Statistical Analysis Plan

(SAP)

OPTIMISE

Real-world clinical patterns of care and outcomes among patients in Africa & Middle East (AfME) with metastatic renal cell carcinoma (mRCC) receiving Sunitinib as first line therapy

Version: 2.0

Modified by: PPD

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Contents

1. List of Acronyms

AE	Adverse Event
AEM	Adverse Event Monitoring
AfME	Africa Middle East
ANOVA	Analysis of Variance approach
BP	Blood Pressure
BSC	Best Supportive Care
CRF	Case Report Form
CR	Complete Response
CSR	Case Study Report
CTCAE	Common terminology criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ESMO	European Society for Medical Oncology
FKSI-19	Functional assessment of cancer therapy Kidney Symptom Index
HRQOL	Health Related Quality Of Life
ICF	Informed Consent Form
MAR	Missing At Random
MMRM	Mixed Models Repeated Measures
mRCC	metastatic Renal Cell Cancer
MSKCC	Memorial Sloan–Kettering Cancer Center
NIS	Non-interventional Study
NCCN	National Comprehensive Cancer Network
ORR	Objective response Rate
OS	Overall Survival
PFS	Progression Free Survival
PR	Partial Response
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SAE	Serious Adverse Events
SU	Sunitinib
TTF	Time to Treatment Failure
TTR	Time to Response
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

2. Introduction

This present document is the SAP for the OPTIMISE study. Some parts are adopted freely from the protocol and integrated into the different sections of the plan.

2.1. Background

- RCC are usually low-grade, early stage tumors with a significant proportion presents with late stage or metastatic disease.
- The mainstays of mRCC treatment consisted of systemic cytokine therapies such as high-dose systemic interleukin-2 (IL-2) or interferon-alpha (IFN- α).
- Recently, several targeted therapies have become available for first- and second- line treatment of mRCC
- The treatment options include ;
  - Multi-targeted receptor tyrosine kinase inhibitors (TKIs) Sunitinib, sorafenib, pazopanib ,Cabozantinib and axitinib
  - VEGF ligand binding monoclonal antibody such as bevacizumab given in combination with IFN-α; and mTOR kinase inhibitors temsirolimus and everolimus, in addition to anti PD-1 monoclonal antibody Nivolumab.
- The current international guidelines recommend a number of these new treatment options for first- and second-line treatment.
- Namely, SU has become the standard of care in many countries as it has the most robust data in the first-line treatment of mRCC.
- Nevertheless, to date there is a gap in regards to the real world setting of care and treatment outcome for mRCC, especially Africa region and the Middle East (AFME).
- Consequently, the current study aim is to describe patterns of treatment and outcomes across multiple lines of treatment in the mRCC setting, among newly diagnosed patients treated in AFME.

2.2. Study Design

- **Global design**

- OPTIMISE is an international prospective, non-interventional, non-controlled, observational multicenter study.
- Patients would be enrolled from several AfME countries including Algeria, Morocco, Tunisia, Egypt, UAE, Qatar and South Africa.
- Investigators will be specialists in charge of adv/mRCC where sites involved will be representative of their respective countries in terms of practice
- Participating physicians will not be influenced in their decision making and routine practice in any way.

- **Populations**

- Patients will be enrolled when newly diagnosed and when the treatment with SU is chosen as 1st line

- Patients enrolled at SU initiation, will be followed-up whatever the post 2nd line SU- different sequence treatment is (AXI, other drugs, no further active treatment OR supportive care).

- The possible 1st and 2nd line sequences of treatment under investigation (i.e. patient pools) will be as follows:

– SU-AXI
– SU- other second line treatment (sorafenib, pazopanib, everolimus, temsirolimus, other)
– SU- not further active treatment (supportive care)

- The population of interest has the below inclusion and exclusion criteria ;

Inclusion criteria:

– Adult patients (males and females) 18 years of age and over.
– Patients being treated with SU as 1st line treatment according to the approved therapeutic indication.
– Histologically confirmed diagnosis of adv/mRCC (clear cell RCC as well as non-clear cell RCC) with measurable disease according to RECIST 1.1
– Evidence of a personally signed and dated informed consent document

Exclusion criteria:

– Patients being treated with cytokines or any other treatment other than SU
– Patients presenting with a known hypersensitivity to SU or its metabolites will not be included in the study per the label.

- **Data sources**

- Data will be collected in routine clinical practice and from medical records

- A case report form (eCRF) will be used for data collection which should be signed by the investigator.

- An investigator performs an assessment of new or ongoing adverse events, relative to a patient's baseline history, at each study visit.

- Generally, the identification of new or ongoing adverse events is determined till the last scheduled visit. CTCAE version 4.0 will be used for the grading of AEs in the eCRF.

Observation period

- The inclusion period of eligible patients is planned for 12 months, with minimum of 1 year follow-up period.
- Patients will be followed-up from their enrollment to the end of the study follow-up period.
- For each subject, after treatment, there would be two follow-up visits (Visit 6-7) in one year, one visit every 6 months (month 18 and 24).

2.3. Study Objectives

- Primary Objective:
  - To assess the impact of SU treatment on Progression Free Survival (PFS) and on Time to Treatment Failure (TTF) for patients with adv/ mRCC.

- Secondary Objectives:
  - To assess the Objective Response Rate (ORR) for adv/ mRCC patients receiving SU as 1st line treatment.
  - To describe the usage of different doses of SU in these patients in terms of: dosing change, dosing schedules and the average dose received during the SU period treatment
  - To assess the impact of the 2nd line sequence SU- different treatment on combined PFS and TTF for patients with adv/mRCC and according to the second line post SU treatment (TK1,mTOR)
  - To describe the safety of 2nd line SU-different sequence treatment and the tolerability of patients receiving it.
  - To measure Quality of Life (QoL) of the patients
  - The following treatment outcomes will also be assessed:
    - Treatment patterns (dose/ duration) for SU
    - Patterns of toxicity exhibited by patients

3. Interim and Final Analysis

- A final report will address the study objectives through detailed analysis of the efficacy and safety endpoints as advised by the protocol.
- There will be no interim analysis for this study.

4. Hypothesis and Decision Rules

- Descriptive and hypothesis testing will be applied for presenting and analysis data
- For all comparisons, the significance threshold will be set at the commonly used 5% level. The type I error will not be adjusted for multiplicity
- Summary tables will contain footnotes in the body of the title that reference any data listings or tables associated with the table or figure (e.g. Reference: Listing 16.X.XX).
- All means and medians will be formatted to one more decimal place than the measured value. Confidence intervals and standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- The number and percentage of responses will be presented in the form XX (XX %) where the percentage as whole numbers will be in parentheses.
- All p-values will be presented with at least 3 decimal places ensuring meaningful representation.

- All summary tables will include the total number of subjects in the population that is being analysed
- Analysis population and subgroups

4.1. Analysis sets

- **Setting population or full analysis set**

  The setting population or full analysis set refers to all eligible patients enrolled in the study, whatever the therapeutic strategy used during the observation period

- **Target population** :

  The target population are patients above 18 suffering from advanced mRCC and residing in AFME to whom the results of the study will be extrapolated

- **Efficacy population**:

  Include full analysis set who received a dose of SU and continued at least 6 month follow up period

- **Safety population**:

  Include full analysis set who exhibited any adverse event after the first dose of SU.

4.2. Subgroups

4.2.1. Subgroups to meet primary and secondary objectives

- Compare efficacy parameters (PFS, OS) for the combined 1st line SU- 2nd line sequences according to the second line post SU :
  - SU in 1st line-Axitinib TKI in 2nd line
  - SU in 1st line- other TKI in 2nd line (sorafenib, pazopanib)
  - SU in 1st line/mTOR in 2nd line (temsirolmus, everolimus)

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5. Endpoints and Covariates

5.1. Efficacy endpoints

The efficacy analyses will be fulfilled based on the below predefined endpoints that meets primary and secondary objectives:

- Progression Free Survival (PFS) for patients on SU
- The PFS will be defined as the time from when the patient receives the first dose of SU to the time of progression or death due to any cause, whichever occurs first.
- The date of the first dose of treatment will be the date of start of therapy completed by the physician during the initiation visit.
- The time of progression will be the date of the first tumor assessment where the progression is notified as response to therapy, over the SU treatment
- The time of death will be the date of the death occurring over the SU treatment (death reported in the SU follow-up visit form or the study discontinuation form).
- Patients who remain progression free and alive at the end of treatment will be evaluated until death or disease progression or the start of a new anticancer therapy up to the end of the study.
- Patients who discontinued the study for any reason, including unacceptable toxicity during the treatment period, who remained alive and without disease progression, will be censored at the last disease assessment that verified lack of disease progression.

Note:

- In patients on SU treatment: the date of progression from a tumor assessment can be completed every 4 weeks;
- In other patients off SU treatment: the date of progression can be completed in the long term follow-up if discontinuation because of progression, every 6 months.

- **Combined PFS**

- Time from when the patient receives the first dose of SU in 1st line, until progression or death due to any cause with the 2nd- line treatment considered in the analysis, whichever occurs first.
- The date of the first dose of SU in 1st line will be the date of SU start of therapy completed by the physician during the SU initiation visit for patients enrolled at SU initiation.
- The time of progression or death will be defined as notified for PFS.
- Similar censoring guidelines to PFS will be used for Combined PFS.
- The time of progression for 2nd-line treatment will be the date of progression reported in the long term follow-up when the treatment is discontinued because of progression.
- The time of death will be the date of the death occurring over the 2nd-line treatment (death reported in the long term follow-up or the study discontinuation form).

- **Time to Treatment Failure (TTF) for SU**

- The TTF will be defined as the time from when the patient receives the first dose of treatment to the date of SU discontinuation
- If no SU discontinuation was reported during the follow-up visits, patients will be censored to the last follow-up visit. This rule concerns both patients who were followed-up along the study and patients lost to follow-up or who discontinued the study voluntarily.
- The date of the first dose of 2nd line will be defined as notified for TTF.
- In case of death when the patient was still treated with SU, date of death will be considered as date of discontinuation.

- **Combined TTF**

- Time elapsed since the patient receives the first dose with SU in 1st line to the time of 2nd line treatment discontinuation
- Similar censoring guidelines to TTF will be used for Combined TTF.
- The date of discontinuation of 2nd-line treatment will be defined as notified for TTF.

- **Overall Survival (OS)**

- The OS will be defined as the time from date of first SU dose to the date of death of any cause.
- For patients not experiencing the event, their survival times will be censored at the last date they are known to be alive.
- The OS at 24 months will be analyzed with the proportion of patients who remain alive at 24 months.

- **Objective Response Rate (ORR)**

- The objective response rate will be the percentage of patients with a complete response (CR) or a partial response (PR) according to RECIST 1.1 criteria as best response, over the SU treatment period.

- Patients who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of ORR. A patient, who initially meets the criteria for a PR and then subsequently becomes a CR, will be assigned a best response of CR.

- **Clinical Benefit Rate (CBR)**

  The Clinical Benefit Rate (CBR) will be the proportion of patients with a CR, PR or Stable Disease according to RECIST 1.1 criteria as best response, over the SU treatment period.

5.2. SU treatment endpoints

The real life usage of SU treatment will be analyzed with following endpoints:

- **Treatment schedules**

- SU dose at initiation;
  - Proportion of patients with the recommended starting dose of SU(5 mg BID);
  - Proportion of patients with other starting doses ;
  - Proportion of patients with moderate chronic liver failure, with 2 mg BID as starting dose;
- Dosing schedules;
  - Average/median total daily dose (mg) received over the SU treatment period;
  - Dose intensity of SU: defined as the sum of SU daily doses divided by the duration of SU treatment in days (delay between the first SU dose and the last dose, including temporary interruption).
  - Proportion of patients who were dose reduced (according SmPC, outside SmPC)
  - Proportion of patients who were dose increased (according to protocol, outside protocol)
- SU interruption and discontinuation
  - Proportion of patients with temporary interruption during the SU treatment period and reasons (AEs, radiotherapy, surgery, other);
  - Median duration of the first interruption in days and of all interruptions together;
  - Proportion of patients with SU discontinuation and reasons (progression, intolerability or death).

- **<u>SU treatment duration</u>**

  - Median duration of treatment i.e. the time in months between the SU initiation and the SU discontinuation date or the last follow-up date with SU treatment.

5.3. Safety and tolerability endpoints

The analysis of safety will be fulfilled based on the below endpoints:

- **Incidence of adverse events (AEs)**
  - Incidence of AEs defined as proportion of patients experiencing at least one AE of any grades by Body system (System Organ Class (SOC) MedDRA) ;
  - Incidence of most common AEs of any grade (occurring in more than 10% of patients in either group) by preferred term (PT) (MedDRA);
  - The following type of AEs will be described whatever the number and proportion of patients concerned: Diarrhea, hypertension, fatigue, asthenia, hand foot syndrome, nausea, stomatitis, neutropenia, lymphopenia and increased lipase.
  - Incidence of serious AEs (grade > 2);

- Incidence of other AEs (grade ≤ 2);
- Incidence of all AE per grade.
- AEs will be analyzed separately for AEs related to SU as solicited and unsolicited AE.

- **Discontinuation due to toxicity**
  - Proportion of patients who discontinued the treatment of interest, because of AEs;
  - Treatment duration until discontinuation for AEs;

- **Deaths**
  - Proportion of patients who died due to any cause, over the treatment period (including the 28 days after the treatment discontinuation) and along the study;
  - Cause of death (tumor-related, other cause).

5.4. Quality of life endpoints

The analyses of the quality of life will be fulfilled based on the following endpoints, assessed every month over the SU treatment:

- **FKSI-19 score**

- The FKSI-19 score will result of completed answers from FKSI-19 questionnaire version 4 (Functional Assessment of Cancer Therapy Kidney Symptom Index-19) presented in appendix 11.1
- This scale assesses symptoms of importance to patients with advanced kidney cancer, with 19 items:
  - 12-item subscale about Disease Related Symptoms - Physical (DRS-P);
  - 1-item subscale about Disease Related Symptoms - Emotional (DRS-E);
  - 3-item subscale about Treatment Side Effects (TSE);
  - 3-item subscale about Function/ Well-Being (FWB).
- This score will be assessed for each subscale and overall, as sum of item scores. Scoring guidelines are presented in appendix 11.2.

- **Change in scores from baseline**

- This endpoint will be defined for the score mentioned above, as the difference between QoL score at baseline and at each follow up visit during SU treatment

5.5. Covariates

- In case of multivariate analyses, baseline characteristics will possibly be used as covariates.
- The final covariates will be selected according to the selection strategy of variables defined in the part 7.6.
- Possible, but not exclusive, baseline covariates related to SU initiation will be limited because of a retrospective part of the data collection, with:
  - Age and sex;
  - ECOG (0, 1, 2, 3, 4), Karnofsky performance status
  - MSKCC risk factors (Favorable, Intermediate, Poor)

- Medical history of hypertension (Yes, No)
- Delay from diagnosis (< 1 year from diagnosis to first metastasis detection/ ≥ 1 year)
- Nephrectomy (Yes, No)
- Number of metastatic sites

- The covariates identified previously will be also explored and act as baseline for second line treatment initiation. In this case, other covariates will be:
  - The response to SU treatment in 1st line;
  - Duration of SU treatment, PFS;
  - Previous treatments for primary tumor (surgery, radiotherapy, other);
  - Additional anti-tumor treatments;

6. Handling missing values

- The majority of data will be collected with a website (except for FKSI-19 questionnaires).
- In this website, the input of certain data will be obligatory, limiting the number of missing values, particularly for endpoints.
- Regarding the descriptive analyses of each variable, it will be based on the available data ("observed-case analysis"), considering missing data as non-informative.
- The number of missing data will be documented for each analysis.
- The analysis of the primary endpoint is a survival analysis which is known to efficiently handle missing data: All patients are included in the analysis and missing data are called right-censored data.
- In case of absence of 20% data and over, for a main parameter such as ORR rate, the Hot-deck imputation method could be used. With this method, the missing value is replaced by the observed value of a patient with similar characteristics X_1, X_2… X_k. If it does not exist such similar patient, the missing value will be amputated
- A sensitivity analysis will be conducted by the imputation of extreme values. In the one hand, analysis in the most unfavorable situation (i.e. missing data considered as failure) and in the other hand, analysis in the most favorable situation, i.e. missing data considered as success (e.g. for ORR, success is to be responder).
- For continuous endpoints (QoL endpoints), a mixed model for repeated measures (MMRM) will be used to analyze longitudinal data. Missing data will not be imputed. However, this analysis will be performed on all patients having a baseline value and at least one post-baseline value. The model will be valid under the assumption of data missing at random (MAR).

7. Statistical Methodology

- Statistical analysis will be performed with SPSS software (version 20 or higher).
- For descriptive and hypothesis testing purposes, the normal distribution assumption will be tested based on the overall shape of the histogram and on the result of the Shapiro-Wilk test if needed

7.1. Descriptive methods

- Descriptive analysis of qualitative and ordinal variables will comprise the count and the frequency of each category.

- Descriptive analysis of quantitative variables will be presented by the mean and standard deviation (SD) for the data that follows a Gaussian distribution and the median and range otherwise.
- The 95% confidence intervals will be presented for main endpoints. The 'exact' Clopper-Pearson confidence interval will be provided to assess 2-sided 95% confidence interval for main binomial proportions (e.g. ORR rate).
- The number of missing values will be reported in the results table for each variable.

7.2. Comparative methods

- For two groups of normal distribution, the means of quantitative variables will be compared using the Student's t- test if the assumption of homogeneity of variance is verified (the Satterthwaite method will be used if the variances are unequal).
- If more than two groups have to be compared, analysis of variance (ANOVA) will be performed for quantitative variables if normality in each group and homoscedasticity are met. Homogeneity of variances will be tested by Levene's test.
- If the assumptions are not verified, alternative parametric testing such as Mann Whitney Wilcoxon and Kruskal-Wallis tests will be applied.
- The association between two qualitative variables will be assessed with the Pearson's Chi-square test. When the number of values will be less than 5, groups of categories will be proposed or the Fisher's exact test will be performed.
- For all tests performed, the significance level will be 5%.

7.3. Logistic regression model

- A logistic regression model will be used in case of multivariate model to analyze prognostic factors for a dichotomous variable (for example: ORR).
- The Hosmer-Lemeshow test will be used to test the adequacy of the logistic regression model.

7.4. Survival analysis methods

- The survival functions for PFS, TTF, TSF, and OS will be estimated with the Kaplan-Meier method. The survival function S (t) is the probability that the event (treatment discontinuation, death or progression) does not occur before a specified time.
- This method will be applied to derive, survival curves, median event time and a 95% confidence interval for the median survival time (time at which half the analyzed patients have presented the event).
- Survival curves will give an idea of whether or not the groups are proportional (i.e. the survival functions are approximately parallel).
- For OS, the share of patients alive at 24 months will also be measured.
- The log-rank test of equality across strata will be used to compare survival curves for categorical variables (sub-groups of interest).
- For continuous variables, a univariate Cox proportional hazard regression will be used.
- For analyses of prognostic factors of survival time, multivariate Cox proportional hazard regressions will be performed.

7.5. Analysis of longitudinal data

- Mixed models with Repeated Measures (MMRM) will be used to analyze longitudinal data (QoL over the SU treatment).
- These models will allow to meet questions as "Are there significant changes in the endpoint from baseline?" or "Do any groups differ at any time point regarding the endpoint?"
- Linear models will be used for dependent variables continuous, assumed to be normally distributed. The missing observations will be considered to be missing at random.
- MMRM will include the fixed, categorical effect of time, as well as the continuous, fixed covariates of the baseline value and baseline-by-time interaction. A significant baseline-by-time interaction would indicate that baseline levels predict change in dependent variable of interest over time.

7.6. Strategy of selection of variables in multivariate models

- The strategy of selection of variables in multivariate models will be as follows:

– Identifying baseline patient characteristics significantly associated with survival time in univariate analyses with a p-value of 0.25.

– All these variables will be included in the model and a backward elimination will be realized (Starting with a complex model and removing terms sequentially until a final model with only explicative variables significantly associated with the survival time, adjusted each other).

8. Statistical Analysis

This chapter presents the planned statistical analyses to meet the study objectives.

8.1. Efficacy analyses

8.1.1. Survival analyses

- **<u>Role:</u>**
  - To meet primary and secondary objectives
  - To assess the impact of SU as a first line therapy on progression free survival (PFS) and on time to treatment failure (TTF) for patients with adv/mRCC in real life setting;
  - To assess the impact of the SU–other sequence on combined PFS and TTF for patients with adv/mRCC.
  - To assess the Overall Survival (OS) (OS median and 24-month OS) for adv/mRCC patients receiving SU in first line followed by other sequence in 2nd line;
  - To assess the time to strategy failure (TSF) for adv/mRCC patients receiving the SU–other sequence;
  - To assess PFS and OS for the combined 1st line SU – 2nd line sequences according to the second line post SU (TKI, mTOR) treatment; (specific objective – "SU – TKI/mTOR" patients)
- **<u>Population:</u>**
  - "SU – other sequence" patients
  - "SU – TKI / mTOR" patients
- **<u>Endpoints:</u>**
  - Progression Free Survival (PFS)
  - Combined PFS
  - Time to Treatment Failure (TTF)
  - Combined TTF
  - Time to Strategy Failure (TSF)

- Overall Survival (median OS and 24-month OS rate)

- **Subgroups:**

- Type of 2nd line treatment post SU: "SU – TKI / mTOR" patients **(SUT-TKI and SUT-mTOR)** (only combined PFS and OS endpoints)

- **Statistical methods:** Survival analysis methods.

- **Method for handling missing values:** see guideline in chapter 7.

8.1.2. Objective response rate

- **Role:**

- To assess the Objective Response Rate (ORR) for adv/mRCC patients receiving 2nd line post SU"

- **Population:**

Study population "SU – other sequence" patients

- **Endpoints:**

- Clinical Benefit Rate (CBR)
- Objective Response Rate (ORR)

- **Statistical methods:**

Descriptive analyses

- **Method for handling missing values:**

Hot-deck imputation method and imputation by extreme values

8.2. Safety and tolerability analyses

- **Role:**

To describe safety and tolerability of patients receiving the SU–other sequence".

- **Population:**

Study population "SU – other sequence" patients

- **Endpoints:**

- Incidence of adverse events (AEs)
- Discontinuation
- Deaths

- **Statistical methods:**

Descriptive methods

- **Method for handling missing values:**

None-Observed-case analysis

8.3. Quality of life analysis

- **Role:**
  - To measure quality of life (QoL) in patients receiving SU treatment".
  - This analysis will provide an insight of the quality of life and the trends over the SU treatment, particularly in terms of physical (severity of symptoms) and mental/emotional conditions
- **Population:**
  - "SU" patients who have completed the baseline QoL questionnaire (at SU initiation) and at least one follow-up QoL questionnaire (expected every months).
- **Endpoints:**
  - FKSI-19 score
  - Change in scores from SU initiation
- **Statistical methods:**
  - Descriptive methods (at each month of SU treatment)
  - Mixed models with repeated measures (modeling change in scores)
- **Covariates used:**
  - Characteristics at SU initiation
  - Covariates of the baseline value and baseline-by-time interaction

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9. Dummy tables and figures

9.1. Cross tabulation of patients' baseline demographic and clinical characteristics according to first line SU treatment and different 2nd line sequence

Patient	SU 1st line	SU-other sequence	SU-axitanib	SU-Bsc	SU-TOR	SU-mTKI
Count(n) %						
Age (Mean ±SD)						
Gender(n,%) Female-Male						
Ethnicity(n,%) Caucausin-Middle Eastern-etc						
Disease						
Metastatic sites(n,%)						
Clear cell(n,%)						
Nephrectomy(n,%)						
MSKCC risk(n,%) Favorable,intermediate,poor						

9.2. Initial dose and schedule of SU in the first line treatment

Initial dose SU	N(%)
50mg 37.5mg 25mg Other	
Schedule	**N(%)**
4 weeks on, two weeks off Continous	

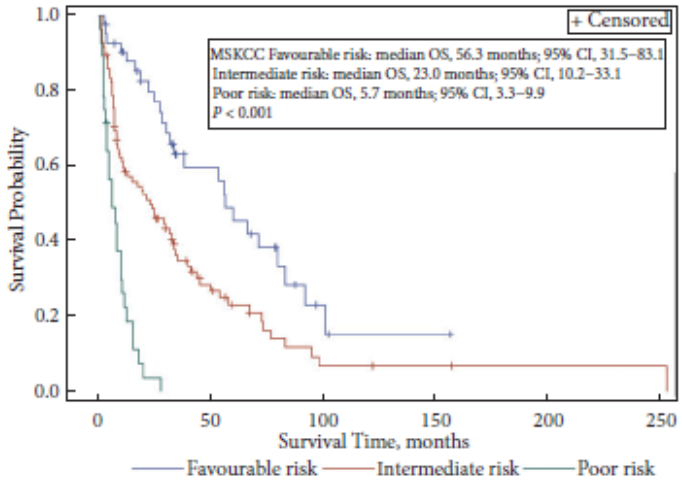
Other	

9.3. Cross tabulation of efficacy end points(PFS,OS,ORR,TTF) for both first line SU treatment as well as for the SU- second line therapy

Efficacy endpoints (months±SD)	**Overall**	**First line SU**	**Second line therapy**			
			SU-Bsc	**SU-AXI**	**SU/TOR**	**SU/TKI**
PFS						
OS						
ORR						
TTF						

9.4. OS based on MSKCC risk stratification

Fig. 1 OS stratified by MSKCC risk classification.



9.5. Cross tabulation of AE experienced throughout the study according to disease grade

	Sunitinib (N = 85)	
N (%) with adverse event	**All grades**	**Grades 3/4**
Any adverse event	83 (97.6)	23 (27.1)
Fatigue/Asthenia	69 (81.2)	8 (9.4)
Mucositis/Stomatitis	50 (58.8)	2 (2.4)
Hand-foot syndrome	29 (34.1)	2 (2.4)
Diarrhea	26 (30.6)	0 (0.0)
Hypertension	35 (41.2)	3 (3.5)
Decreased taste sensation	36 (42.4)	0 (0.0)
Abdominal pain	19 (22.4)	3 (3.5)
Nausea	25 (29.4)	3 (3.5)
Lack of appetite	12 (14.1)	0 (0.0)
Pain	13 (15.3)	0 (0.0)
Anorexia	15 (17.6)	5 (5.9)
Vomiting	15 (17.6)	5 (5.9)
Hemorrhage	12 (14.1)	0 (0.0)
Constipation	6 (7.1)	0 (0.0)
Edema	12 (14.1)	1 (1.2)
Dermatitis	6 (7.1)	0 (0.0)
Anemia	5 (5.9)	1 (1.2)
Erythema	7 (8.2)	1 (1.2)
Hypothyroidism	6 (7.1)	1 (1.2)
Skin rash	2 (2.4)	0 (0.0)
Dyspnea	4 (4.7)	0 (0.0)
Hemorrhoids	5 (5.9)	0 (0.0)
Alopecia	1 (1.2)	0 (0.0)

10. Appendices

10.1. Appendix 1: FKSI-19 questionnaire

NCCN-FACT FKSI-19

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
	BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	L2	I have been coughing	0	1	2	3	4
	HI12	I feel weak all over	0	1	2	3	4
	RCC 2	I have had blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
TSE	GP2	I have nausea	0	1	2	3	4
	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
FWB	GF1	I am able to work (include work at home)	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

Source: www.facit.org

10.2. Appendix 2: FKSI-19 (version 4) – Scoring guidelines

Instructions:
1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the symptom index score.
4. As with all FACIT questionnaires, a high score is good. Therefore, a score of "0" is a severely symptomatic patient and the highest possible score is an asymptomatic patient.

Note: If >50% of items were completed, the FKSI scores were calculated as the sum of the item responses divided by the number of items completed multiplied by the total number of items in the scale (eg, 19 in the case of the FKSI-19).

If fewer than 50% of the items were completed, the scores were considered missing.

Scale	Item Code	Reverse item		Item response	Item Score
FKSI-19	GP1	4	-	_____	=_____
Total	GP4	4	-	_____	=_____
Score range: 0-76	C2	4	-	_____	=_____
	HI7	4	-	_____	=_____
	B1	4	-	_____	=_____
	BRM3	4	-	_____	=_____
	BP1	4	-	_____	=_____
	L2	4	-	_____	=_____
	HI12	4	-	_____	=_____
	RCC2	4	-	_____	=_____
	C6	0	+	_____	=_____
	GF5	0	+	_____	=_____
	GE6	4	-	_____	=_____
	GP2	4	-	_____	=_____
	C5	4	-	_____	=_____
	GP5	4	-	_____	=_____
	GF1	0	+	_____	=_____
	GF3	0	+	_____	=_____

	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 19: _____

Divide by number of items answered: _____=FKSI-19 score

Subscale	Item Code	Reverse item		Item response	Item Score
FKSI-DRS-P	GP1	4	-	_____	=_____
(Disease Related	GP4	4	-	_____	=_____
Symptoms-Physical)	C2	4	-	_____	=_____
Score range: 0-48	HI7	4	-	_____	=_____
	B1	4	-	_____	=_____
	BRM3	4	-	_____	=_____
	BP1	4	-	_____	=_____
	L2	4	-	_____	=_____
	HI12	4	-	_____	=_____
	RCC2	4	-	_____	=_____
	C6	0	+	_____	=_____
	GF5	0	+	_____	=_____

Sum individual item scores: _____

Multiply by12: _____

Divide by number of items answered: _____=FKSI-DRS-P score

Subscale	Item Code	Reverse item		Item response	Item Score
FKSI-DRS-E					
(Disease Related					
Symptoms-Emotional)	GE6	4	-	_____	
Score range: 0-4	=_____=**FKSI-DRS-E score**				

Subscale	Item Code	Reverse item		Item response	Item Score
FKSI-TSE	GP2	4	-	_____	=_____
(Treatment	C5	4	-	_____	=_____
Side Effects)	GP5	4	-	_____	=_____

Score range: 0-12

Sum individual item scores: _____

Multiply by 3: _____

Divide by number of items answered: _____**=FKSI-TSE score**

Subscale	Item Code	Reverse item		Item response	Item Score
FKSI-F/WB	GF1	0	+	_____	=_____
(Function/	GF3	0	+	_____	=_____
Well-Being)	GF7	0	+	_____	=_____

Score range: 0-12

Sum individual item scores: _____

Multiply by 3: _____

Divide by number of items answered: _____**=FKSI-F/WB score**

Appendix 3: List of covariate and outcomes in the study

Variable	Role	Operational definition
Age	Covariate	Defined as the date of birth of the participant
Gender	Covariate	Defined as the male or female sex
Ethnicity	Covariate	Defined as race of Middle Eastern, Indian, Caucasian or African descendant
ECOG	Covariate	The ECOG Scale of Performance Status describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.)
Number of metastatic sites	Covariate	Total number of site where metastasis is detected
Nephrectomy	Covariate	Surgical removal of the kidney
MSKCC risk	Covariate	The MSKCC risk system stratifies patients with mRCC into poor-, intermediate- and favorable-risk categories based on the number of adverse clinical and laboratory parameters present
Hypertension	Covariate	Presence of high systolic blood pressure>13mmHg
Previous medical treatment	Covariate	Presence of medical treatment related to the disease prior to SU initiation
PFS	Outcome	The PFS will be defined as the time from when the patient receives the first dose of SU to the time of progression or death due to any cause, whichever occurs first
OS	Outcome	OS defined as the time from date of first SU dose to the date of death of any cause.
ORR	Outcome	The objective response rate is the percentage of patients with a complete response (CR) or a partial response (PR) according to RECIST 1.1 criteria as best response, over the SU treatment period.
TTF	Outcome	TTF is defined as the time from when the patient receives the first dose of treatment to the date of SU discontinuation
Combined PFS	Outcome	The time from when the patients receives the first dose of SU as first line, until progression or death due to any cause while on the 2nd line treatment, whichever occurs first during the 2nd line sequence treatment.
Combined TTF	Outcome	The time from when the patient receives the first dose with SU as first line, to the time of 2nd line sequence discontinuation