were Hypertension (4 [1.3%] patients), Thrombocytopenia (2 [0.7%] patients), Dehydration (2 [0.7%] patients) and Vomiting (2 [0.7%] patients).

The mean and median time from randomization to discontinuation due to an AE in the sunitinib arm were 5.1 months and 4.5 months, respectively.

Most AEs leading to discontinuation were reported as resolved or resolving (87%). Of the 38 Grade 3 events that led to permanent treatment discontinuation, 84% were reported as recovered/recovering. All Grade 4 events leading to permanent treatment discontinuation were reported as recovered/recovering; they were single occurrences in single patients, with the exception of pulmonary embolism occurring in 2 patients in the sunitinib arm and 1 patient in the placebo arm.

Figure 30: Discontinuations due to AEs by cycle - Study A6181109 – As treated population



Temporary Discontinuations and Dose Reductions

Dose modifications (i.e. dose reductions, dose delayed, dose interruption) were more common in the sunitinib arm. Summary tables are presented below:

Table 71: dosing interruptions, delays, reductions - S-TRAC study, As treated population

	Number (%) of Patients	
	Sunitinib (N = 306)	**Placebo (N = 304)**
Patients With Dose Reductions	140 (45.8)	15 (4.9)
Total Number of Dose Reductions	188	16
Reason for Dose Reductions		
Adverse Event(s)	174 (92.6)	13 (81.3)
Other	12 (6.4)	3 (18.8)
Not Reported	2 (1.1)	0
Patients With Dose Delayed	127 (41.5)	81 (26.6)
Total Number of Dose Delayed	214	122
Reason for Dose Delayed		
Adverse Event(s)	124 (57.9)	26 (21.3)
Other	90 (42.1)	96 (78.7)
Patients With Dose Interruptions	166 (54.2)	84 (27.6)
Total Number of Dose Interruptions	592	123
Reason for Dose Interruption		
Adverse Event(s)	328 (55.4)	35 (28.5)
Other	264 (44.6)	88 (71.5)
Patients With Dose Increase	10 (3.3)	3 (1.0)
Total Number of Dose Increase	13	3
Reason for Dose Increase		
Other	13 (100.0)	3 (100.0)

Patients requiring > 6 weeks (i.e. 1 treatment cycle) of dosing interruption or dose reductions below 37.5 mg were considered for permanent discontinuation from study treatment.

Temporary discontinuation: 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 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).

Dose reductions: A total of 106 (34.6%) patients in the sunitinib arm and 6 (2.0%) patients in the placebo arm had a dose reduction in response to an AE. 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).

Post marketing experience

No post-marketing data have been submitted.

The Periodic Safety Update Report (PSUR), covering the reporting period 01 May 2015 to 30 April 2016, has been recently reviewed by the PRAC (see discussion on Clinical safety).

2.5.1. Discussion on clinical safety

Safety data supporting the application in adjuvant RCC are based on the pivotal Phase 3 study S-TRAC. Safety population included 306 patients treated with sunitinib and 304 patients who received placebo. Treatment regimen consisted in oral sunitinib 50 mg OD 4 weeks on/2 weeks off for up to 9 cycles (approximately 1 year). The cut-off date for safety data was 7th April 2016.

Additional safety information in the adjuvant RCC setting are provided by the ASSURE study (629 patients received sunitinib and 633 placebo). Due to differences between S-TRAC and ASSURE, also related to collection and reporting of safety data, only Grade 3-5 events have been compared, where possible which was acceptable.

Patients received treatment for a median of 12.4 months in both arms, and at a median dose intensity of 88.4% vs. 99.7% in the sunitinib and placebo arm respectively.

TEAEs were experienced by all but one patients in the sunitinib arm (99.7%) vs. 88.5% in the placebo arm. Grade 3 and 4 TEAEs were observed in 61.8% vs. 20.1% of patients. Five patients in each arm (1.6%) experienced a TEAE with Grade 5 in severity. The overall incidence and severity of TEAEs appeared to be higher between 0 and 3 months from the first dose of sunitinib.

A total of 301 (98.4%) and 230 (75.7%) treatment-related TEAEs were reported for patients in the sunitinib and placebo arms, respectively.

The SOCs with the highest frequencies of treatment-related TEAEs in the sunitinib arm were: Gastrointestinal disorders (83%), Skin and subcutaneous tissue disorders (75.2%), General disorders and administration site conditions (71.6%) and nervous system disorders (50.7%).

More than half of the patients suffered from diarrhoea and PPE related to sunitinib. The most common (≥ 20% of the patients) treatment-related TEAEs in the sunitinib arm were diarrhoea (55.9%), PPE syndrome (50.3%), fatigue (36.6%), hypertension (35.9%), dysgeusia (33.7%), mucosal inflammation (33.7%), nausea (33.3%), stomatitis (26.1%), dyspepsia (25.5%), neutropenia (23.5%), asthenia (22.2%), hair colour change (21.9%) and thrombocytopenia (20.6%). The most common (≥ 5%) Grade ≥3 treatment-related TEAEs reported in the sunitinib arm were PPE syndrome (16.0% vs. 0.3% in the placebo arm), Neutropenia (8.5% vs. 0%), Hypertension (7.8% vs. 0.7%), and Thrombocytopenia (6.2% vs. 0%). The most common Grade 4 treatment-related TEAE events were thrombocytopenia (1.3%), neutropenia (1%) and PPE syndrome (1%) (vs. none in the placebo arm). No Grade 5 treatment-related TEAEs were reported in either treatment arms.

The pattern of treatment-related AEs in S-TRAC study is consistent with the known safety profile of sunitinib, with the exception of an apparent higher than expected frequency of PPE syndrome (50.3%), compared to approximately 28% the pivotal study of sunitinib in the RCC metastatic setting, as well as in the last PSUR. The rate of Grade 3 PPE is instead similar to what observed in the ASSURE study (15%) in the same adjuvant setting. PPE syndrome is a well-known cutaneous side effect of TKI. Although it is not life-threatening and usually self-limiting, the symptom burden may significantly reduce quality of life. PPE was indeed the most common treatment-related AE leading to permanent discontinuation, temporary discontinuation and dose reduction of sunitinib in S-TRAC study. No baseline factors that could account for this difference, the longer exposure might have played a role, and the frequency of thyroid dysfunctions and cardiac events increased over time. The higher rate of PPE seen in adjuvant compared to metastatic RCC setting has been reflected in the SmPC section 4.8.

The high rate of treatment discontinuation due to AEs, especially in cycle 1, and in several cases due to low grade (1-2) events, underlines the toxicity and the difficulty to be compliant with the proposed sunitinib regimen, considering it is in an adjuvant setting.

Reduction in neutrophils was the most common Grade 3 laboratory abnormality observed, however it is reassuring that no cases of neutropenia/neutropenic infections nor cases of neutropenia required hospitalization were reported.

Treatment-related SAEs were reported in 13.1% vs. 2.3% of patients in the sunitinib and placebo arms, respectively. The most common sunitinib-related SAEs were thrombocytopenia and hypertension. A SAE of “Tympanic membrane perforation”, which was considered treatment-related by investigator, has been reported. A review of safety database through 2012 did not identify further cases of tympanic membrane perforation. One serious case spontaneously reported of tympanic membrane perforation has been found according to the last PSUR. The MAH will further monitor events related to the tympanic membrane in the next PSURs.

No deaths in either group were attributed to study treatment toxicity. However, 2 Grade 5 events in the sunitinib arm should be discussed: a cardiac arrest (happened 3 years after stopping sunitinib, however this patient experienced a myocardial infarction while on sunitinib, therefore a causal relationship with the drug cannot be excluded) and a vena cava thrombus (related to disease under study, although a contribution of drug cannot be excluded). Two Grade 5 events were reported also in the placebo arm. The most common cause of death in both arms was the disease under study.

During the follow-up period, investigators were only required to report treatment-related SAEs. The incidence of AEs occurred ≥ 12 months after the last dose of study drug was similar in the sunitinib and placebo arm (7.2% vs. 9.9%). *Cardiac disorders* and *Neoplasms benign, malignant, and unspecified* were the 2 most common SOCs recorded in both arms. A higher number of secondary primary malignancies have been reported in the placebo arm compared to the sunitinib arm. Whether this could be reflective of a possible “protective” effect of sunitinib from malignancy or just a chance finding is unknown. No trends in the type and primary of second malignancies reported are noted. Two SAEs occurred in the follow-up period were considered related to sunitinib treatment by the investigator: PT Gastritis haemorrhagic and Tympanic membrane perforation, both reported during the interval 0 + 28 Days-<3 months. No SAEs were reported after 3 months post study treatment.

TEAEs of special interest were thyroid disorders and cardiovascular events, both known adverse reactions to sunitinib. Hypothyroidism was the most common thyroid disorder. The frequency of thyroid dysfunctions steadily increased from Cycle 4 through Cycle 9. No data on the resolution of thyroid events are available. Reassuringly, most of the event were Grade 1 and 2.

Overall, the number of cardiovascular events (according to the MAH’s definition including PT that fall under the HLGTs cardiac arrhythmia, coronary artery disorder, heart failure, embolism and thrombosis

and central nervous system vascular disorder; excluding hypertension, occurring in 35.9% of patients taking Sutent vs 9.5% on placebo) occurred in the sunitinib arm was quite similar to the placebo arm (8.9% vs 9.8%). When including all MedDRA PTs in the cardiac disorder SOC, as well all MedDRA PTs in the HLGTs embolism and thrombosis (including the PT of pulmonary embolism), central nervous system vascular disorders, and cardiac and vascular investigations, CV events were 19.3% for sunitinib vs 15.5% for placebo, with left ventricular dysfunction and pulmonary embolism being the most common CV sunitinib-related events. When the SOC "Cardiac Disorders" is considered, sunitinib still appeared more toxic compared to placebo (within this SOC, treatment-related TEAEs were 8.2% vs 4.6% and treatment-related SAEs were 1.6% vs 0.7%).

Patients were carefully screened and those with CV comorbidities were excluded. Mean age of patients experiencing CV events was 56 vs 60 years in sunitinib vs placebo arm, with 20.8% vs 13.1% of patients < 65 years experienced a CV AEs in Sutent and placebo arm respectively. Although no specific trends in CV events distribution can be identified in younger vs older patients, grade ≥3 CV events were experienced by 8.7% vs 4% of patients < 65 vs ≥ 65 years respectively, confirming the known cardiovascular toxicity of Sutent, including high grade events, even in a young population. A SAE of grade 3 non-infectious myocarditis (resolved), which was determined to be unexpected, for which a reasonable possibility of an association with sunitinib could not be excluded, was reported. The possible occurrence of myocarditis should be mentioned in section 4.4 of the SmPC.

Permanent discontinuations were more frequent in the sunitinib arm compared to the placebo arm (44.4% vs. 30.6%), the most common reason for sunitinib being treatment-related AEs (25.2% vs. 4.3%). In the sunitinib arm, 11.8% of patients discontinued treatment during cycle 1, almost all cases were due to AEs or patient refusal: this rate is fairly higher compared to all subsequent cycles. Approximately 41% AEs leading to permanent discontinuations were grade 1 or 2 in severity, indicating the lower threshold of patients treated in the adjuvant setting for accepting toxicities. On the other hand, discontinuation were grade 3-4 in almost 60% of cases. The 84% of Grade 3 events and 100% of Grade 4 events leading to treatment discontinuation were reported as resolved. Even though reassuring, it remains that a not negligible rate of patients did not recover. The rate of treatment discontinuation due to sunitinib-related AEs was similar to what reported in the ASSURE study.

Temporary discontinuation due to AEs occurred in 46.4% vs. 13.2% of patients treated with sunitinib and placebo respectively. Dose reductions due to AEs occurred in 34.6% vs. 2.0% of patients treated with sunitinib and placebo respectively (only one dose reduction level was allowed, i.e. not below 37.5 mg). Dose delays occurred in 41.5% vs. 26.6% of patients in the sunitinib and placebo arm respectively. The delays were due to AEs in 57.9% in the sunitinib arm (vs. 21.3% in the placebo).

In the ASSURE study, treatment regimen was initially the same as in S-TRAC (sunitinib 50 mg OD 4 weeks on / 2 weeks off for 9 cycles). However, after having observed a high rate of treatment discontinuation due to adverse events or patient refusal, the starting dose of sunitinib/placebo was reduced to 37.5 mg OD, and then escalated if patients experienced no grade ≥ 2 toxicities. 30.4% of patients started sunitinib with the reduced dose. A meaningful increase in sunitinib tolerance by reducing starting dose was however not seen (discontinuation due to AEs went down from 22.2% to 14.1%). Although exposure data were captured differently between the two studies, the overall median exposure to sunitinib in ASSURE seems to be lower than in the S-TRAC study.

2.5.2. Conclusions on clinical safety

No new safety findings were identified in S-TRAC trial. The clinical safety profile is considered in overall consistent with the known safety profile of Sutent with the exception of a higher incidence of PPE compared to the metastatic RCC setting, which is included in section 4.8. The frequency of thyroid

dysfunctions and cardiac events increased over time. In the context of an adjuvant setting the toxicities with Sutent resulted in a high rate of treatment discontinuation and difficulties with compliance.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) which were reviewed and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found unacceptable for the following reasons:

The User consultation was performed only in 2005 at the time the first approval, in which the most represented age group was in the range 18-34 years.

Since the initial MA, 19 variations (type II/IB), 2 renewals and 2 extensions of indication impacting the PIL have been submitted for Sutent.

Therefore, considering the aspects potentially impacting the readability of the PIL, the enrollment of younger participants than the target population of Sutent and the amount of revisions suffered by the PIL, in order to ensure a correct and safe use of the medicinal product, a further User test is recommended. The MAH agreed to perform and to submit a new user testing in the next relevant variation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The present extension of indication application for Sutent is aimed at including the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy. Patients with high-risk features represent about 11% of all RCC cases in EU. Up to 60% of them will recur and developed metastatic disease within 5 years, with the majority of recurrences occuring within the first 2-3 years.

3.1.2. Available therapies and unmet medical need

The treatment of choice for localized RCC (Stage I-III) is surgical resection, which is the only curative therapy. Several approaches have been assessed in the adjuvant RCC setting (e.g. IL-2, IFN-α, vaccine therapy, chemotherapy, novel agents), mostly with negative results. After nephrectomy, observation remains the standard of care, and no treatment is currently approved in the adjuvant setting. Several large phase III trials testing targeted agents approved in the metastatic RCC setting (TKIs, mTOR inhibitor) are ongoing or have been recently reported (ASSURE, S-TRAC, PROTECT). Anti-PD1 and anti-PD-L1 drugs are under investigation in this setting as well.

3.1.3. Main clinical studies

The main evidence for efficacy and safety to support the present extension of indication is the Phase III study A6181109 (S-TRAC), an international, multicenter, randomized, double-blind trial of adjuvant sunitinib 50 mg OD on Schedule 4/2 (4 weeks on, 2 weeks off) for 9 cycles (i.e. approximately 1 year) vs. placebo. The ITT population includes 615 patients (309 in sunitinib arm and 306 in the placebo arm).

Additional data regarding the phase III study ASSURE (E2805), a randomized, double-blind, placebo controlled phase III study led by the ECOG-ACRIN cooperative group, investigating adjuvant treatment with sunitinib or sorafenib vs. placebo in previously untreated patients with resected RCC, have been presented and discussed. 647 patients each were enrolled in the sunitinib and in the placebo arm.

3.2. Favourable effects

Median DFS according to BICR (primary endpoint) was 6.8 years (95%CI: 5.8, NR) for sunitinib vs. 5.6 years (95%CI: 3.8, 6.6) in the placebo arm, with HR 0.761 (95%CI: 0.594, 0.975), p = 0.030 (2-sided p-value from the log-rank test stratified by UISS High Risk Group).

In the subgroup analysis of DFS by BICR, a HR of 0.737 (95%CI: 0.548, 0.993; p= 0.044) in favor of sunitinib was obtained in patients belonging to the higher risk groups (T3 high + Other [T4 and N+]).

For the secondary endpoint DFS by Investigator, results were numerically in favor of the sunitinib arm (HR 0.811, 95%CI: 0.643, 1.023, p= 0.077 2-sided from the log-rank test stratified by UISS High Risk Group).

Efficacy was further explored on the basis of the classification of population in:

- *Highest risk of recurrence (T3 and Fuhrman's Grade >2 or T4 or Any T N+)*

n=398 (65% of population); DFS by BICR: HR 0.727, 95% CI: 0.544 -0.972, p-value 0.031

- *Lowest risk of recurrence (T3 and Fuhrman's Grade 1 or 2)*

  n=215 (35% of population); DFS by BICR: HR 0.869, 95% CI: 0.544, 1.387, p-value 0.555

Two patients could not be classified due to missing Fuhrman's Grade data.

Compared to the UISS score used for stratification and analyses, which include both objective (T stage and Fuhrman's Grade) and subjective (ECOG) prognostic parameters, the new proposed population is defined only according to T stage and Fuhrman's Grade.

3.3. Uncertainties and limitations about favourable effects

Multiple post-hoc trial changes have modified the statistical component of the study design, questioning the integrity of the trial.

The strength of the evidence for the primary endpoint, DFS by BICR, is limited. The observed HR of 0.761 is higher than the pre-specified efficacy HR of 0.69. Of note, there is an imbalance in the rate of censoring in the first portion (i.e. ≤1 year) of the DFS curve by BIRC, with higher rates observed in the sunitinib arm (50 [16.2%] vs. 21 [6.9%] patients). Among the censored patients, those who discontinued/withdrew treatment due to AEs were 16 in the sunitinib arm vs. 4 in the placebo arm.

Most sensitivity analyses do not support the primary analysis. Of major concern is the observation that when all DFS events regardless of new anti-cancer therapy or missed assessment are included the analysis (as per the EMA guidelines), there is no benefit of sunitinib treatment over placebo. Additional sensitivity analyses requested by CHMP, considered closer to the ITT principle (i.e. including further therapy as event and regardless missed assessment, regardless of the start of new anticancer therapy or missed assessment), or more correctly capturing the effect on the prevention of recurrence (i.e. not considering second primary cancers as events and regardless of missed assessment), all showed lower magnitude of benefit of sunitinib over placebo compared to the primary analysis.

For the secondary endpoint DFS by Investigator, statistical significance was not reached (HR 0.811, p= 0.077).

OS data are largely immature (approximately 20% of the total events). At present, no statistically significant difference in OS between arms is apparent (HR 1.014, 95%CI 0.716-1.435). Updated data (23% of the population with an OS event) showed an HR for OS = 0.918, 95%CI: 0.659, 1.279. The MAH is not planning to collect further OS data. Based on the limited OS data available, it is not possible to conclude that adjuvant sunitinib did not adversely affect the efficacy of subsequent follow-up anti-angiogenic therapy given at relapse.

The positive results on the primary endpoint obtained in the S-TRAC are not supported by data from the ASSURE study that failed to demonstrate any advantage in DFS for sunitinib over placebo in the adjuvant RCC setting, both in the ITT population (HR 1.02, 97.5%CI 0.85-1.23, stratified Logrank p = 0.80), as well as in subgroup analyses for pT3-pT4 disease, clear cell histology, or in patients started at full dose (to reflect the S-TRAC study).

3.4. Unfavourable effects

TEAEs were experienced by most of the patients in the sunitinib arm (99.7% vs. 88.5% in the placebo arm), with a large increase in terms of grade 3 and 4 TEAEs, compared to placebo (61.8% vs. 20.1%).

The most common treatment-related TEAEs in the sunitinib arm were diarrhoea (55.9%), PPE syndrome (50.3%), fatigue (36.6%) and hypertension (35.9%). The most common Grade ≥3 treatment-related TEAEs in the sunitinib arm were PPE syndrome (16.0% vs. 0.3% in the placebo arm), Neutropenia (8.5% vs. 0%), Hypertension (7.8% vs. 0.7%) and Thrombocytopenia (6.2% vs. 0%).

The most common sunitinib-related SAEs were thrombocytopenia and hypertension (2.3% each).

All-causality TEAEs belonging to the SOC "cardiac disorder" were experienced by 38 (12.4%) patients in the sunitinib arm vs. 30 (9.9%) patients in the placebo arm, which were G≥3 TEAE in 3.3% vs. 1.6% of patients in sunitinib and placebo arm respectively. A more extended classification of CV events showed a frequency of 19.3% vs 15.5% for sunitinib vs placebo respectively, with left ventricular dysfunction and pulmonary embolism being the most common CV sunitinib-related events. Mean age of patients experiencing CV events was 56 vs 60 years in sunitinib vs placebo arm, with 20.8% vs 13.1% of patients < 65 years experienced a CV AEs in Sutent and placebo arm respectively. A Grade 3 (resolved) unexpected event of myocarditis possibly sunitinib-related was reported.

The incidence of AEs occurred ≥ 12 months after the last dose of study drug was 7.2% in the sunitinib arm vs. 9.9% in placebo arm. *Cardiac disorders* (1.6% vs. 2% in sunitinib vs. placebo arm) and *Neoplasms benign, malignant, and unspecified* (2% vs. 2.3% in sunitinib vs. placebo arm) were the most common SOCs recorded in both arms during the follow-up period after active treatment.

Permanent discontinuations and dose reductions due to treatment-related AEs were much more frequent in the sunitinib arm compared to placebo (25.2% vs. 4.3%, and 34.6% vs. 2.0%, respectively). AEs leading to permanent discontinuation in >1% of patients in the sunitinib arm were PPE syndrome (4.2%), Hypertension (2.0%) and Asthenia (1.3%). In the sunitinib arm, discontinuations due to AE higher in cycle 1 (8.2%) compared to all other cycles (min 1.6%, max 3.3%).

PRO endpoints (EORTC QLQ-C30 and EORTC EQ-5D scores) were statistically significantly worse for sunitinib compared to placebo arm. Diarrhoea and appetite loss reached the pre-specified clinically important difference in points published in literature.

In ASSURE study, starting dose of sunitinib was reduced in about 30% of the patients after having observed a high rate of treatment discontinuation due to adverse events or patient refusal (and then individually titrated based on tolerability). However, a meaningful increase in sunitinib tolerance by reducing starting dose was not seen (discontinuation due to AEs went down from 22.2% to 14.1%).

3.5. Uncertainties and limitations about unfavourable effects

An apparent higher frequency of PPE syndrome compared to the pivotal study of sunitinib in the metastatic RCC was reported. The reason for this observation appeared unknown and there were no baseline factors that could account for this. A relevant statement has been included in the SmPC.

The frequency of thyroid dysfunction, experienced by 63 vs 11 patients in the sunitinib vs. the placebo arm, steadily increased from Cycle 4 through Cycle 9. Data regarding the resolution of thyroid dysfunction after the end of the treatment are not available. Thyroid dysfunction has been also observed in the metastatic setting and described in the SmPC.

3.6. Effects Table

Effects Table for Sutent (sunitinib) for adjuvant treatment of loco-regional RCC at high risk of recurrence following nephrectomy (data cut-off: 7 April 2016) - A6181109 (S-TRAC) study

Effect	Short Description	Unit	Treatment SUTENT (309)	Control PLACEBO (306)	Uncertainties / Strength of evidence
DFS by BICR	Median (95% CI)	years	6.8 (5.8, NR)	5.6 (3.8, 6.6)	Observed HR higher than the pre-specified efficacy HR of 0.69; overlapping of confidence intervals; censoring rules not in line with EMA guidance; not supported by sensitivity analysis closer to ITT principle / independent radiologic assessment
	HR (95% CI)		0.761 (0.594, 0.975) p = 0.030		
DFS by investigator	Median (95% CI)	years	6.5 (4.7, 7.0)	4.5 (3.8, 5.9)	Secondary endpoint; not statistically significant; not fully supportive of the primary endpoint DFS by BICR
	HR (95% CI)		0.811 (0.643, 1.023) p = 0.077		
OS	Median (95% CI)	years	NR	NR	Secondary endpoint; immature data (~20% of the ITT population) Updated OS (cut-off date 31.01.17, ~23% of the ITT population): Median OS NR for either arm. No further OS data will be collected post-approval.
	HR (95% CI) 2-sided p-value		1.014 (0.761, 1.435) p = 0.938		
	Updated 31.01.17		0.918 (0.659, 1.279) p= 0.612		
PROs	Global health status (EORTC QLQ-C30)	ESTD mean (95%CI)	- 4.76 (- 6.82, - 2.71) p<0.0001		Secondary endpoint; difference in all scales of QLQ-C30 were statistically significant worse for sunitinib; diarrhoea and appetite loss reached the pre-specified important difference of ≥10 points
	Diarrhoea (symptom scale)	ESTD mean (95%CI)	12.00 (9.62, 14.38) p<0.0001		
	Appetite loss (symptom scale)	ESTD mean (95%CI)	10.04 (7.88, 12.20) p<0.0001		
Tolerability	drug-related AEs	%	98.4	75.7	Low tolerance to treatment with sunitinib
	drug-related Gr≥3 AE	%	57.2	8.2	
	drug-related SAE	%	13.1	2.3	
	death due to study-treatment toxicity	%	0	0	
	permanent discontinuation due to drug-related AEs	%	25.2	4.3	
	temporary discontinuations due to AE	%	46.4	13.2	
	dose reduction due to AE	%	34.6	2.0	
Drug related AEs	*Diarrhoea*	*%*	*55.9*	*18.1*	*PPE incidence higher than in the metastatic RCC setting; myocarditis G3 unexpected SAE possibly related was reported*
	PPE	%	50.3	10.2	
	PPE Gr≥3	%	16.0	0.3	
	Fatigue	%	36.6	19.7	
	Hypertension	%	35.9	9.5	
	Neutropenia	%	23.5	0.7	
	Thyroid disorder (any AE)	%	20.6	3.6	
	Cardiac disorder (SOC)*	%	12.4	9.9	
	CV events **	%	19.3	15.5	

Notes: p-value are 2 sided log-rank test stratified by UISS groups.
* All-causality TEAEs belonging to the SOC cardiac disorder
** Cardiovascular Adverse Events: MedDRA PTs in the cardiac disorder SOC, high level group terms embolism and thrombosis (including the PT of pulmonary embolism), central nervous system vascular disorders and cardiac and vascular investigations

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoint DFS by BICR reached statistical significance. However, the clinical relevance of the obtained result is considered limited, with an observed HR worse than the pre-specified value. A numerical trend towards higher benefit of sunitinib vs. placebo is seen in higher UISS risk groups, with higher benefit seen for RCC with higher risk of recurrence according to UISS score (T3 high + Other).

The strength of the evidence appears weak due to the limited support given by other analyses. Indeed, the magnitude of the effect on DFS when evaluated by investigator was smaller compared to DFS by BICR and did not reach statistical significance, and the most important among the sensitivity analysis, more in line with the ITT principle according to EMA guidelines, resulted negative. No advantage in OS is seen, although data are immature. In addition, even acknowledging the differences with the S-TRAC study, the ASSURE trial did not demonstrate any advantage of sunitinib in the adjuvant setting, including in the subgroup with higher stage and higher risk. Further, the multiple post-hoc trial changes may have jeopardized the integrity of the trial, adding uncertainties to the estimates.

The pattern of treatment-related AEs reported is consistent with the known safety profile of sunitinib, with no new ADR identified (an unexpected event of myocarditis Grade 3 possibly related was reported). However, the toxicity of sunitinib in the adjuvant setting is relevant, with nearly 60% of the patients experiencing grade ≥ 3 treatment-related AEs and almost one in four patients permanently discontinued sunitinib due to treatment related AEs. An apparently higher frequency of PPE, which was also the most common reason for treatment discontinuation, dose delay and reduction, compared to the metastatic RCC setting, were observed. Results on quality of life endpoints, statistically significant worse for sunitinib compared to placebo, reflects the poor tolerability of sunitinib in the adjuvant setting.

Given the adjuvant setting and the expected long-term patients' survival, the apparent increase of cardiac disorders, also in younger patients, as well as thyroid dysfunction which incidence steadily increased with increased number of cycles, are also of concern. Moreover, based on the available data, it is not possible to exclude that sunitinib treatment in the adjuvant setting is not going to adversely affect the efficacy of subsequent follow-up anti-angiogenic therapy, approved in the metastatic RCC setting, given at relapse.

3.7.2. Balance of benefits and risks

A statistically significant improvement of limited clinical relevance in the primary endpoint DFS by BICR has been observed for sunitinib in the overall adjuvant population of high risk RCC compared to placebo, in the absence of sound support from all other endpoints, sensitivity analyses and data from the trial ASSURE. The unclear magnitude of the observed sunitinib effect and the low strength of the evidence supporting it greatly questions the benefit of sunitinib treatment in the adjuvant setting.

The high rate of dose reductions and discontinuations, the large proportion of patients experiencing grade ≥ 3 treatment-related AEs and the negative impact on PROs clearly indicate a poor tolerability of the sunitinib proposed regimen in the adjuvant setting, which is of significant concern, and in some cases difficult to manage by dose reduction. Doubts are therefore raised on the reproducibility of the beneficial effect observed in the S-TRAC study in the real clinical practice. Moreover, based on the available data, it is not possible to evaluate the impact of adjuvant sunitinib treatment to the efficacy of subsequent follow-up anti-angiogenic therapy, approved in the metastatic RCC setting.

The purpose of adjuvant treatment is to provide long-term benefit, in particular to increase cure rate and OS (Guideline EMA/CHMP/205/95/Rev.5). No evidence has emerged that DFS can be used as a surrogate for OS in patients with localized RCC (Harshman, Cancer 2017). Therefore the clinical relevance of the observed statistically significant DFS effect in the context of adjuvant treatment remains unclear; the KM curves for DFS do not indicate a higher cure rate for the experimental arm over the placebo arm; the sensitivity analyses are not robust and did not reach statistical significance and there is no support from the ASSURE study, nor from the secondary endpoints including OS.

Possible adverse effects of sunitinib on subsequent anti-angiogenic therapy (e.g. due to cross-resistance of TKIs) cannot be excluded due to limited provided data on this subject. Moreover, no further support on this topic will be available as the MAH will stop collecting OS data.

In addition to uncertainties regarding efficacy, it is agreed that the toxicity and poor tolerability of sunitinib in the adjuvant setting remain worrisome. There was a high rate of dose reductions and discontinuations due to AEs in the sunitinib arm. Most permanent discontinuations occurred within the first 3 cycles and there is evidence that DFS may be decreased for patients who discontinued treatment compared to those who completed all 9 treatment cycles. Also, there appears to be an increased risk for severe and potentially life threatening CV events in sunitinib patients, also in younger ones.

PRO data analysis based on post-hoc assigned thresholds for clinically relevant differences does not change the fact that QoL was statistically significant worse in the sunitinib arm compared to the placebo arm.

3.8. Conclusions

The overall B/R of Sutent in the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy is negative.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation not acceptable and therefore does not recommend by a majority the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation rejected		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of Indication to include adjuvant treatment of patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy for Sutent; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated based on the study A6181109 (a randomised double-blind phase 3 study of adjuvant sunitinib vs. placebo in subjects at high risk of recurrent RCC). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the SmPC and Package Leaflet and in addition, to fulfil PAM (FU2

22.5). Furthermore, the PI is brought in line with the latest QRD template version 10. Moreover, updated RMP version 16 has been submitted.

Grounds for refusal

Whereas

- In the pivotal S-TRAC study, the observed DFS improvement (HR 0.761; 95%CI: 0.594, 0.975 with a p-value of 0.030) in the ITT population BICR analysis identified as primary was of borderline statistical significance. The same applies to the subgroup of patients considered at the highest risk (HR 0.727; 95%CI: 0.544, 0.972 with a p-value of 0.0305). In the secondary, investigator analysis, statistical significance was not reached (HR 0.811 (95% CI 0.643, 1.023)). Sensitivity analyses performed, including the use of EU preferred censoring rules, do not show a statistical significant effect on DFS. Further, early censoring occurs in the sunitinib arm to a greater extent than in the placebo arm. The potential for bias to be introduced by the model assumption of non-informative censoring further questions the demonstration of a treatment effect. No impact on OS has been shown. Moreover, the ASSURE study, performed in a population partially overlapping with that of S-TRAC, does not provide support for the efficacy of Sutent in the adjuvant setting.
- Thus efficacy has not been demonstrated.

Therefore, the benefit / risk ratio of sunitinib in the adjuvant treatment of patients at high risk for recurrent RCC following nephrectomy, is negative.

The CHMP has recommended the refusal of the variation to the terms of the marketing authorisation.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Sutent is not similar to Torisel within the meaning of Article 3 of Commission Regulation (EC) No 847/200.

Appendix

1. Divergent positions to CHMP opinion

References

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Appendix 1:

DIVERGENT POSITION DATED 22 February 2018

Sutent EMEA/H/C/000687/II/0065

The undersigned members of the CHMP did not agree with the CHMP's negative opinion recommending the refusal of the variation to the terms of the marketing authorisation.

The reasons for divergent opinion were the following:

- The benefit observed for sunitinib in the ITT population in terms of the primary endpoint DFS by BICR is considered of limited clinical relevance, and is deemed not robust enough to outweigh the concerns raised by the toxicity profile. However, results from subgroup analyses suggested a higher benefit in highest risk patients (T3 high/other), and therefore the MAH had been requested to discuss the B/R in a restricted population, even providing pooled data from S-TRAC and ASSURE trials. In patients at highest risk (defined as T3 and Fuhrman's Grade >2 or T4 or Node Positive with any T) a clinically meaningful benefit is observed in terms of DFS by BICR (HR 0.727; 95%CI: 0.544, 0.972 with a p-value of 0.0305), with a median DFS of 6.0 years (95% CI: 4.1, NR) and 3.9 years (95% CI: 2.5, 5.8) for sunitinib and placebo, respectively. Conversely, no benefit was evident in the complementary lowest risk subgroup, T3 and Fuhrman's Grade 1 or 2 (DFS by BICR: HR 0.869, 95% CI: 0.544, 1.387, p-value 0.555).
- Based on the totality of data, even acknowledging the post-hoc nature of the analysis, the B/R of Sutent in "the adjuvant treatment of adult patients at a high risk of recurrent RCC (defined as T3 and Fuhrman's Grade >2 or T4 or Node Positive with any T) following nephrectomy" is considered positive.

Daniela Melchiorri

Tuomo Lapveteläinen

DIVERGENT POSITION DATED 22 February 2018

Sutent EMEA/H/C/000687/II/0065

The undersigned members of the CHMP did not agree with the CHMP's negative opinion recommending the refusal of the variation to the terms of the marketing authorisation.

The reasons for divergent opinion were the following:

- The study S-TRAC met its primary endpoint, showing a median DFS by BICR of 6.8 years vs. 5.6 years in the sunitinib and placebo arm respectively and HR = 0.761 (95%CI: 0.594, 0.975), p = 0.030. In the restricted population of highest risk of recurrent RCC median DFS was 6.0 years vs 3.9 years and HR= 0.727 (95%CI: 0.544, 0.972 with a p-value of 0.0305). These results are considered clinically meaningful in this population of high risk where there is an unmet medical need.

- Overall, more AEs, SAEs, Grade 3-4 AEs and discontinuations due to AEs were observed in the sunitinib arm. No Grade 5 AEs were observed. The most common AEs (>25% of patients) are diarrhoea, PPE syndrome, hypertension, fatigue, nausea, dysgeusia, mucosal inflammation, dyspepsia and stomatitis. All occurring more frequently in the sunitinib arm. The safety profile of sunitinib is well-known and well-characterised with clinically manageable adverse reactions. The discontinuation rate due to AEs is higher in the active arm compared to placebo (28.1% vs. 5.9%), but those patients, who do not discontinue, have a benefit from sunitinib.

- The totality of evidence taken together shows clinically meaningful efficacy with a well-known and clinically manageable toxicity and therefore a positive benefit – risk of Sutent in "the adjuvant treatment of adult patients at a high risk of recurrent RCC following nephrectomy."

Sinan B.Sarac

Agnes Gyurasics

Mila Vlaskovska