EORTC
European Organisation for Research and Treatment of Cancer
AISBL International Non-Profit Association under Belgian law IVZW

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Intergroup Study (EORTC 30073)

Randomized Phase III trial comparing immediate versus deferred nephrectomy in patients with synchronous metastatic renal cell carcinoma.

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Coordinating Group: EORTC Genito-Urinary Cancers Group

Collaborative Groups: NCRI Renal Clinical Studies Group - Wales Cancer Trials Unit

Canadian Uro-Oncology Group (CUOG)

Study Coordinators: Axel Bex

John B.A.G. Haanen

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Warning:

This is an Intergroup study coordinated by the EORTC. The present protocol is written according to the EORTC template and is fully applicable to all **collaborative groups** (with the exception of EORTC specific chapters or other collaborative group(s) specific appendix and unless otherwise specified).

The chapters 18 to 20 and the PIS/IC are fully applicable to **EORTC investigators** only.

Corresponding items and contact addresses for non EORTC investigators are provided in their **Group specific appendix** that supersedes the contents of chapters 18-20 (unless otherwise specified).

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Protocol summary

Title of the Study	Randomized Phase III trial comparing immediate versus deferred nephrectomy in patients with synchronous metastatic renal cell carcinoma.
Objective(s)	The principal objective of the trial is to investigate whether the sequence of the nephrectomy in patients who receive sunitinib has an effect on patient outcome.
Methodology	This is a randomized multicenter phase III comparison trial. Eligible patients will be randomized between immediate versus deferred nephrectomy.
Number of patients Number planed (Statistical design) Number analyzed	458 patients will be enrolled in this trial over 36 months. The final analysis will be performed after observation of 380 progressions or deaths and a minimum follow-up of 1.5 years for all patients.
Diagnosis and main criteria for inclusion	♦ Histologically confirmed metastatic Renal Cell Cancer of clear-cell subtype with a resectable asymptomatic in situ primary. ♦ Metastatic RCC (mRCC): distant metastases are not completely resectable at the time of surgery or during an additional intervention. Multiple distant lesions at one site mean that the patient is not a candidate for a complete resection. ♦ Resectable tumor: primary tumor must be resectable and resectability should not be doubtful at entry. Patients with bulky locoregional lymph node metastases larger than the primary tumor can be included if resectability of the lymph nodes is surgically feasible. ♦ Histology "clear-cell" subtype: If the diagnosis is not established patients need to undergo a transcutaneous tru-cut needle biopsy of the primary tumor (Refer to chapter 10.). ♦ Asymptomatic primary: is defined as the absence of symptoms which can be exclusively assigned to the primary tumor such as flank pain and/or gross hematuria necessitating blood transfusion. As para-neoplastic symptoms cannot be assigned to the primary tumor alone in metastatic disease, they are not included in this definition. Note: the following patients are not eligible: ♦ Patients for whom complete surgical remission can be achieved by removing metastatic sites at nephrectomy or during an additional intervention. ♦ Patients with symptomatic primary necessitating nephrectomy. ♦ Patients with previous partial or total nephrectomy ♦ Patients with unresectable bulky locoregional lymph node metastases

	larger than the primary tumor. ♦ Patients with only bone metastases. ♦ In addition, patients having more than 3 of the following surgical risk factors will not be eligible: ♦ serum albumin CTCAE v4.0 grade 2 or worse ♦ serum LDH > 1.5 x ULN ♦ liver metastases ♦ symptoms at presentation due to mestastases ♦ retroperitoneal lymph node involvement ♦ supra-diaphragmatic lymph node involvement ♦ clinical stage T3 or T4 ♦ Patients who will receive Sunitinib (Sutent®) as background therapy ♦ Measurable disease, both primary and metastatic, according to RECIST 1.1 criteria. ♦ Prior therapies: ♦ Prior systemic therapy for metastatic RCC is not allowed ♦ Prior local radiotherapy for bone lesions is allowed ♦ Concomitant medications ♦ Investigational or systemic therapy for metastatic RCC must not be used during the period of protocol treatment. ♦ No systemic corticosteroid and/ or other immunosuppressive systemic therapies ♦ Age ≥ 18 years ♦ Life expectancy > 3 months ♦ WHO performance status 0 or 1 (Appendix B) ♦ Adequate bone marrow function (Leucocytes > 3.0 x 10^9/l, platelets > 100 x 10^9/l, hemoglobin > 6.0 mmol/l or > 10.0 g/dL.) ♦ Prothrombin time (PT) or international normalized ratio (INR) ≤ 1.2 x upper limit of normal (ULN) ♦ Partial thromboplastin time (PTT) ≤ 1.2 x ULN ♦ Adequate hepatic function (bilirubin ≤ 1.5 x ULN, SGPT/ALT ≤ 2.5 x ULN or ≤ 5 x ULN if liver lesions)

	♦ Serum calcium < 10.0 mg/dL ♦ Adequate renal function: calculated or measured clearance creatinine > 30 ml/min (see Appendix C) ♦ Clinically normal cardiac function based on the institutional lower limit of normal LVEF assessed by MUGA or ECHO and normal 12 lead ECG. No serious cardiac illness (myocardial infarction and/or (un)treatable angina pectoris not responding to treatment) within the past 12 months. ♦ No uncontrolled high blood pressure (BP) defined as BP ≥ 150/100 mm Hg despite optimal medical therapy ♦ No clinical signs of CNS involvement ♦ No current pulmonary disease ♦ No patients with active or uncontrolled infections or with serious illnesses, malabsorption syndrome or medical conditions, including patients with a history of chronic alcohol abuse, hepatitis, HIV and/or cirrhosis. ♦ No history, within the past five years, of malignancies other than renal cell carcinoma (except: basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, resected incidental prostate cancer staged pT2 with Gleason Score ≤ 6 and postoperative PSA < 0.5 ng/ml). Patients with any history of malignancies who are disease-free for more than 5 years are eligible. ♦ Women must be post-menopausal with a total cessation of menses of >1 year, or if of childbearing potential must not be pregnant (negative serum pregnancy test at entry) or lactating; and must agree to use effective contraceptive methods (with a documented failure rate < 1% e.g.; vasectomized partner sterile prior to trial entry and sole sexual partner or double-barrier contraception) from 2 weeks before to enrollment. The duration of the contraception will depend on the treatment that patient will receive. ♦ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be assessed with the patient before registration in the trial. ♦ Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations. ♦ Participation in the translational research program (refer to chapter 10) Patients will be eligible for the translational research program if they are eligible for the clinical trial and have given their written informed consent to participate in this program. If patient refuses to take part in the translational research project, patient remains eligible for the clinical trial.

Treatment Test product, dose and mode of administration	♦ Arm A: Immediate nephrectomy (Nephrectomy → Sunitinib) ♦ Arm B: Deferred nephrectomy (Sunitinib → Nephrectomy → Sunitinib)
Duration of treatment	Patients will remain on treatment until progression of the disease, occurrence of second malignancy, unacceptable toxicity based on investigator's judgment, or patient decision.
Reference therapy, dose and mode of administration	Not applicable
Criteria for evaluation	
Efficacy	Primary end-point: overall progression free survival (PFS). Progression will be defined according to the "RECIST" 1.1 criteria. Secondary end-points include ♦ Overall survival ♦ Morbidity ♦ Overall response to treatment in the deferred nephrectomy arm including the proportion of patients who become unresectable ♦ Effect of nephrectomy on early progression in both arms.
Safety	The safety profile will be assessed according to CTCAE version 4.0
Statistical methods	The median progression free survival on the immediate nephrectomy arm is assumed to be 9 months. In order to detect an increase of 3 months in the median progression free survival to 12 months (Hazard Ratio (HR) = 0.75, Median Ratio (MR) = 1.333) on the deferred nephrectomy arm based on a two sided logrank test at error rates alpha = 0.05 and beta = 0.20, a total of 380 events (progressions or deaths) is required. Assuming a patient entry rate of 150 patients per year, a further follow up period of 1.5 years after the last patient has been entered and allowing for 5% loss to follow up, a total of 458 patients entered over 3 years is required.
Translational research	A translational research program has been designed to identify potential response criteria based on histopathology and molecular research on tumor tissue. Biological material: Tumor tissue will be collected at baseline (deferred surgery arm: tru-cut needle biopsy) and at time of surgery (both arms). Tumor tissue samples will include paraffin embedded tumor block (mandatory) and fresh frozen tissue (optional depending on the local facilities) In both arms, blood samples will be collected at baseline, week 18 and 6 months post randomization. The collection of these samples is optional depending on the local facilities.

Trial organization

- This trial is an Intergroup Trial, jointly conducted by several national/international cancer clinical research groups in different countries of European Union and third countries.
- The EORTC will be the Sponsor in all European countries
  In summary:

Country	Recruiting group(s)	Sponsor
Canada	CUOG	CUOG
United Kingdom	NCRI Renal Clinical Studies Group / WCTU	EORTC
Other countries	EORTC	EORTC

- The EORTC is the coordinating group in this trial and will therefore centrally manage trial design and activation, attribution of duties and responsibilities between participating research groups, data collection and quality control of data, statistical analysis and publication.
- Each participating group / Sponsor locally manages the notification/submission of all necessary documents to the Competent Authorities and/or Ethics Committees and gets the confirmation of the review by IRB/IEC following the applicable national law.
- This protocol is to be followed by all participating groups. Chapters 1 to 17 are fully applicable to all groups. Chapters 18-20 are specific to the EORTC participants. All particularities of participation of each individual group are included is the Group Specific Appendixes annexed at the end of the protocol.
- The participation in this trial is only possible through one of the participating clinical cancer research groups. For contacts and addresses please refer to the Group Specific Appendix of the group of your membership or of your national group (should you have any difficulty in identifying such a group, please contact the EORTC Headquarters).
- For EORTC members all patients will be accounted for the membership independently from the group they participate through (see EORTC Policy 10).

This trial is an academic trial with a restricted educational grant support from the industry.

1 Background and introduction

1.1 Background

In the United States, renal cell carcinoma (RCC) accounted for 31,000 new cancer diagnoses and 11, 900 cancer related deaths in the year 2000. Renal cell cancer is the 7th most frequent cancer and accounts for 2-3 % of all new cancer cases worldwide. The majority of renal cell carcinomas consist of the clear cell type (80-85 %) followed by papillary (11 %) and chromophobe (4 %) subtypes.

For patients with RCC and disease confined to the kidney the only effective therapy with a high probability of cure is surgical removal of the primary tumor. Unfortunately, up to 30 % of all patients with renal cell carcinoma have metastatic disease at the time of diagnosis with the primary tumor in situ. Surgery alone is ineffective for the majority of patients with primary metastatic renal cell carcinoma and multiple non-resectable metastases, apart from the few patients who present with solitary metastases in whom surgical complete resection of the lesion in conjunction with nephrectomy may lead to prolonged survival and possibly cure in exceptional cases. Randomized controlled trials (Southwest Oncology Group (SWOG) S8949 and European Organization for Research and Treatment of Cancer (EORTC) 30947) have shown a small but statistically significant survival benefit of cytoreductive nephrectomy (CN) before immunotherapy with interferon alfa in the treatment of metastatic renal cell carcinoma (mRCC) versus interferon alpha alone (Ref. 1, Ref. 2). A combined analysis of both trials demonstrated a survival advantage for CN followed by interferon with a median survival of 13.6 months versus 7.8 months for interferon therapy alone (p=0.002) (Ref. 3). This has led to a multimodal concept of CN followed by immunotherapy in which CN became standard before administration of interferon or interleukin-2.

The mechanism behind the observed survival benefit following CN remained elusive. Both arms had a similar response to interferon which suggested that CN did not improve the effectiveness of immunotherapy, as was often believed prior to performing the trials. Possible explanations may be abrogation of immunosuppressive activity of the primary tumor by CN (Ref. 4, Ref. 5) as well as elimination of increased serum levels of vascular endothelial growth factor (VEGF) produced by the primary tumor (Ref. 6). Removal of a bulky primary tumor may decrease levels of circulating VEGF and counteract disease progression. In this respect, it remains intriguing, that the only reported curative treatment in mRCC in highly selected patients is a combination of high-dose IL-2 and surgery. Cure in these patients would not have been achieved without a nephrectomy, because IL-2 does not lead to complete responses in the primary tumor.

From the information gained from the two controlled trials, it became evident that CN should not be used indiscriminately. Rather, patients should be selected for surgery along certain prognostic risk factors that have all shown to influence survival. Performance score has been established as one of the most important factors and the Memorial Sloan Kettering Cancer Center (MSKCC) risk score, that incorporates 5 easily obtainable factors for assessment of response to therapy and survival is now widely used to select patients for therapy, including novel agents and CN (Ref. 7, Ref. 8). Since all patients are metastatic, CN alone cannot achieve cure and is generally viewed as part of a multimodality management that comprises systemic therapy. Therefore, patients undergoing CN should be candidates for systemic therapy. It had been demonstrated that cytokines are most effective for metastatic RCC of clear-cell subtype (with 70-80 % the most prominent subtype) but little effect on other subtypes. Other criteria to select for CN include significant tumor burden of the primary tumor, absence of significant comorbidity, absence of central nervous system metastasis and low risk of surgical morbidity (Ref. 9). In a very recent evaluation of the long-term results from the SWOG S8949 trial, performance status and early progressive disease remained strong predictors of overall survival (OS) (Ref. 10). Interestingly, retrospective studies and population-based assessments revealed that CN and metastasectomy significantly improved survival in patients with

mRCC when compared to those assigned to the same risk group who did not undergo surgery (Ref. 11, Ref. 12).

Oral tyrosine kinase inhibitors targeting VEGF and platelet-derived growth factor (PDGF) receptors have altered the systemic treatment of mRCC (Ref. 13). Compared with cytokine therapy sunitinib at a dose of 50 mg daily for 4 weeks on and 2 weeks off induces a high partial response (PR) rate of up to 40% at metastatic sites (Ref. 14, Ref. 15). Sunitinib is standard of treatment for clear cell subtype, which comprise 70-80 % of all mRCC, but not necessarily standard for other cell types. Sunitinib was evaluated in a phase III trial of 750 patients with largely good- or intermediate-prognosis metastatic clear cell RCC who had not received prior systemic treatment (Ref. 16). The objective response rate was significantly increased with sunitinib (39 versus 8 percent with IFNa). Median PFS was significantly prolonged (11 versus 5 months, hazard ratio [HR] 0.54). This benefit included patients at good, intermediate, and poor risk (PFS 14.5 versus 7.9, 10.6 versus 3.8, and 3.7 versus 1.2 months, respectively). Based on this pivotal trial, sunitinib was registered in the US and Europe in 2007 for the treatment of metastatic RCC and became the approved first-line therapy for all patients including patients with primary tumors in situ. Due to its pharmacodynamics and safety profile sunitinib can be administered in close timing with surgery and is therefore the first-line drug of choice for a combination with surgery.

The final analysis of the trial showed that OS was prolonged with sunitinib (median 26.4 versus 21.8 months, hazard ratio [HR] 0.82, 95% CI 0.67-1.00, p=0.051) (Ref. 17). The same regimen of sunitinib leads to responses in the primary tumor at a rate previously unknown for cytokine treatment (Ref. 18), where the primary tumor rarely responded.

The improvements in the treatment of mRCC and the observed responses seen in the primary tumor have led some researchers to question the need for CN and its benefit in the metastatic setting. There are no results from randomized controlled trials that demonstrate that CN is beneficial before targeted therapy, or in other terms, demonstrate that sunitinib alone is as effective. Currently, a common approach is to manage synchronous mRCC in analogy to the results of the SWOG S8949 trial that is immediate CN followed by systemic therapy. Many centers perform immediate nephrectomy followed by the approved first-line drug sunitinib as a ‘surrogate standard’ in the absence of high-level evidence.

The arguments for immediate CN are based on the recognition, that the benefit of sunitinib has largely been demonstrated in a nephrectomized population. The majority of patients enrolled in the pivotal phase III trial had undergone a nephrectomy (Ref. 16). Therefore, the prolonged median PFS and OS apply largely to patients with synchronous or metachronous metastatic disease without the primary in situ. There are limited and biased data from a subgroup analysis comparing progression free survival (PFS) of patients who did and did not undergo initial CN. In the mentioned phase III trial of sunitinib versus IFNa 90 % in the sunitinib arm underwent CN (n=339), while 10 % (n=36) did not. PFS was 11 months (range 11-13) for the CN plus sunitinib group versus 6 months (range 4-11) for the sunitinib only group (p=0.0889) (Ref. 17). In addition, a potential advantage of CN may be the debulking of tumor burden which may eliminate immunosuppression and VEGF production. This advantage may be universal and independent from a combination with systemic therapy. Long-term results from the SWOG trial of CN followed by interferon versus interferon alone revealed, that after a median follow up of 9 years patients randomized to nephrectomy continued to have improved OS. A benefit of CN was seen across all prespecified patient subsets. There was no evidence of an interaction of performance status, measurable disease or lung metastases with nephrectomy (each p>0.30) (Ref. 10). How this theoretical and clinical advantage for CN applies to targeted therapies is currently unresolved.

While there are data suggesting that CN improves survival in patients treated with sunitinib, a randomized controlled trial of CN followed by sunitinib versus sunitinib alone would be required for evidence. However, there are some potential drawbacks for a trial in which one arm of patients will not undergo a nephrectomy.

1. One point of concern is the inevitable progression in metastatic patients despite being treated with more potent therapies. In the cytokine era patients failing therapy for mRCC and with the primary in situ were more likely to die of distant metastatic disease rather than local progression with a median OS of 10 months. However, this may be different for targeted therapies. An initially resectable primary tumor may progress to unresectability or develop symptoms. In the sunitinib trial patients with an intermediate risk profile had a PFS of 11 months but a median OS of 26 months (Ref. 17), resulting in a median time interval from progression to death of 15 months. PD of the primary tumor under sunitinib does occur. In a recent retrospective study of 19 patients who received neoadjuvant sunitinib with advanced RCC and the primary in situ, 9 (47 %) had PD in the primary tumor (Ref. 19).This may indicate that patients randomized to the sunitinib-only arm are at risk of progression of the primary in situ.

2. In addition, there are reports that patients treated with a combination of sunitinib and surgery were rendered disease free with complete remissions for months in which they were taken off treatment which may improve quality of life (Ref. 20, Ref. 21). Though in contrast to IL-2 cure has not yet been reported with tyrosine kinase inhibitors, it cannot be excluded that some patients may develop long term remissions with 'drug holidays', which would not be achieved without a CN.

3. As has been mentioned, the benefits of sunitinib have been demonstrated in phase III trials in a largely nephrectomized population. There is a certain risk, that if patients are randomized indiscriminately to sunitinib only, they may be denied the treatment that has yielded a median PFS of 11 months and an OS of 26 months, which was the combination of CN and sunitinib.

In summary, there is evidence that mRCC patients with a good performance, good and intermediate MSKCC risk, low risk of surgery and a clear cell subtype receiving sunitinib as approved systemic treatment may benefit from CN. However, despite these selection criteria, individual prediction of a CN benefit remains elusive. Rather than investigating indiscriminately among this group whether or not CN is beneficial, studies should be designed to identify those individuals in whom CN alters the natural history of mRCC. Identification would require understanding of new clinical and molecular predictors. Therefore, there is a rationale for deferred nephrectomy following targeted therapy and investigation of pretreated primary tumor tissue (Ref. 22). In addition, deferred nephrectomy may improve the clinical outcome. Recently cases have been described in which the surgical management in advanced RCC was altered by pretreating the tumor in situ with targeted agents (Ref. 23, Ref. 24, Ref. 25, Ref. 26). Experience from phase II trials investigating deferred surgery after targeted therapy in renal and other tumors suggest that sunitinib discontinued at least 24 hours prior to surgery is safe (Ref. 27, Ref. 28). The effect of downsizing the primary tumor is most prominent in the first two to three months (Ref. 18) suggesting that two to three presurgical cycles of sunitinib may be sufficient. In renal and other cancers, a few days of treatment with tyrosine kinase inhibitors have been shown in patients and animal models to induce a maximal inhibition of cell proliferation and induction of apoptosis (Ref. 29).

Several potential clinical benefits of deferred CN can be identified:

1. Downsizing the primary tumor could facilitate resectability, reduce the amount of normal tissue that needs to be removed and decrease operative risk (Ref. 30).

2. Depending on the presurgical tumor reduction patients may have access to minimally invasive surgical procedures which may reduce surgical morbidity.

3. Presurgical sunitinib may result in a reduction of cancer-related morbidity prior to surgery.

4. Presurgical inhibition of proliferation and induction of apoptosis may counteract the potential risk of disease progression during the recovery period following CN.

5. CN carries the potential risk of surgery-related morbidity which may exclude patients postoperatively from receiving systemic therapy at all. Those having been treated for a period of time before deferred

nephrectomy may have a benefit if they cannot continue postoperatively. Points 1-5 may have an impact on the clinical outcome in patients with mRCC that may translate into a prolongation of PFS or OS.

6. In addition, some patients with immediate nephrectomy will suffer from rapid disease progression and may have been exposed to a needless intervention. This is supported by an analysis of the long-term results of the SWOG trial randomizing CN followed by interferon versus interferon alone. Early progressive disease was a strong predictor of OS (Ref. 10). Rather than observing PD after CN, absence of PD after presurgical therapy may be used to select patients for deferred CN. An approach with deferred nephrectomy provides an opportunity for observation and patients with rapidly progressing metastases may be excluded from a surgical intervention (Ref. 31, Ref. 32).

Furthermore, a presurgical approach has implications for translational research:

Access to tumor tissues in the majority of the enrolled patients, both pretreated and untreated, may lead to the discovery of biomarkers that can be linked to evidence of cellular and clinical activity.

Reliable imaging criteria have yet to be developed to assess the biological response in the tumor. Preliminary data suggest that changes on CT and MRI scans may correspond to a biological response in tumor tissue (Ref. 33) while the lesion does not qualify for a response according to the anatomical RECIST criteria (Ref. 34, Ref. 35, Ref. 36). Due to the past study designs no histology is available to correlate these observations to tumor tissue changes.

1.2 Conclusion

Currently, sunitinib is the only approved first-line treatment for patients with metastatic RCC, including those with a primary tumor in situ, which, due to its safety profile, can be used right up to or soon after surgery. The sunitinib related improvements in the treatment of mRCC and the observed responses seen in primary tumors challenges the need for CN and its benefit in the metastatic setting. Despite the lack of randomized controlled trials, there is sufficient evidence to support that a subgroup of mRCC patients benefits from CN in combination with the approved first-line therapy. Rather than investigating indiscriminately whether or not CN is beneficial, those individuals in whom CN alters the natural history of mRCC should be identified. Identification would require understanding of new clinical and molecular predictors. This has led to a rationale for changing the sequence of CN and sunitinib to deferred nephrectomy and investigation of pretreated primary tumor tissue in vitro .In addition, several potential clinical benefits can be identified for deferred nephrectomy following targeted therapy that may improve the clinical and surgical outcome. This randomized trial proposes to answer the following questions: does deferred nephrectomy following sunitinib result in improved surgical and clinical outcome for patients with mRCC when compared to immediate nephrectomy followed by sunitinib?

2 Objectives of the trial

2.1 Objectives

The principal objective of the trial is to investigate whether deferring nephrectomy in patients who receive sunitinib has an effect on disease control by optimizing the sequence of surgery for metastatic RCC.

2.2 End points

The primary end-point is overall progression free survival. Progression will be defined according to the "RECIST" 1.1 criteria (Ref. 37).

Secondary end-points include

- Overall survival
- Morbidity
- Overall response to treatment in the deferred nephrectomy arm including the proportion of patients who become unresectable
- Effect of nephrectomy on early progression in both arms

2.3 Translational research

A translational research program has been designed to identify potential response criteria based on histopathology and molecular research on tumor tissue. Tumor tissue will be collected at baseline (deferred surgery arm) and at time of surgery (both arms) to assess possible differences in gene- expression. In addition, blood samples will be drawn to evaluate the potential impact of serum proteins on the clinical outcome of patients.

3 Patient selection criteria

- Histologically confirmed metastatic Renal Cell Cancer of clear-cell subtype with a resectable asymptomatic in situ primary.
- Metastatic RCC (mRCC): distant metastases are not completely resectable at the time of surgery or during an additional intervention. Multiple distant lesions at one site mean that the patient is not a candidate for a complete resection.
- Resectable tumor: primary tumor must be resectable and resectability should not be doubtful at entry. Patients with bulky locoregional lymph node metastases larger than the primary tumor can be included if resectability of the lymph nodes is surgically feasible.
- Histology “clear-cell” subtype: If the diagnosis is not established patients need to undergo a transcutaneous tru-cut needle biopsy of the primary tumor (Refer to chapter 10.).
- Asymptomatic primary: is defined as the absence of symptoms which can be exclusively assigned to the primary tumor such as flank pain and/or gross hematuria necessitating blood transfusion. As para-neoplastic symptoms cannot be assigned to the primary tumor alone in metastatic disease, they are not included in this definition.

Note: the following patients are not eligible:

- Patients for whom complete surgical remission can be achieved by removing metastatic sites at nephrectomy or during an additional intervention.
- Patients with symptomatic primary necessitating nephrectomy.
- Patients with previous partial or total nephrectomy.
- Patients with unresectable bulky locoregional lymph node metastases larger than the primary tumor.

- Patients with only bone metastases.

- In addition, patients having more than 3 of the following surgical risk factors will not be eligible:
  - serum albumin CTCAE v4.0 grade 2 or worse
  - serum LDH > 1.5 x ULN
  - liver metastases
  - symptoms at presentation due to mestastases
  - retroperitoneal lymph node involvement
  - supra-diaphragmatic lymph node involvement
  - clinical stage T3 or T4
- Patients who will receive Sunitinib (Sutent®) as background therapy
- Measurable disease, both primary and metastatic, according to RECIST 1.1 criteria.
- Prior therapies:
  - Prior systemic therapy for metastatic RCC is not allowed
  - Prior local radiotherapy for bone lesions is allowed
- Concomitant medications
  - Investigational or systemic therapy for metastatic RCC must not be used during the period of protocol treatment.
  - No systemic corticosteroid and/ or other immunosuppressive systemic therapies
- Age ≥ 18 years
- Life expectancy > 3 months
- WHO performance status 0 or 1 (Appendix B)
- Adequate bone marrow function (Leucocytes > 3.0 x 10^9/l, platelets > 100 x 10^9/l, hemoglobin > 6.0 mmol/l or > 10.0 g/dL.)
- Prothrombin time (PT) or international normalized ratio (INR) ≤ 1.2 x upper limit of normal (ULN)
- Partial thromboplastin time (PTT) ≤ 1.2 x ULN
- Adequate hepatic function (bilirubin ≤ 1.5 x ULN, SGPT/ALT ≤ 2.5 x ULN or ≤ 5 x ULN if liver lesions)
- Serum calcium < 10.0 mg/dL
- Adequate renal function: calculated or measured clearance creatinine > 30 ml/min (see Appendix C)
- Clinically normal cardiac function based on the institutional lower limit of normal LVEF assessed by MUGA or ECHO and normal 12 lead ECG. No serious cardiac illness (myocardial infarction and/or (un)treatable angina pectoris not responding to treatment) within the past 12 months.
- No uncontrolled high blood pressure (BP) defined as BP ≥ 150/100 mm Hg despite optimal medical therapy
- No clinical signs of CNS involvement
- No current pulmonary disease

- No patients with active or uncontrolled infections or with serious illnesses, malabsorption syndrome or medical conditions, including patients with a history of chronic alcohol abuse, hepatitis, HIV and/or cirrhosis.
- No history, within the past five years, of malignancies other than renal cell carcinoma (except: basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, resected incidental prostate cancer staged pT2 with Gleason Score ≤ 6 and postoperative PSA < 0.5 ng/ml). Patients with any history of malignancies who are disease-free for more than 5 years are eligible.
- Women must be post-menopausal with a total cessation of menses of >1 year, or if of childbearing potential must not be pregnant (negative serum pregnancy test at entry) or lactating; and must agree to use effective contraceptive methods (with a documented failure rate < 1% e.g.; vasectomized partner sterile prior to trial entry and sole sexual partner or double-barrier contraception) from 2 weeks before to enrollment. The duration of the contraception will depend on the treatment that patient will receive.
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be assessed with the patient before registration in the trial.
- Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.
- Participation in the translational research program (refer to chapter 10)

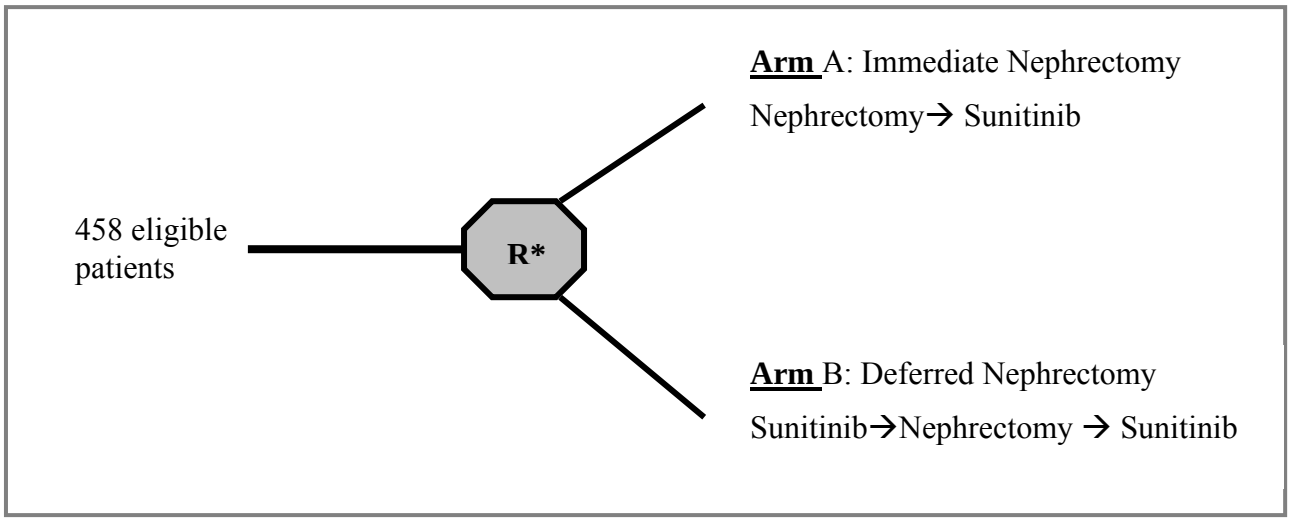
Patients will be eligible for the translational research program if they are eligible for the clinical trial and have given their written informed consent to participate in this program. If patient refuses to take part in the translational research project, patient remains eligible for the clinical trial.

4 Trial design

4.1 General design

This is a randomized multicenter phase III comparison trial

Patients will be randomized at the EORTC Headquarters prior to the start of treatment, and after verification of all eligibility criteria. Patients will be randomized to immediate vs deferred nephrectomy.



5 Therapeutic regimen

A “treatment period” or “cycle of therapy” is defined as a 6 week interval.

5.1 Standard therapy

In the context of this trial, the prescription of sunitinib malate is considered as the standard treatment.

Sunitinib malate 50 mg will be self-administered orally, once daily without regard to meals according to the standard "schedule 4/2": 4 consecutive weeks of treatment followed by 2-weeks off to comprise a complete cycle of 6 weeks.

5.2 Nephrectomy

Cytoreductive nephrectomy (CN) will be performed either immediately followed by sunitinib or deferred to the day after the last dose of sunitinib. Experience from presurgical phase II trials in a variety of tumors demonstrated that discontinuing inhibiting agents at least 24 hours prior to surgery does not interfere with wound healing (Ref 27). CN in metastatic patients follows a different aim than standard radical nephrectomy (RN) for non metastatic patients performed with curative intent.

Therefore the following guidelines are given:

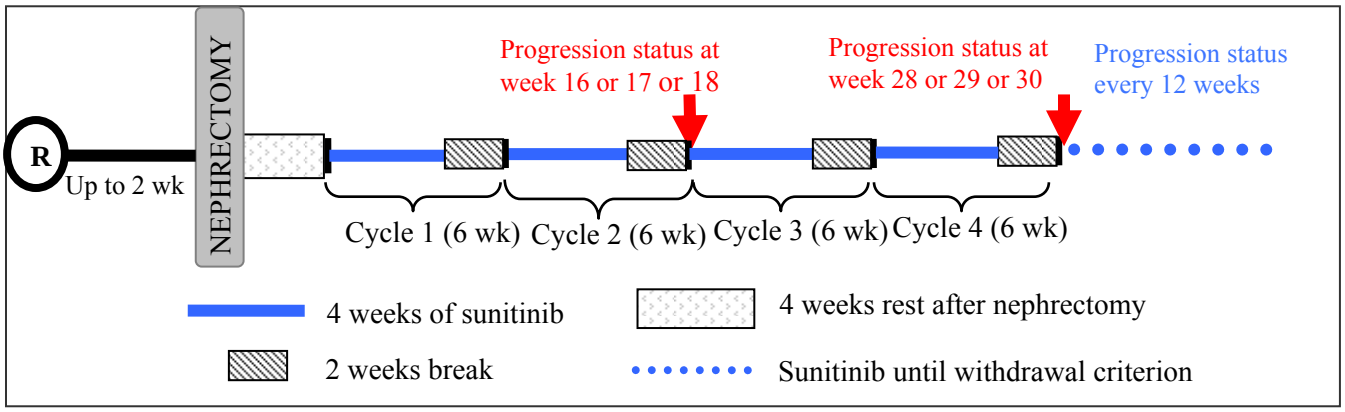
- The aim of nephrectomy is maximal surgical cytoreduction through removal of the entire primary tumor bearing kidney with perinephric fat.
- Adjacent tumor burden such as concomitant clinically evident loco-regional lymph node metastases or adjacent intra-abdominal lesions that can be technically resected together with the removal of the primary tumor, must be resected at the time of nephrectomy to achieve maximal surgical cytoreduction. Removal of these adjacent lesions will be documented on a surgery form.
- The surgical approach is left at the discretion of the urologic surgeon.
- Depending on the size of the primary tumor, adjacent resectable retroperitoneal or intraabdominal metastases and the surgical skills of the team, CN can either be performed as an open or laparoscopic transperitoneal or retroperitoneal nephrectomy.
- If reduction in tumor size in the deferred arm may allow for cytoreductive partial nephrectomy, it may be performed if desired and indicated, as this has been shown to have no influence on survival and cancer control in metastatic RCC (Ref 39).
- Due to the inclusion of patients with metastasis that cannot be resected by surgery alone, a loco-regional lymph node dissection is not necessary in case of clinically node negative disease.
- The same applies for adrenalectomy. A standard adrenalectomy is not necessary and should be avoided, unless the patient has a clinically evident adrenal metastasis.

Data on the chosen approach, extent and morbidity of the surgical intervention will be collected on a surgery form.

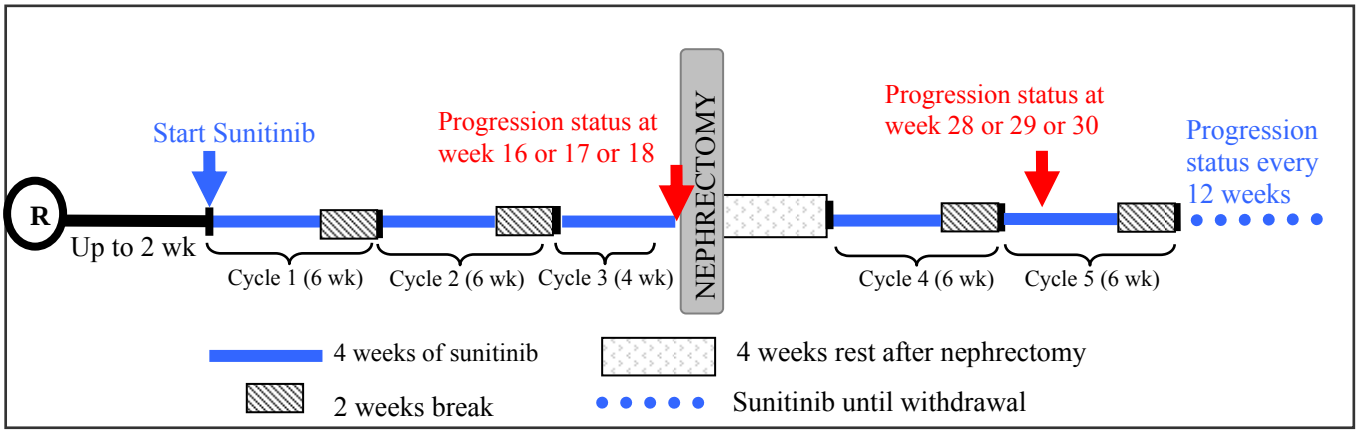
5.3 Treatment schedule

In the 2 study arms, "Time 0" corresponds to the date of randomization and not to the start of the treatment.

5.3.1 Arm A Immediate Nephrectomy



5.3.2 Arm B Deferred Nephrectomy



5.3.2.1 Thromboembolic events

Patients with limited tumor thrombus can be included in the trial if they fulfill the definition of resectability. However, due to some reports on thromboembolic complications during treatment with sunitinib, we advise to treat these patients with a dose of low-molecular weight heparin according to the requirements for the treatment of deep venous thrombosis (DVT).

5.3.2.2 Interruption sunitinib malate for surgery

At cycle 3 (approximately at the end of week 4) sunitinib will be stopped the day before nephrectomy

5.3.2.3 Criteria for nephrectomy

- Non systemic progressive disease (RECIST 1.1 criteria). In case of systemic disease progression, it will not be recommended to perform nephrectomy but the choice of further treatment is left at the discretion of each investigator. Refer to chapter 5.4.2.2.1.
- Recovery from toxicity due to sunitinib specifically interfering with surgery. Refer to chapters 5.4.2.2 and 7.4.3.3.
- Patients must not have more than 3 surgical risk factors. Refer to chapter 3.

5.4 Treatment schedule modifications

5.4.1 Pre-surgical period

Dose and schedule modifications of sunitinib will follow the standard recommendations of the drug and the decision will be based on the investigator's judgment.

5.4.2 Nephrectomy

5.4.2.1 Immediate nephrectomy arm

A delay in the planned surgery date exceeding 48 hours should be recorded on the surgical case report form.

Given the primary endpoint, if the interval from baseline disease assessment to surgery date exceeds 6 weeks, re-staging of the disease should be performed again.

Eligible patients should have resectable asymptomatic primary tumors on imaging Therefore, at the time of the surgery, inability to remove the primary tumor will be recorded on the surgical case report form.

5.4.2.2 Deferred nephrectomy arm

A delay in the planned surgery date exceeding 48 hours interval should be recorded on the on the surgical case report form.

The delay will be discriminated between treatment-related toxicity or factors unrelated to treatment.

If during the course of cycle 3, a patient has to interrupt sunitinib due to a side effect, the disease assessment must be performed after recovery as close as possible to surgery.

In case of severe hematuria necessitating intervention during the three pre-surgical courses, sunitinib must be stopped temporarily.

Severe hematuria is defined as bleeding from the primary tumor into the genitourinary tract necessitating

a) repeated transfusion of packed cells within a week,

b) hospital admission due to repeated ureteral colic caused by passing blood clots or

c) hospital admission due to blood clots in the bladder necessitating bladder irrigation or

a combination of a)-c).

It is at the discretion of the local investigator to perform either an embolization of the renal artery or feeding blood vessel or an emergency nephrectomy.

In case of embolization of the renal artery, the patient can resume sunitinib treatment provided the hematuria is controlled. The patient will undergo deferred nephrectomy in the absence of progressive disease as scheduled and will remain eligible for the evaluation of primary and secondary endpoints with the exception of translational research. Due to the embolization the tissue will not be suited for research.

In case of an early emergency nephrectomy in the deferred nephrectomy arm, the patient will be excluded from evaluation of the primary endpoint but will be followed for final analysis of secondary endpoints and outcome. The tumor tissue will be suited for translational research provided the patient had a presurgical exposure to sunitinib of 4 weeks.

In case of an overdose of sunitinib, surgery should be delayed by 3 days according to the half life of the active metabolite.

Eligible patients should have resectable asymptomatic primary tumors. Therefore, inability to remove the primary tumor at surgery will be recorded on the surgical case report as well as any change of surgical approach due to either an increase or decrease in primary tumor volume.

5.4.2.2.1 Progressive patients in the deferred nephrectomy arm

Given the primary endpoint, a disease assessment (RECIST 1.1 criteria) has to be performed before surgery in order to detect an early progression. This assessment will concern the primary tumor and the metastatic lesions. In case of progression (RECIST 1.1 criteria, chapter 7), the patient will have reached the criterion for the primary endpoint in this trial. Nevertheless, follow up must be provided until death.

However, the decision to perform CN or not is left at the discretion of the individual center. If the decision is taken not to perform surgery, either because of rapid disease progression at metastatic sites or due to progression of the primary tumor to irresectability, we strongly advise to perform a tru-cut biopsy in those patients not amenable for surgery. It will be of great importance to investigate tissue from progressive patients and associate the findings with prognosis.

5.4.3 Post nephrectomy period

In both arms, postoperative sunitinib will be continued after a 4 week rest period until a withdrawal criterion occurs. (Ref. chapter 5.5)

5.4.3.1 Sunitinib Malate

Dose and schedule modifications of sunitinib after surgery will follow the standard recommendations of the drug and the decision will be based on the investigator's judgment. Due to side effects following surgery, the investigator may decide to (re)start sunitinib at a lower dose level. This decision will be adequately documented in the patient chart and recorded on the case report forms (CRFs).

5.4.3.2 Immediate nephrectomy arm

In case of a delay exceeding the 4 week recovery period after CN, the following applies:

If adverse events after surgery (7.4.3) delay the schedule of sunitinib in the immediate nephrectomy arm the delay will be adequately documented in the patient chart and recorded on the CRFs. The decision to delay sunitinib treatment due to side effects of surgery is based on the investigator's judgement. If the delay is longer than the 4 week recovery period the patient will not be eligible for evaluation of the primary endpoint, but will be followed for evaluation of secondary endpoints. A delay longer than the recovery period will result in less than 2 cycles exposure to sunitinib before progression will be determined. This period may be too short to evaluate progression safely.

5.4.3.3 Deferred nephrectomy arm

In case of a delay exceeding the 4 week recovery period after CN, the following applies:

If adverse events after surgery (7.4.3) delay the schedule of sunitinib in the deferred nephrectomy arm the delay will be adequately documented in the patient chart and recorded on the CRFs. The decision to delay sunitinib treatment due to side effects of surgery is based on the investigator's judgement. If the delay is longer than the 4 week recovery period the patient will not be eligible for evaluation of the primary endpoint, but will be followed for evaluation of secondary endpoints. A delay longer than the recovery period will result in less than 6 weeks exposure to sunitinib before progression will be determined. This period may be too short to evaluate progression safely.

5.5 Treatment withdrawal criteria

Withdrawal criteria are defined as:

- Disease progression
- Occurrence of second malignancy
- Unacceptable toxicity based on the investigator's judgment.
- Patient decision.

In case patients withdraw due to other reason than disease progression, they should not receive any other cancer treatment before their disease progresses, unless this is clearly not in the best interest of the patient. Follow up must be continued for progression and survival as per protocol.

5.6 Concomitant Medication(s)

Supportive care is left at the investigator's discretion.

For any further information please contact medical monitors (e-mail: 30073medicalmonitors@eortc.be).

5.6.1 Not Permitted

- Concomitant Radiotherapy (except palliative radiotherapy see chapter 5.6.2)
- Investigational or systemic therapy for metastatic RCC must not be used during the period of protocol treatment, and concurrent participation in another clinical trial testing treatment(s) for any disease including renal cell carcinoma is not allowed.

5.6.2 Permitted

- Anticoagulants

Warfarin: doses up to 2 mg daily are permitted for DVT prophylaxis. Low molecular weight heparin or aspirin are allowed.

- Palliative radiotherapy

Palliative radiotherapy for bone lesions may be given during the study. The irradiated area should be limited and should not involve more than 10% of the bone marrow. The irradiated area cannot be used for tumor response assessment. When palliative radiotherapy is planned, investigator must contact the medical monitors for agreement.

- Other Concomitant Medications

Anti-inflammatory or narcotic analgesics may be offered as needed. Packed red blood cell and platelet transfusions should be administered as clinically indicated.

Patients on this trial may be supported with appropriate hormone replacement therapy in the event that they develop adrenal insufficiency.

6 Clinical evaluation, laboratory tests and follow-up

In the 2 arms, the time-points of clinical evaluation will depend on the interval between the randomization and the start of the treatment (up to 2 weeks). In any case, the date of randomization will be considered as "Time 0".

6.1 Before randomization for arms A and B

Interval between the randomization and the start of treatment should not exceed 2 weeks.

Biopsy: if the diagnosis (histology "clear-cell" subtype) is not established patients need to undergo a transcutaneous tru-cut needle biopsy of the primary tumor.

6.1.1 Within 4 weeks prior to randomization

Radiological assessment includes the primary tumor and the metastases according to RECIST 1.1 criteria

- Disease will be assessed by standard methodology using CT scans and/or MRIs as appropriate (refer chapter 7)
- The same method should be used for repeated measurements throughout the study.
- The disease staging will be recorded on CRF

6.1.2 Within 2 weeks prior to randomization

The initial examination should include:

- Medical history
- WHO performance status, blood pressure, pulse rate, body weight and height (to estimate the Body Mass Index)
- Cancer signs and symptoms
- Assessment of adverse events according to CTCAE 4.0
- Cardiac function: LVEF (MUGA or ECHO scan) and 12-lead ECG
- Serum pregnancy test (for women of childbearing potential)
- Complete blood counts including Red Blood Cell (RBC), hemoglobin, White Blood Cell (WBC), Absolute Neutrophil Count (ANC) and platelets. Serum chemistry including sodium, potassium, serum calcium, creatinine*, bilirubin, alkaline phosphatase, ALT, LDH, glucose, albumin, PT/INR, PTT.

** Calculated or measured clearance creatinine (see Appendix C)*

6.1.3 Translational research (refer to table 6.3.3 and chapter 10)

Tumor tissue:

- In the deferred nephrectomy arm: tru-cut biopsy samples that had been taken to determine "clear-cell subtype" will be evaluated and compared to gene expression signatures in tissue obtained from nephrectomy specimen.
- In the immediate nephrectomy arm: native tumor tissue will be analyzed after nephrectomy.

Blood sample: one blood sample of 10 ml will be drawn

6.2 During treatment

6.2.1 Arm A Immediate Nephrectomy

6.2.1.1 Nephrectomy

Translational research: tumor tissue will be collected at time of surgery.

6.2.1.2 Week 4 or 5 or 6

The time-point of this evaluation depends on the interval between the randomization and the surgery:

- Week 4 if nephrectomy immediately (within 48 hours) post randomization
- Week 5 if nephrectomy one week after randomization
- Week 6 if nephrectomy 2 weeks after randomization

In any case, week 4 or 5 or 6 corresponds to the evaluation performed 4 weeks post nephrectomy before initiating sunitinib:

- WHO performance status, blood pressure, pulse rate and body weight
- Cancer signs and symptoms
- Assessment of adverse events.
- Complete blood counts including RBC, hemoglobin, WBC, ANC and platelets. Serum chemistry including sodium, potassium, serum calcium, creatinine*, bilirubin, alkaline phosphatase, LDH, ALT, glucose, albumin, PT/INR, PTT.

** Calculated or measured clearance creatinine (see Appendix C)*

- Cardiac function testing: at the investigator's discretion
- Radiological assessment for disease re-staging: all sites that were found to be involved at the initial assessment will be re-investigated by the same method.

6.2.1.3 Week 16 or 17 or 18

The time-point of this evaluation depends on the interval between the randomization and the surgery:

- Week 16 if nephrectomy immediately (within 48 hours) post randomization
- Week 17 if nephrectomy one week after randomization
- Week 18 if nephrectomy 2 weeks after randomization

In any case, week 16 or 17 or 18 corresponds to the evaluation performed at the end of cycle 2.

- WHO performance status, blood pressure, pulse rate and body weight
- Cancer signs and symptoms
- Assessment of adverse events

- Complete blood counts including RBC, hemoglobin, WBC, ANC and platelets. Serum chemistry including sodium, potassium, serum calcium, creatinine*, bilirubin, alkaline phosphatase, LDH, ALT, glucose, albumin, PT/INR, PTT

** Calculated or measured clearance creatinine (see Appendix C)*

- Cardiac function testing: at the investigator's discretion
- Radiological assessment

All sites that were found to be involved at the initial assessment will be re-investigated by the same method;

All lesions chosen as target during the initial assessment will be measured by the same method.

All investigations will be consistent with baseline in order that the development of new lesions in previously normal areas can also be determined.

- The medical monitoring is left to the investigator's discretion
- Translational research: one blood sample of 10 ml will be drawn

6.2.1.4 Week 28 or 29 or 30

The time-point of this evaluation depends on the interval between the randomization and the surgery:

- Week 28 if nephrectomy immediately (within 48 hours) post randomization
- Week 29 if nephrectomy one week after randomization
- Week 30 if nephrectomy 2 weeks after randomization

In any case, week 28 or 29 or 30 corresponds to the evaluation performed at the end of cycle 4.

- Radiological assessment

All sites that were found to be involved at the initial assessment will be re-investigated by the same method.

All lesions chosen as target during the initial assessment will be measured by the same method.

All investigations will be consistent with baseline in order that the development of new lesions in previously normal areas can also be determined.

- The medical monitoring is left to the investigator's discretion.

6.2.1.5 After week 28 or 29 or 30

After week 28 or week 29 or week 30, every 12 weeks until disease progression:

- Radiological assessment

All sites that were found to be involved at the initial assessment will be re-investigated by the same method.

All lesions chosen as target during the initial assessment will be measured by the same method.

All investigations will be consistent with baseline in order that the development of new lesions in previously normal areas can also be determined.

- The medical monitoring is left to the investigator's discretion

6.2.1.6 Six months post randomization

Approximately 6 months after randomization: one blood sample of 10 ml will be drawn for translational research.

6.2.2 Arm B Deferred Nephrectomy

6.2.2.1 Week 4 or 5 or 6

The time-point of this evaluation depends on the interval between the randomization and the start of sunitinib:

- Week 4 if sunitinib starts immediately (within 48 hours) post randomization
- Week 5 if sunitinib starts one week after randomization
- Week 6 if sunitinib starts 2 weeks after randomization

In any case, week 4 or 5 or 6 corresponds to the evaluation performed at the end of week 4 of cycle 1.

- WHO performance status, blood pressure, pulse rate and body weight
- Cancer signs and symptoms
- Assessment of adverse events.
- Complete blood counts including RBC, hemoglobin, WBC, ANC and platelets. Serum chemistry including sodium, potassium, serum calcium, creatinine*, bilirubin, alkaline phosphatase, LDH, ALT, glucose, albumin, PT/INR, PTT.

** Calculated or measured clearance creatinine (see Appendix C)*

- Cardiac function testing: at the investigator's discretion

6.2.2.2 Week 16 or 17 or 18

The time-point of this evaluation depends on the interval between the randomization and the start of sunitinib:

- Week 16 if sunitinib starts immediately (within 48 hours) post randomization
- Week 17 if sunitinib starts one week after randomization
- Week 18 if sunitinib starts 2 weeks after randomization

In any case, week 16 or 17 or 18 corresponds to the evaluation performed at the end of week 4 of cycle 3, just before nephrectomy.

- WHO performance status, blood pressure, pulse rate and body weight
- Cancer signs and symptoms
- Assessment of adverse events
- Complete blood counts including RBC, hemoglobin, WBC, ANC, and platelets. Serum chemistry including sodium, potassium, serum calcium, creatinine*, bilirubin, alkaline phosphatase, LDH, ALT, glucose, albumin, PT/INR, PTT.

** Calculated or measured clearance creatinine (see Appendix C)*

- Cardiac function testing

- Radiological assessment

All sites that were found to be involved at the initial assessment will be re-investigated by the same method.

All lesions chosen as target during the initial assessment will be measured by the same method.

All investigations will be consistent with baseline in order that the development of new lesions in previously normal areas can also be determined.

- Translational research: one blood sample of 10 ml.

6.2.2.3 Nephrectomy

Translational research: tumor tissue will be collected at time of surgery.

For patients who will not undergo surgery, it is recommended to perform transcutaneous tru-cut needle biopsy of the primary tumor.

6.2.2.4 Week 20 or 21 or 22

The time-point of this evaluation depends on the interval between the randomization and the start of sunitinib:

- Week 20 if sunitinib starts immediately (within 48 hours) post randomization
- Week 21 if sunitinib starts one week after randomization
- Week 22 if sunitinib starts 2 weeks after randomization

In any case, week 20 or 21 or 22 corresponds to the evaluation performed after nephrectomy: at the end of the 4 weeks rest period, before re-initiating sunitinib.

- WHO performance status, blood pressure, pulse rate and body weight
- Cancer signs and symptoms
- Assessment of adverse events.
- Complete blood counts including RBC, hemoglobin, WB, ANC, and platelets. Serum chemistry including sodium, potassium, serum calcium, creatinine*, bilirubin, alkaline phosphatase, LDH, ALT, glucose, albumin, PT/INR, PTT.

** Calculated or measured clearance creatinine (see Appendix C).*

- Cardiac function testing: at the investigator's discretion
- Radiological assessment for disease re-staging: all sites that were found to be involved at the initial assessment will be re-investigated by the same method.

6.2.2.5 Week 28 or 29 or 30

The time-point of this evaluation depends on the interval between the randomization and the start of sunitinib:

- Week 28 if sunitinib starts immediately (within 48 hours) post randomization
- Week 29 if sunitinib starts one week after randomization
- Week 30 if sunitinib starts 2 weeks after randomization

In any case, week 28 or 29 or 30 corresponds to the evaluation performed at the end of week 2 of cycle 5.

- Radiological assessment

All sites that were found to be involved at the initial assessment will be re-investigated by the same method.

All lesions chosen as target during the initial assessment will be measured by the same method.

All investigations will be consistent with baseline in order that the development of new lesions in previously normal areas can also be determined.

- The medical monitoring is left to the investigator's discretion.

6.2.2.6 Week 32 or 33 or 34

The time-point of this evaluation depends on the interval between the randomization and the start of sunitinib:

- Week 32 if sunitinib starts immediately (within 48 hours) post randomization
- Week 33 if sunitinib starts one week after randomization
- Week 34 if sunitinib starts 2 weeks after randomization

In any case, week 32 or 33 or 34 corresponds to the evaluation performed at the end of cycle 5.

- WHO performance status, blood pressure, pulse rate and body weight
- Cancer signs and symptoms
- Assessment of adverse events
- Complete blood counts including RBC, hemoglobin, WB, ANC, and platelets. Serum chemistry including sodium, potassium, serum calcium, creatinine*, bilirubin, alkaline phosphatase, LDH, ALT, glucose, albumin, PT/INR, PTT

** Calculated or measured clearance creatinine (see Appendix C).*

- Cardiac function testing: at the investigator's discretion

6.2.2.7 After week 28 or 29 or 30

After week 28 or 29 or 30, every 12 weeks:

- Radiological assessment

All sites that were found to be involved at the initial assessment will be re-investigated by the same method.

All lesions chosen as target during the initial assessment will be measured by the same method.

All investigations will be consistent with baseline in order that the development of new lesions in previously normal areas can also be determined.

- The medical monitoring is left to the investigator's discretion.

6.2.2.8 Six months post randomization

Approximately 6 months after randomization: one blood sample of 10 ml will be drawn for translational research.

6.2.3 For those patients who discontinue treatment due to disease progression

In both arms:

When the patient will have reached the criterion for the primary endpoint (PFS) in this trial, follow ups must still be provided until death for survival.

6.2.4 For those patients who discontinue treatment in absence of progression

In both arms:

In case patients withdraw due to other reason than disease progression, follow ups must still be provided for the study endpoints (progression free survival and overall survival).

In addition, for patients that withdraw due to adverse event, follow up for adverse event will continue on a weekly basis until any associated adverse event has resolved or clinical judgment deems necessary. It will consist of:

- Medical examination
- Assessment of adverse events
- Complete blood counts, if needed
- Serum chemistry, if needed
- Cardiac function, if needed
- Other tests, if needed

6.3 Summary table

6.3.1 Arm A Immediate Nephrectomy

	Before randomization	Post surgical period				Fol.up weekly if discontinue due tox.	Fol. up until PD	after PD Q 12 weeks for survival
		4 or 5 or 6 wks post random. (4 weeks post surgery)	16 or 17 or 18 wks post random. (16 weeks post surgery)	28 or 29 or 30 wks post random. (28 weeks post surgery)	After week 28 or 29 or 30 wks post random. (28 weeks post surgery) Q 12 wks			
Medical history	♦							
WHO PS, BP, PR, W, H (1)	♦	♦	♦			♦		
Cancer signs and symptoms	♦	♦	♦					
Adverse events	♦	♦	♦			♦		
Cardiac function	♦	❖	❖			❖		
Serum pregnancy test	♦							
Hematology (2)	♦	♦	♦			❖		
Serum chemistry (3)	♦	♦	♦			❖		
Radiological assessment (RECIST 1.1)	♦ (4 wks)	♦ (Re-staging)	♦	♦	♦		♦ (Q 12 wk)	
Survival status								♦

♦ in all cases ❖ only if clinically indicated

1. WHO performance status (PS), blood pressure (BP), pulse rate (PR), body weight (W) and height (H; only at baseline)

2. Hematology includes RBC, hemoglobin, WBC, ANC and platelets

3. Serum chemistry includes sodium, potassium, serum calcium, creatinine, bilirubin, alkaline phosphatase, LDH, ALT, glucose, albumin, PT/INR, PTT

6.3.2 Arm B Deferred Nephrectomy

	Before randomization	Pre-surgical period		Post surgical period				Fol.up weekly if discontinue due tox.	Fol. up until PD	after PD Q 12 weeks for survival
		4 or 5 or 6 wks post random. (4 weeks after starting sunitinib)	16 or 17 or 18 wks post random. (16 weeks after starting sunitinib)	20 or 21 or 22 wks post random. (4 weeks post surgery)	28 or 29 or 30 wks post random. (12 weeks post surgery)	32 or 33 or 34 wks post random. (16 weeks post surgery)	After week 28 or 29 or 30 wks post random. (12 weeks post surgery), Q 12 wks			
Medical history	♦									
WHO PS, BP, PR, W, H (1)	♦	♦	♦	♦		♦		♦		
Cancer signs and symptoms	♦	♦	♦	♦		♦				
Adverse events	♦	♦	♦	♦		♦		♦		
Cardiac function	♦	❖	♦	❖		❖		❖		
Serum pregnancy test	♦									
Hematology (2),	♦	♦	♦	♦		♦		❖		
Serum chemistry(3)	♦	♦	♦	♦		♦		❖		
Radiological assessment (RECIST 1.1)	♦ (4 wks)		♦	♦ (Re-staging)	♦		♦		♦ (Q 12 wk)	
Survival status										♦

♦ in all cases ❖ only if clinically indicated
1. WHO performance status (PS), blood pressure (BP), pulse rate (PR), body weight (W) and height (H; only at baseline)
2. Hematology includes RBC, hemoglobin, WBC, ANC and platelets
3. Serum chemistry includes sodium, potassium, serum calcium, creatinine, bilirubin, alkaline phosphatase, LDH, ALT, glucose, albumin, PT/INR, PTT

6.3.3 Translational research

	Before random.	During treatment		
		Week 16 or 17 or 18	Surgery	6 months after random.
Paraffin embedded tumor block	♦[1] (tru-cut biopsy)		♦[2] (specimen from surgery)	
Fresh frozen tissue	♦[1] (tru-cut biopsy)		♦[2] (specimen from surgery)	
Blood sample 10 ml	♦	♦		♦

1. In the immediate nephrectomy arm: native tumor tissue will be obtained from nephrectomy specimen.

2. In deferred surgery arm: for those patients who will not undergo surgery, it's strongly recommended to perform a transcutaneous tru-cut needle biopsy of the primary tumor

7 Criteria of evaluation

7.1 Progression free survival

Progression free survival will be computed from the date of randomization to the first date of progression (local or distant) or death due to any cause. Progression will be defined according to the RECIST 1.1 criteria In case the patient is still alive without progression, the date of progression/death will be censored at the date of last follow up.

The diagnosis of progression should be based on tumor measurements, according to the RECIST criteria 1.1 (Ref. 37).

Four weeks after nephrectomy, a radiological assessment will be performed in order to establish the post surgical staging.

In a small percentage of patients, early progression may be observed post surgery due to physiological environment changes (suppression of immune system, cytokines, and growth factors release). In most of the cases this progression is controlled by systemic therapy. In the deferred arm, the interruption of systemic therapy during the 4 week recovery may additionally contribute to this early progression.

In this trial, if an early progression is observed during the 4 week recovery period following the surgery, the patient will either not have received systemic therapy at all before surgery (immediate arm) or has interrupted sunitinib for surgery. In both cases, it is to be expected that the progression will be controlled by administering sunitinib after surgery. Therefore, the patient will be kept on protocol treatment until the disease assessment at week 16 (or 17 or 18) (immediate arm) and at week 28 (or 29 or 30) (deferred arm)

confirms the progression or not. In case of progression, the patient will be followed until death for overall survival.

7.2 Evaluation of efficacy

Objective tumor response and time of progression will be measured according to the RECIST version 1.1 (Ref. 37).

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and- together with other lesions that are denoted as non-target lesions - followed until disease progression.

The following paragraphs are a quick reference to the RECIST criteria version 1.1. The complete criteria are included in the published RECIST document (Ref. 37) also available at http://www.eortc.be/RECIST.

7.2.1 Measurability of tumor lesions at baseline

7.2.1.1 Definitions

- **Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - *tumor lesions* that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥ 10 mm with CT scan or clinical examination [using calipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component > 10 mm by CT scan). Malignant lymph nodes must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
- **Non-measurable lesions** - All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.
- **Target Lesions**. When more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to *a maximum* of **5,** *lesions total* (and a maximum of 2 *lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5 is to be calculated and recorded.

- **Non-target Lesions**. All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

7.2.1.2 Methods of measurements

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

- **Clinical Lesions**. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.
- **Chest X-ray**. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions > 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- **CT, MRI**. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).
- **Ultrasound**. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT should be obtained.
- **Endoscopy, Laparoscopy**. The utilization of these techniques for objective tumor evaluation is not advised.
- **Tumor Markers**. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

- **Cytology, Histology**. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease

7.2.1.3 Tumor response evaluation

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10 mm and considered CR). Tumor markers must have normalized .Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example or where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Table 1: Integration of Target, non-Target and New lesions into response assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
Patients with Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once ≥ 4 wks. from baseline [note, protocol may define; 6-8 weeks is recommended]
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Patients with Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, all tumor nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression [or evidence of unequivocal disease progression] at that time should be reported as “symptomatic deterioration”. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

7.2.1.4 Frequency of tumor re-evaluation

In the present study, tumors will be re-evaluated at weeks 16 (or 17 or 18), 28 (or 29 or 30)and then every 12 weeks during treatment. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated every 12 weeks. Patients who start a new anti-cancer treatment prior to documented progression must continue to be followed for progression in accordance with this protocol.

In this protocol, the response does not need to be confirmed except in case of doubt.

7.2.1.5 Date of progression

This is defined as the first day when the RECIST (version 1.1) criteria for PD are met. However in case of early progression within 4 (or 5 or 6) weeks after surgery, the actual date of progression (if confirmed) will be at week 16 in the immediate arm and week 28 in the deferred arm (see section 7.1).

7.2.1.6 Reporting of tumor response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death from malignant disease, early death from toxicity, early death from other cause or unknown (not assessable, insufficient data).

Early death is defined as any death occurring before the first per protocol time point of tumor re-evaluation. The responsible investigator will decide if the cause of death is malignant disease, toxicity or other cause.

Patients' response will be classified as "unknown" if insufficient data were collected to allow evaluation per these criteria.

7.2.1.7 Response duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented.

7.2.1.8 Stable disease duration

Stable disease duration will be measured from the time of start of treatment (or randomization for randomized studies) until the criteria for progression are met.

7.3 Overall survival

In this protocol, overall survival will be computed from the date of randomization to the date of death due to any cause. In case the patient is still alive, the date of death will be censored at the date of last follow up.

7.4 Evaluation of safety

7.4.1 Adverse events and side effects

All adverse events will be recorded; the investigator will assess whether those events are surgery or/and drug related (unrelated, likely, not assessable) and this assessment will be recorded in the database for all adverse events.

7.4.2 General evaluation of side-effects

This study will use the International Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, for adverse event reporting. A copy of the CTCAE can be accessed on the CTEP home page (http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/ctc.htm). A link to this page is provided on the EORTC web site http://www.eortc.be/; if the location is moved to another site, this link will be updated.

Planned safety analysis and tabulations are described in the statistics section.

7.4.3 Surgical morbidity

7.4.3.1 Adverse events and side effects

Adverse events and side effects possibly related to surgery must be recorded on the case report forms (CRFs) to evaluate the safety of immediate and deferred cytoreductive surgery.

A surgical case report form has been prepared to collect the information related to surgery and its complications.

7.4.3.2 Adverse events and side effects related to surgery (direct and indirect)

Adverse events and side effects either directly or indirectly related to surgery and its sequence can be attributed to:

- adverse events and side effects related to deferring surgery
- adverse events and side effects related to intra- and postoperative morbidity of surgery in both arms
- adverse events and side effects related to general premedication/anesthesia required to perform surgery in both arms

a) Potential consequences or side effects related to deferring nephrectomy in arm B are:

- local progression of the tumor with inability to remove the primary tumor after three courses of sunitinib
- severe hematuria caused by the primary tumor necessitating intervention as described in chapter 5.4.2.2.
- extension of the surgical approach to achieve resection with a potential increase in blood loss, duration of surgery and delayed recovery

In the surgical case report form the investigator must record for the deferred nephrectomy arm if surgery was either not attempted, aborted or more extensive due to local progression of the primary tumor during presurgical treatment. The questionnaire will enable us to specify why surgery was not attempted (for example, due to rapid progression of metastasis or progression of primary) and – in case of local progression – if surgery was more extensive, if it was attempted but aborted due to unresectability (surgically unresectable) or if it was not attempted based on imaging (clinically unresectable).

b) All adverse events related to direct intra-operative or postoperative side effects of surgery must be recorded on the CRF for both arms.

The intra-operative period is defined as the time of surgery beginning at the start of the incision to the complete closure of the wound.

The postoperative period will commence at complete closure of the wound until 30 days post surgery.

Intra-operative complications monitored will be:

- Spleen damage with splenectomy
- Bowel damage
- Vascular damage
- Pancreatic damage
- Pleural damage
- Liver damage

In addition, the following data will be collected:

- Duration of surgery
- Estimated blood loss
- Blood volume transfused during surgery
- Hospitalization (date of surgery and date of hospital discharge)

Postoperative complications are evaluated with regard to:

- Prolongation of hospitalization > 20 days following surgery: yes/no
- Reason for prolonged hospitalization due to impaired wound healing, cancer related morbidity or other
- Re-admission within 30 days after surgery
- Type of complication including focus on wound healing
- Re-operation within 30 days after surgery with indications specified

c) In exceptional cases, premedication or anesthesia may result in a delay or an inability to perform or even abortion of surgery. These instances must also be recorded in the CRF

For completion of the surgical case report form please refer to CRF guidelines.

The evaluation of case report forms will allow us to establish the safety of deferred nephrectomy following sunitinib in comparison to immediate nephrectomy.

7.4.3.3 Adverse events and side effects related to treatment with sunitinib in the deferred nephrectomy arm

Patients in the deferred nephrectomy arm may experience certain side effects related to sunitinib that may cause a delay in the scheduled surgery. In chapter 5.4.2.2, schedule modifications are outlined for the deferred nephrectomy arm. Adverse events related to sunitinib that may specifically interfere with surgery are:

- Severe cardiac toxicity
- Severe uncontrolled or symptomatic hypertension
- Myxoedema (severe hypothyroidism)
- Grade 3/4 thrombocytopenia
- Thrombo-embolic complications
- General deterioration status (ECOG Performance status ≥ 3)

In case these side effects delay the scheduled surgery, investigators must report them on the surgical CRF. Please refer to CRF guidelines for reporting.

7.4.4 Serious adverse events

Serious adverse events are defined by the Good Clinical Practice Guideline.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter 15 on Reporting adverse events)

7.4.5 Toxic deaths

Toxic death is defined as death due to toxicity (defined as adverse events at least possibly related to study treatment). The cause of death must be reported as "toxicity".

The evaluation of toxic deaths is independent of the evaluation of response (patients can die from toxicity after a complete assessment of the response to treatment).

7.4.6 Evaluability for safety

All patients who have started the treatment will be included in overall safety analyses.

For hematological events, the medical review team may decide that blood counts have not been performed and/or reported according to the protocol and are therefore inadequate for the evaluation of one/several hematological parameters in some patients.

Patients who have discontinued treatment because of toxicity will always be included in the toxicity analyses.

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

This randomized phase III trial compares deferred to immediate nephrectomy in patients treated by sunitinib. The primary endpoint is the duration of progression free survival.

The median progression free survival on the immediate nephrectomy arm is assumed to be 9 months. In order to detect an increase of 3 months in the median progression free survival to 12 months (Hazard Ratio (HR) = 0.75, Median Ratio (MR) = 1.333) on the deferred nephrectomy arm based on a two sided logrank test at error rates alpha = 0.05 and beta = 0.20, a total of 380 events (progressions or deaths) is required. Assuming a patient entry rate of 150 patients per year, a further follow up period of 1.5 years after the last patient has been entered and allowing for 5% loss to follow up, a total of 458 patients entered over 3 years is required.

The analysis of the secondary endpoint, overall duration of survival, will be carried out when 374 deaths have been observed, which will occur approximately 2.5 years after the last patient has been entered. At this time, a two sided logrank test at alpha = 0.05 will have a power of 0.68 to detect an increase in median overall survival from 14 months on the immediate nephrectomy arm to 18 months on the deferred nephrectomy arm (HR = 0.778, MR = 1.286).

If at the final analysis of progression free survival (380 events) the difference in progression free survival is not statistically significant, an interim analysis of survival for futility will be carried out. It is estimated that 85% of the deaths (319 deaths) will have been observed at the time of this interim analysis. Using an O'Brian-Fleming stopping boundary, a one sided logrank test will have a power of 95% of rejecting the alternative hypothesis if the null hypothesis is true.

If an interim survival analysis for futility is carried out and it does not reject the alternative hypothesis, then the final analysis for survival will be based on a one sided logrank test for superiority at alpha = 0.025 for the alternative hypothesis of 18 months median survival on the deferred nephrectomy arm instead of the two sided test mentioned above.

8.1.2 Randomization and stratifications

Patients will be centrally randomized (for practical details, see chapter on registration / randomization procedure). A minimization technique will be used for random treatment allocation stratifying by institution, performance status (0 versus 1) and number of metastatic sites (one versus two or more).

8.2 Statistical analysis plan

8.2.1 Primary and secondary endpoints

The primary endpoint is the duration of progression free survival: the time interval between the date of randomization and the first date of progression (local or distant) or death due to any cause. Progression will be defined according to the RECIST 1.1. In case the patient is still alive without progression, the date of progression/death will be censored at the date of last follow up.

In case of early progression within 4 weeks after surgery, the actual date of progression (if confirmed) will be at week 16 in the immediate arm and week 28 in the deferred arm (see section 7.1).

For analysis purposes:

Immediate nephrectomy arm: any progression occurring prior to the start of cycle 3 will be counted as occurring at week 16 and any progression occurring after the start of cycle 3 but before the start of cycle 5 will be counted as occurring at week 28.

Deferred nephrectomy arm: any progression occurring prior to nephrectomy will be counted as occurring at week 16 and any progression occurring after surgery and prior to or during the assessment in cycle 5 will be counted as occurring at week 28.

Secondary endpoints include:

- The duration of survival: the time interval between the date of randomization and the date of death due to any cause. In case the patient is still alive, the date of death will be censored at the date of last follow up.
- The response rate in the patients treated in the deferred nephrectomy arm: the percent of patients who achieve a complete or partial response during the period of pre-surgery treatment. Response will be assessed according to the RECIST 1.1. The number and percent of patients in the deferred nephrectomy arm who do not undergo nephrectomy will also be assessed along with the reason.
- Effect of nephrectomy on early progression in both arms.
- Adverse events measured according to CTCAE version 4.0
- Translational research as defined in chapter 10

8.2.2 Analysis populations

- Intention-to-treat population (ITT): All randomized patients will be analyzed in the arm they were allocated by randomization.
- Per protocol population: All patients who are eligible and have started their allocated treatment.
- Safety population: All patients who have started their allocated treatment.

A patient will be considered to be eligible if he/she did not have any major deviation from the patient entry criteria listed in chapter 3 of the protocol. Potential eligibility will be assessed by the Clinical Research Physician at the time of medical review.

8.2.3 Statistical methods

For the analysis of the duration of progression free survival, duration of survival and the response rate, the ITT patient population will be used. The duration of PFS and duration of survival along with their medians and associated two sided 95% confidence intervals will be estimated in each treatment group using the Kaplan-Meier technique and compared using a stratified Cox proportional hazards regression model (two sided test for superiority at alpha = 0.05) with adjustment for the following 3 stratification factors at entry: performance status (0 versus 1), number of metastatic sites (one versus two or more) and lung metastases only versus other sites. For the analysis of the response rate in the deferred nephrectomy arm, the response rate will be assessed according to RECIST 1.1 and the results provided in a frequency table. 95% two sided confidence intervals will be provided for the estimates of the PFS and survival hazard ratios, the response rate (complete plus partial) and the non nephrectomy rate.

For the analysis of toxicity, the safety population will be used. Descriptive tables will be produced by treatment group which provide the worst degree of toxicity measured over all the treatment period according to the CTCAE version 4.0. No formal toxicity comparisons with p values will be provided due to the problem of multiple comparisons.

8.2.4 Pre-planned sensitivity or exploratory analyses

Sensitivity analyses of progression free survival, survival and response as described above will be carried out in the Per Protocol patient population. An additional sensitivity analysis of progression free survival and survival without adjustment for any stratification factors will also be carried out in the ITT population.

A separate analysis of the outcome of patients who do not undergo nephrectomy in the sunitinib pre-surgery arm will be carried out. No other subgroup analyses are foreseen.

8.2.5 Prognostic factor analyses

The predictive and prognostic value of translational research factors relative to the clinical prognostic factors will be assessed in exploratory analyses.

8.2.6 Translational Research

Whenever possible, genomic and proteomic data will be analyzed using standard statistical procedures. For example Kaplan-Meier curves, the logrank test and Cox proportional hazards regression will be used for the analysis of time to event endpoints. The Wilcoxon rank sum test and logistic regression will be used for the analysis of ordered categorical data. Longitudinal analysis techniques (i.e. mixed models) will be used to model changes, for example in serum protein expression, over time. The bootstrap validation technique will be applied for sensitivity analyses and adjustment techniques will be implemented to account for multiple comparisons.

If more sophisticated biostatistical or bioinformatic techniques must be used, separate technical appendices will be written to describe their objectives and methods.

All analyses will be performed in close collaboration with the laboratories in charge of the assays and the investigators responsible for the project.

8.2.7 Data recoding and display

Frequency tables will be tabulated (by treatment group or otherwise) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1) and presented using the median and range. For example, on the randomization checklist, the date of last administration of prior treatment (or the date of first diagnosis of the cancer) will be presented as the time elapsed (in days, weeks, months or years, as appropriate) since the day of the last administration and the date of entry on study (date of randomization – last administration/diagnosis +1).

Other delays (eg. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used). Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (ULN) and the degree to which it is above the ULN (for example > 2.5 x ULN, > 5 x ULN, > 10 x ULN). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose …) are presented using the median and range (minimum, maximum). If appropriate, continuous data may also be presented in categories (for example, age may also be grouped in decades).

8.3 Interim analyses

No formal interim efficacy analyses are foreseen except for a possible interim futility analysis of survival as described above. The DMSB will monitor the study for safety as described in chapter 9**.**

8.4 End of study

End of study occurs when all of the following criteria have been satisfied:

1. The trial is mature for the analysis of the primary endpoint as defined in the protocol

2. The database has been fully cleaned and frozen for this analysis

9 Data Monitoring

Safety data are reviewed within the EORTC Headquarters on a regular basis as part of the Medical Review process. Problems which are identified will be discussed with the Study Coordinators who will take appropriate measures. Safety information will also be included in trial status reports which serve as a basis of discussion during EORTC Group meetings. These reports will be made available to investigators participating in the study.

The EORTC Data Safety Monitoring Board (DSMB), a subcommittee of the EORTC Independent Data Monitoring Committee (IDMC), will review all safety problems identified by the EORTC Headquarters for which an advice is sought. This DSMB has early trials/drug development expertise and will provide a separate review process, having no access to outcome data. The EORTC DSMB will be primarily for phase I and non randomized phase II studies, but will also provide recommendations as an initial step in phase III trials to advise if the study should then go to the full IDMC.

The EORTC IDMC is charged with the interim review (planned or not planned) of randomized phase II and phase III studies. When interim analyses are carried out, the interim monitoring of efficacy and safety data is performed according to the Statistical Considerations chapter in this protocol and EORTC Policy 004 on “Independent Data Monitoring Committees and Interim Analyses”.

The results of the interim analyses are confidential and are discussed by the EORTC IDMC. The IDMC will subsequently recommend to the EORTC Group whether any changes should be made to the study.

No efficacy results will be presented at EORTC Group meetings or elsewhere before the trial is closed to recruitment and the data are mature for the analysis of the primary endpoint, unless recommended otherwise by the EORTC IDMC.

10 Translational research

10.1 Objectives

A translational research program has been designed to identify potential response criteria based on histopathology and molecular research on tumor tissue. Tumor tissue will be collected at baseline and at time of surgery to assess possible differences in gene- expression. In addition, blood samples will be drawn to evaluate the potential impact of serum proteins on the clinical outcome of patients.

10.2 Informed Consent

Patients will be eligible for the translational research project if they are eligible for the clinical trial and have given their written informed consent to take part in this project.

At the time of patient randomization, the investigator should specify whether a patient has consented for this research.

If patient refuses to take part in the translational research project, he/she remains eligible

10.3 Gene expression signatures

At two time points tissue from patients in the deferred nephrectomy arm will be investigated by microarray gene expression profiling using the human WG-6 V3 bead chip expression array (Illumina™, for fresh frozen tissue, www.illumina.com) with 48.000 gene probes. Tru-cut biopsy samples that had been taken to determine clear-cell subtype will be evaluated and compared to gene expression signatures in tissue obtained from nephrectomy specimen. In the immediate nephrectomy arm native tumor tissue will be analyzed after nephrectomy. Differences in gene expression tissue in two arms will be of special interest and analyzed in correlation to response and overall survival.

Tumor tissue samples will include paraffin embedded tumor block (mandatory) and fresh frozen tissue (optional depending on the local facilities).

10.3.1 The transcutaneous tru-cut needle biopsy of the primary tumor

The biopsy should be taken in three-fold. One biopsy is stored in formaldehyde and processed for paraffin embedding, the other two biopsies are stored immediately in -80° C for future research. In case the subtype cannot be established on the paraffin-embedded sample, one, and if necessary, both snap-frozen biopsies can be thawed and paraffin embedded. Tumor tissue collected at time of surgery

10.3.1.1 Paraffin embedded tumor block

Tissue obtained from nephrectomy specimen must be processed for paraffin embedded. For handling and storage details refer to the Guidelines for the collection and shipment of biological samples.

10.3.1.2 Fresh frozen tissue

For institutions that have adequate facilities, frozen tissue samples of primary tumor will also be prepared. It will be of great importance to collect this tissue, because as described in section 10.3 the extensive gene expression profiling can only be carried out in frozen material. In addition, these samples will be of significance to determine the angiogenic profile and the status of endothelial cell anergy. In contrast to paraffin embedded tissue, frozen material has the advantage that it is unprocessed and will therefore retain more information.

For centers without a facility to store frozen tissue, all three biopsies should be embedded in paraffin.

10.3.1.3 Future research

Any left material from primary tumor might be used for future research.

Details for handling and storage will be provided in the Guidelines for the collection and shipment of biological samples.

10.4 Serum protein profile

Serum proteins strongly associated with overall survival in metastatic RCC are apolipoprotein A-II (ApoA2), serum amyloid alpha (SAA) and transthyretin. For institutions that have adequate facilities, serum will be collected:

- Arm A (immediate nephrectomy): at baseline, week 16 (or 17 or 18) and 6 months after randomization.
- Arm B (deferred nephrectomy): at baseline, week 16 (or 17 or 18) before surgery and 6 months after randomization.

Serum will be screened by SELDI-TOF mass spectrometry. Identified proteins will be analyzed for their association with response, prognosis and overall survival by Cox regression analysis and Kaplan-Meier curves.

Details for handling and storage will be provided in the Guidelines for the collection and shipment of biological samples.

10.5 Patient identification

Same process as described in chapter 17.2 will be applied.

10.6 Data transfer

Data relating to the gene expression signatures and serum protein profiles that are identified externally will be provided to the EORTC Headquarters so that they can be analyzed together with the clinical data included in the master study database. The process for transferring data to the EORTC Headquarters will be discussed with the laboratories in charge of the assays.

11 Publication policy

The final publication of the trial results will be written by the Study Coordinator on the basis of the final analysis performed at the EORTC Headquarters. After revision by the EORTC Headquarters, the EORTC GU Group Executive Committee and other co-authors (and the Sponsor, if applicable) the manuscript will be sent to a major scientific journal.

Authors of the manuscript will include at least the Study Coordinator, the investigators who have included more than 5% of the eligible patients in the trial (by order of inclusion), and a minimum of two members of the EORTC Headquarters team who have contributed to the trial.

The title of all manuscripts will include “EORTC”, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, the EORTC Headquarters staff involved in the study, as well as supporting bodies (NCI, cancer leagues, sponsors…).

All publications (papers, abstracts, presentations…) including data from the present trial will be submitted for review to the EORTC Headquarters, the EORTC GU Group Executive Committee and to all co-authors prior to submission.

The Group Chairman, the Study Coordinator and the EORTC Headquarters Team must approve all publications, abstracts and presentations of data pertaining to patients included in this study.

This is applicable to any individual patient registered/randomized in the trial, or any subgroup of these. Such publications must comply with the terms specified in the EORTC Policy 009 “Release of Results and Publication Policy”. Therefore, such a publication cannot include any comparisons between randomized treatment arms (for randomized trials) or an analysis of any of the study end-points unless the final results of the trial have already been published by the Study Coordinator.

It is the EORTC’s policy not to release trial results before data maturity has been reached for the primary endpoint(s) of the trial unless the publication is authorized by an Independent Data Monitoring Committee. If the group wishes to publish or present study data before the publication of the primary trial endpoint, this may be authorized under the conditions specified in the EORTC Policy 009 “Release of Results and Authorship Policy” available from http:\\www.eortc.be, or authorized by an Independent Data Monitoring Committee.

12 Investigator authorization procedure

Investigators will be authorized to register and/or randomize patients in this trial only once they have returned the following documents to their Data Center (for EORTC investigators see below, for investigators participating via one of the collaborative groups: see your group specific appendix):

- The updated signed and dated curriculum vitae of the Principal Investigator.
- The (updated) list of the normal ranges for their own institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator's institution.
- A Commitment Statement and Study Agreement between EORTC and Principal Investigator, stating that the investigator will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the Commitment Statement and Study Agreement.

- A copy of the favorable opinion of the local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly stated on each page.
- The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations. In case patients receive treatment at a satellite institution, i.e. outside the authorized institution, details on the satellite institution, including the CV of the local investigator, normal lab ranges and the approval of an ethics committee will have to be transmitted to the EORTC Headquarters. Please keep in mind that all communication is done ONLY between the primary institution and the EORTC Headquarters.
- The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.

The center specific list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law.

The new investigator will be added to the "authorization list", and will be allowed to register/randomize patients in the trial as soon as

- All the above mentioned documents are available at their Data Center.
- All applicable national legal and regulatory requirements are fulfilled.

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

13 Patient randomization procedure

Patient randomization will only be accepted from authorized investigators (see chapter on “investigator authorization procedure").

A patient can only be randomized after verification of eligibility. Both the eligibility check and randomization must be done before the start of the protocol treatment.

STANDARD INFORMATION REQUESTED:

- EORTC institution number
- EORTC protocol number
- step number: 1
- name of the responsible investigator
- patient's code (*maximum 4 alphanumerics*)
- patient's birth date (*day/month/year*)

PROTOCOL SPECIFIC QUESTIONS:

- all eligibility criteria will be checked one by one
- actual values for the eligibility parameters will be requested when applicable
- stratification factors
- date of written informed consent (*day/month/year*)
- date foreseen for protocol treatment start

At the end of the procedure, the treatment will be randomly allocated to the patient, as well as a **sequential patient identification number (“seqID”)**. The sequential identification number attributed to the patient at the end of the randomization procedure will allow the identification of the patients in the VISTA/Remote Data Capture system (VISTA/RDC) that will be used to complete the Case Report Forms.

All participants should randomize patients directly on the **EORTC online randomization system** (ORTA = online randomized trials access), accessible 24 hours a day, 7 days a week, through the internet. To access the interactive randomization program, the investigator needs a username and a password (which can be requested at www.eortc.be/random).

In case of problems participants can phone the EORTC Headquarters from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday to randomize patients via the EORTC call center. Randomization via the phone is not available on Belgian holidays. A list of these holidays is available on the EORTC web site (www.eortc.be/random) and it is updated annually.

Through Internet:	www.eortc.be/random
In case of problems randomization by phone:	+32 2 774 16 00

14 Forms and procedures for collecting data

14.1 Case report forms and schedule for completion

Data will be reported on the forms specifically designed by the EORTC Headquarters for this study. Forms should be electronically sent to the EORTC Headquarters through the VISTA/RDC (Remote Data Capture) system, with the exception of the SAE form which is a paper CRF.

SERIOUS ADVERSE EVENTS SHOULD BE IMMEDIATELY REPORTED ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL (see chapter on Reporting Serious Adverse Events).

A. Before the treatment starts:

- The patient must be randomized in the trial by INTERNET or in case of problems by phone.

The electronic CRFs to be completed for a patient are available on the VISTA/RDC website one day after the randomization on http://rdc.eortc.be or on http://www.eortc.be in the section for investigators.

The paper SAE form will be made available to the institution at the time the institution is authorized.

B. During/after treatment

The list of forms to be completed for this study and their submission schedule are available on the VISTA/RDC website and are also described in the "guidelines for completion of case report forms" that are provided to each participating investigator.

ALL Forms must be electronically approved and sent by the responsible investigator or one of his/her authorized staff members with the exception of the paper SAE form which needs to be signed and dated individually by the responsible investigator or one of his/her authorized staff members.

14.2 Data Flow

The forms must be completed electronically, with the exception of the paper SAE form, according to the schedule defined in the guidelines for completion of Case Report Forms.

The list of staff members authorized to enter data (with a sample of their signature) must be identified on the signature log and sent to the EORTC Headquarters by the responsible investigator before the start of the study. To enter the RDC system, the investigator or authorized staff member needs to use the same username and password that are used to access the interactive randomization program (ORTA).

In all cases, it remains the responsibility of the principal investigator to check that data are entered in the database as soon as possible and that the electronic forms are filled out completely and correctly.

The EORTC Headquarters will perform extensive consistency checks on the received data and will issue Queries in case of missing and/or inconsistent data. The queries for the electronic forms will appear in the VISTA/RDC system and must be answered there. The EORTC data manager will subsequently apply the corrections into the database.

When satellite institutions are involved all contacts are done exclusively with the primary institution, for purposes of data collection and all other study related issues.

If an investigator (or an authorized staff member) needs to modify a CRF after the form has been electronically sent to the EORTC Headquarters, he/she should create a request for data correction in the VISTA/RDC system.

15 Reporting of Serious Adverse Events

ICH GCP requires that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

15.1 Definitions

As this protocol will investigate whether deferring nephrectomy in patients who receive sunitinib (standard systemic therapy) has an effect on disease control by optimizing the sequence of surgery for metastatic RCC, the definition of adverse event related to surgery and unexpected adverse event related to surgery is included in this chapter. Hereinafter sunitinib (standard systemic therapy) is referred to as “medicinal product”.

AE: An **Adverse Event** is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver or bleeding), symptoms (such as nausea or chest pain or abdominal pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the surgery or the medicinal product.

AR: An **Adverse reaction of a** marketed medicinal products is defined as “a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function."

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship

An **Adverse Event related to Surgery** will be defined as “any noxious and unintended response to the surgery ".

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the surgery qualify as adverse events. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

An **Unexpected Adverse Event related to Surgery** is “any adverse event, the nature, or severity of which is not consistent with the standard pattern of adverse event in surgical practice.

When the outcome of the adverse event is not consistent with the standard pattern of adverse events in surgical practice, this adverse event should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- results in death
- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient's hospitalisation (e.g. re-admission or re-exploration for adverse event related to surgery) or prolongation of existing inpatients´ hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- results in any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above), e.g. severe wound healing complications, secondary malignancy, AE as a result of an overdose

SAR: A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a **Serious Adverse Reaction**

Inpatient or in-patient's hospitalisation: A patient who is admitted to a hospital or clinic for at least one overnight stay.

15.2 Exceptions

The following situations are not considered to be SAEs and should not be reported on the SAE form:

- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment
- A hospitalisation which was planned before the patient consented for study participation and where admission did not take longer than anticipated
- Hospitalisation for nephrectomy
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital, palliative care, rehabilitation, overdose without occurrence of an adverse event)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention, clinical events related to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, unless the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

15.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_v40.

15.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following definitions in this table:

Relationship to the protocol treatment	Description
UNRELATED	There is no evidence of any causal relationship to the protocol treatment
LIKELY RELATED	There is (some) evidence to suggest a causal relationship to the protocol treatment and influence of other factors is unlikely or absent.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgment of the causal relationship to the protocol treatment.

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the Serious Adverse Event form, if necessary with the reasoning of the principal investigator.

15.5 Expectedness assessment

The expectedness assessment is the responsibility of the coordinating group of the study. The expectedness assessment will be performed against the following reference document:

- For Drug sunitinib: Summary of Product Characteristics (SmPC) which can be found on EMA website

15.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject is randomized until 16 weeks after nephrectomy and to any SAE that occurs outside of the SAE detection period (after the 16 weeks period), if it is considered to be likely related to [surgery] or [surgery + sunitinib].

Randomization till 16 weeks after nephrectomy:	All SAEs
From week 17 after nephrectomy:	Only SAEs related to [surgery] or [surgery + sunitinib]

All reporting must be done by the principle investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All investigators from European centers must fax all SAE-related information to:

EORTC Pharmacovigilance Unit:

Fax No. +32 2 772 8027

Investigators from non-European centers should consult their Group Specific Appendix for further details on the reporting of Serious Adverse Events.

To enable the sponsor to comply with reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), the suspected cause (surgery, with or without involvement of standard systemic therapy), an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the EORTC Pharmacovigilance Unit will make a written request to the investigator/coordinating data center.

Queries sent out by the EORTC Pharmacovigilance unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principle investigator or any authorized staff member (i.e. on the signature list).

15.7 Reporting to investigators and competent authorities

For European centers:

The EORTC Pharmacovigilance Unit will forward all SAE reports within 24 hours of receipt to the appropriate persons within the EORTC Headquarters and to the pharmacovigilance contact at the pharmaceutical company, if applicable.

All SUSARs will additionally be forwarded to all participating investigators and Ethics committees whenever applicable.

The EORTC Pharmacovigilance Unit will take in charge the expedited reporting to the Competent Authorities and EVCTM whenever applicable.

The EORTC Pharmacovigilance Unit will provide a six-monthly summary which will be added in the group meeting report and which will be distributed to all participating investigators.

For non-European centers:

Investigators from non-European centers should consult their Group Specific Appendix for further details.

15.8 Pregnancy reporting

For European centers:

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational procedure to the father prior to sexual intercourse.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed from randomisation and until 16 weeks after nephrectomy must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form/Fax
- If a Serious Adverse Event (SAE) occurs in conjunction with the pregnancy, please also complete an SAE form as explained above

For non-European centers:

Investigators from non-European centers should consult their Group Specific Appendix for further details.

16 Quality assurance

16.1 Control of data consistency

Data forms will be entered in the database of the EORTC Headquarters by using the RDC system. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

16.2 On-site quality control

The EORTC HQ will perform the on-site monitoring for EORTC investigators.

Three monitoring site visits will be scheduled per site during the study.

The aim of on-site visits will be:

- to evaluate the local facilities available to the responsible investigators for performing clinical trials, and to comply to all requirements of the present protocol
- to assess the consistency of the data reported on the case report forms with the source data
- to check that all serious adverse events have been properly reported
- to resolve all unanswered queries

Investigators participating through one of the collaborative groups should refer to their Group Specific Appendix for more information on eventual monitoring performed by their group.

16.3 Audits

The EORTC Quality Systems and Compliance Unit (QS&C) regularly conducts audits of institutions participating in EORTC protocols. These audits are performed to provide assurance that the rights, safety and wellbeing of subjects are properly protected, to assess compliance with the protocol, processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at anytime to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files, …) to these authorized individuals. All onsite facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives, …).

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QS&C unit immediately (contact at: qualitysystemandcompliance@eortc.be). In this way EORTC can provide help in preparing and/or facilitating the inspection.

This procedure does not apply to non-EORTC investigators who should refer to their Group Specific Appendix for the information on eventual audits by their group.

17 Ethical considerations

17.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

17.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth will also be reported on the case report forms.

17.3 Informed consent

All patients will be informed about

- the aims of the study
- the possible adverse events
- the procedures and possible hazards to which the patient will be exposed
- the mechanism of treatment allocation
- strict confidentiality of any patient data
- medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The bold sections of the informed consent document must be reflected in any translation. The content of these bold sections can either be translated literally or translated in any way that best captures the information given.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

Chapters 18 through 20 pertain specifically to the participation of EORTC investigators. Participants from other organizations should consult the appendix that is specific to their group to determine if the contents of these chapters are superseded by procedures specific to their group.

18 Administrative responsibilities

18.1 The study coordinator

The Study Coordinator (in cooperation with the EORTC Headquarters) will be responsible for writing the protocol, contributing to the medical review, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will assist the Clinical Research Physician for answering some clinical questions concerning eligibility, treatment, and the medical review of the patients.

Study coordinator:

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18.2 The EORTC Headquarters

The EORTC Headquarters will be responsible for writing the protocol and PIS/IC, reviewing the protocol, setting up the trial, collecting case report forms, controlling the quality of the reported data, organizing the medical review and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Headquarters.

EORTC HEADQUARTERS

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: +32 2 7723545

Registration of patients:

http://www.eortc.be/random
Or
Phone (in case of problems): +32 2 774 16 00

18.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the ad interim board of the group.

For new membership contact Membership Committee at membership@eortc.be

GUCG EORTC group

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19 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC participants.

The contact details of the EORTC are:

EORTC Headquarters
Avenue E. Mounierlaan 83/11
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e-mail: jerome.krulik@pfizer.com

20 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

Appendix A: References

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Ref. 3 Flanigan RC, Mickisch G, Sylvester R, Tangen C, van Poppel H, Crawford ED (2004) Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 171: 1071-1076.

Ref. 4 Crispen PL, Sheinin Y, Roth TJ, Lohse CM, Kuntz SM, Frigola X, Thompson RH, Boorjian SA, Dong H, Leibovich BC, Blute ML, Kwon ED (2008) Tumor cell and tumor vasculature expression of B7-H3 predict survival in clear cell renal cell carcinoma. Clin Cancer Res 14: 5150-5157.

Ref. 5 Tatsumi T, Herrem CJ, Olson WC, Finke JH, Bukowski RM, Kinch MS, Ranieri E, Storkus WJ (2003) Disease stage variation in CD4+ and CD8+ T-cell reactivity to the receptor tyrosine kinase EphA2 in patients with renal cell carcinoma. Cancer Res 63: 4481-4489.

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Ref. 7 Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J (1999) Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol 17: 2530-2540.

Ref. 8 Motzer RJ, Bukowski RM, Figlin RA, Hutson TE, Michaelson MD, Kim ST, Baum CM, Kattan MW (2008) Prognostic nomogram for sunitinib in patients with metastatic renal cell carcinoma. Cancer 113: 1552-1558.

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Ref. 10 Lara PNJr, Tangen CM, Conlon SJ, Flanigan RC, Crawford ED (2008) Predictors of survival of advanced renal cell carcinoma: long-term results from Southwest Oncology Group Trial S8949. J Urol. 181:512-517.

Ref. 11 Russo P, O'Brien MF (2008) Surgical intervention in patients with metastatic renal cancer: metastasectomy and cytoreductive nephrectomy. Urol Clin N Amer 35: 679-686.

Ref. 12 Zini L, Capitanio U, Perrotte P, Jeldres C, Shariat SF, Arjane P, Widmer H, Montorsi F, Patard JJ, Karakiewicz PI (2008) Population-based assessment of survival after cytoreductive nephrectomy versus no surgery in patients with metastatic renal cell carcinoma. Urology.181:497

Ref. 13 Motzer RJ, Hoosen S, Bello CL, Christensen JG (2006) Sunitinib malate for the treatment of solid tumours: a review of current clinical data. Expert Opin Investig Drugs 15: 553-561.

Ref. 14 Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, Redman BG, Margolin KA, Merchan JR, Wilding G, Ginsberg MS, Bacik J, Kim ST, Baum CM, Michaelson MD (2006) Sunitinib in patients with metastatic renal cell carcinoma. JAMA 295: 2516-2524.

Ref. 15 Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, Ginsberg MS, Kim ST, Baum CM, DePrimo SE, Li JZ, Bello CL, Theuer CP, George DJ, Rini BI (2006) Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-

derived growth factor receptor, in patients with metastatic renal cell carcinoma. J Clin Oncol 24: 16-24.

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Appendix B: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix C: Calculation of the glomerular filtration rate (GFR)

COCKCROFT AND GAULT FORMULA

For the calculation of GFR age is measured in years and weight is measured in kilograms.

If serum creatinine is measured in µmol/l, the following formula applies:

In males: $GFR[ml/min] = \frac{1.23 \times (140 - age) \times weight}{serum\ creatinine}$

In females: $GFR[ml/min] = \frac{1.05 \times (140 - age) \times weight}{serum\ creatinine}$

If serum creatinine is measured in mg/dl, the following formula applies:

In males: $GFR[ml/min] = \frac{(140 - age) \times weight}{72 \times serum\ creatinine}$

In females: $GFR[ml/min] = \frac{0.85 \times (140 - age) \times weight}{72 \times serum\ creatinine}$