**Official Title:** Clinical Study Protocol

An open-label, randomized, controlled, multicenter, phase II study evaluating safety and efficacy of intratumorally administered Intuvax pre-nephrectomy followed by Sunitinib post-nephrectomy, compared to Sunitinib post-nephrectomy in metastatic renal cell carcinoma patients

**Document date:** 12 February 2019

**NCT number:** NCT02432846

IMMUNICUM

CONFIDENTIAL

# CLINICAL STUDY PROTOCOL

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An open-label, randomized, controlled, multicenter, phase II study evaluating safety and efficacy of intratumorally administered Intuvax pre-nephrectomy followed by Sunitinib post-nephrectomy, compared to Sunitinib post-nephrectomy in metastatic renal cell carcinoma patients

| | | | |
|---|---|---|---|
| Study code: | IM-201 | Study development phase: | II |
| EudraCT number: | 2014-004510-28 | Investigational medicinal product: | Intuvax (pre-activated allogeneic dendritic cells) |
| | | Indication: | Metastatic Renal Cell Carcinoma (mRCC) |
| Version: | Final 9.0 | Date: | 12 February 2019 |

Document history: This version of the Clinical Study Protocol includes:

- Protocol Amendment No.1 (Substantial), Final 1.0 (26 May 2015)
- Protocol Amendment No.2 (Substantial), Final 1.0 (04 December 2015)
- Updates made to meet ANSM requests (09 August 2016)
- Protocol Amendment No.4 (Substantial), Final 1.0 (26 October 2016)
- Updates made to meet ANSM requests (06 December 2016)
- Protocol Amendment No.4_FR (Substantial), Final 1.0 (01 March 2017)
- Protocol Amendment No. 5 (Substantial), Final 1.0 (17 October 2017)
- Protocol Amendment No. 6 (Substantial), Final 1.0 (20 June 2018)
- Protocol Amendment No. 7 (Substantial), Final 1.0 (12 February 2019)

  *Comment: Amendment No. 3 (Substantial), Final 1.0 (11 July 2016) was submitted to FDA (US) only and was never implemented*

[redacted]

# 1 SYNOPSIS

| | |
|---|---|
| **Name of the Sponsor/Company:**<br>Immunicum AB (publ) | **Study Code:**<br>IM-201 |
| **Name of Investigational Medicinal Product:**<br>Intuvax | **EudraCT No.:**<br>2014-004510-28 |
| **Development Phase of the Study:**<br>Phase II | **Trial under an IND:**<br>IND No.: 17081 |
| **TITLE OF THE STUDY:** An open-label, randomized, controlled, multicenter, phase II study evaluating safety and efficacy of intratumorally administered Intuvax pre-nephrectomy followed by Sunitinib post-nephrectomy, compared to Sunitinib post-nephrectomy in metastatic renal cell carcinoma patients | |

**OBJECTIVES:**

The primary objectives are:

- To evaluate median overall survival (OS) from randomization in metastatic renal cell carcinoma (mRCC) patients overall and by subgroup, i.e. in high-risk and in intermediate-risk patients separately, receiving two (2) vaccine doses of Intuvax pre-nephrectomy, followed by sunitinib initiated five (5) to eight (8) weeks post-nephrectomy and in non-vaccinated mRCC patients receiving sunitinib initiated five (5) to eight (8) weeks post-nephrectomy
- To evaluate 18-month survival rate from randomization in mRCC patients overall and by subgroup, i.e. in high-risk and in intermediate-risk patients separately, receiving two (2) vaccine doses of Intuvax pre-nephrectomy followed by sunitinib post-nephrectomy and in non-vaccinated patients receiving sunitinib post-nephrectomy

The secondary objectives are:

- To evaluate safety and tolerability in high- and intermediate-risk mRCC patients receiving two (2) vaccine doses of Intuvax pre-nephrectomy followed by sunitinib post-nephrectomy and in non-vaccinated patients receiving sunitinib post-nephrectomy
- To evaluate progression free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria from Sunitinib Start Visit in intermediate- and high-risk mRCC patients after receiving two (2) vaccine doses of Intuvax pre-nephrectomy followed by sunitinib post-nephrectomy and in non-vaccinated patients receiving sunitinib post-nephrectomy*
- To evaluate response and its duration according to RECIST 1.1 criteria from Sunitinib Start Visit in intermediate- and high-risk mRCC patients receiving two (2) vaccine doses of Intuvax pre-nephrectomy followed by sunitinib post-nephrectomy and in non-vaccinated patients receiving sunitinib post-nephrectomy*
- To evaluate time to progression (TTP) from Sunitinib Start Visit in intermediate- and high-risk mRCC patients receiving two (2) vaccine doses of Intuvax pre-nephrectomy followed by sunitinib post-nephrectomy and in non-vaccinated patients receiving sunitinib post-nephrectomy*
- To evaluate the number of infiltrating CD8+ T-cells in available diagnostic pre-biopsy (sample from either primary tumor or metastasis acceptable) and in the resected primary renal tumor in intermediate- and high-risk mRCC patients receiving two (2) vaccine doses of Intuvax pre-nephrectomy and in non-vaccinated patients

*_Note_: For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, baseline for PFS, response and its duration, and TTP is defined as the first imaging assessment after nephrectomy.

[redacted]

| **Name of the Sponsor/Company:**<br>Immunicum AB (publ) | **Study Code:**<br>IM-201 |
|---|---|
| **Name of Investigational Medicinal Product:**<br>Intuvax | **EudraCT No.:**<br>2014-004510-28 |
| **Development Phase of the Study:**<br>Phase II | **Trial under an IND:**<br>IND No.: 17081 |

**OVERALL STUDY DESIGN:**

The study is an open-label, randomized, controlled, two (2) armed, multicenter, phase II study. Intermediate- and high-risk mRCC patients according to Heng criteria are eligible for participation. Stratified randomization based on Heng-risk categories applies.

The patients are randomized in a consecutive manner into one (1) of the following two (2) treatment arms;

(i) Two (2) doses of Intuvax ($10x10^6$ DCs) administered intratumorally into the primary tumor 14 ±3 days apart followed by nephrectomy at least three (3) days after the second vaccine dose.

AND

Sunitinib treatment initiated five (5) to eight (8) weeks after nephrectomy. Administered dose in accordance with the Summary of Product Characteristics (SmPC)/United States Product Insert (USPI)

(ii) Sunitinib treatment initiated five (5) to eight (8) weeks after nephrectomy. Administered dose in accordance with the SmPC/USPI

The estimated number of patients to be randomized is around 90 (with a stratification of intermediate-risk versus high-risk patients).The patients will be randomized in a 2:1 (vaccine treatment arm [i]: control treatment arm [ii]) ratio.

Patients randomized to treatment arm (i) are scheduled for 12 study visits during a study period of 78 weeks. Patients randomized to treatment arm (ii) are scheduled for 10 study visits during a study period of 78 weeks. The same visits as for patients randomized to treatment arm (i) apply except for the two (2) vaccination visits. In addition, all patients being exposed to any of the Investigational Medicinal Products (IMPs) will have a safety evaluation done for collection of SAEs up to 30 days after last dose of IMP administered in the study.

All patients will be encouraged to contact the clinic in between study visits if they experience adverse events (AEs) or have any concerns. If follow-up of any symptoms is needed between the planned visits, the patient will be scheduled for a visit as soon as possible and applicable assessments will be performed.

Post-study survival data (date of death) collection will continue on a yearly basis for a maximum of 5 years after collection of the last patient's 18 months survival data.

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|---|---|
| **Name of Investigational Medicinal Product:**<br>Intuvax | **EudraCT No.:**<br>2014-004510-28 |
| **Development Phase of the Study:**<br>Phase II | **Trial under an IND:**<br>IND No.: 17081 |

**INVESTIGATIONAL MEDICINAL PRODUCT:**
Intuvax (a cryopreserved dendritic cell suspension of 11.7 x$10^6$ viable and Human Leukocyte Antigen (HLA) class II expressing cells in 1 mL heat-inactivated AB plasma, supplemented with 10% dimethyl sulfoxide [DMSO]).

Sunitinib (marketed products).

**NUMBER OF PATIENTS:**

Approximately 90 patients (with a stratification of intermediate-risk versus high-risk patients at randomization).

**NUMBER OF STUDY CENTERS:**

Approximately 25 sites in EU and approximately 5 sites in US

**MAIN INCLUSION AND EXCLUSION CRITERIA:**

Inclusion criteria:

1) Newly (<6 months) diagnosed RCC (histological/cytological verification is optional) with at least one (1) CT-verified metastasis ≥10 mm for which complete metastasectomy is not planned. US patients must have verified clear-cell tumor histology
2) Planned resection of primary tumor
3) Primary tumor diameter ≥40 mm
4) Candidate for first-line therapy with sunitinib initiated five (5) to eight (8) weeks after nephrectomy
5) Female or male ≥18 years of age
6) Willing and able to provide informed consent
7) Adequate hematological parameters, i.e.:
   - B-Leukocyte count ≥4.5 x$10^9$/L
   - B-Platelet count ≥150 x$10^9$/L
   - B-Hemoglobin (Hb) ≥90 g/L
8) Serum-creatinine and serum-bilirubin ≤1.5 × ULN. Serum-ALAT and serum-ASAT ≤2.5 × ULN (or ≤5 in case of liver metastases)
9) Female who has been post-menopausal for more than one (1) year or female of childbearing potential agreeing to use a highly efficient method of contraception (i.e. a method with less than 1% failure rate [e.g. sterilization, hormone implants, hormone injections, some intrauterine devices, or vasectomized partner or combined birth control pills]) from Screening until 90 days after last dose of Intuvax and/or until completed sunitinib treatment whichever occurs later. Female of childbearing potential must have a negative blood pregnancy test at Screening, and if randomized to vaccination a negative blood or urine pregnancy test within one (1) day before each dose of Intuvax) and must not be lactating

   or

   Male agreeing to use condoms from Screening until 90 days after last dose of Intuvax and/or until completed sunitinib treatment whichever occurs later, or male having a female partner who is using a highly efficient method of contraception as described above

Exclusion criteria:

1) Life expectancy less than 4 months

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2) Central nervous system (CNS) metastasis that is symptomatic or progressing or untreated or that requires current therapy (e.g. evidence of new or enlarging CNS metastasis or new neurological symptoms attributable to CNS metastases)

3) Active autoimmune disease which requires treatment with systemic immunosuppressive agents, e.g. inflammatory bowel disease, multiple sclerosis, sarcoidosis, psoriasis, autoimmune hemolytic anemia, rheumatoid arthritis, SLE, vasculitis, Sjögren's syndrome, scleroderma, autoimmune hepatitis, and other rheumatological diseases

4) Treatment with per oral systemic corticosteroids exceeding 10 mg/day within 7 days before Screening until Nephrectomy (inhaled, intranasal, and local steroids acceptable irrespective of dose)

5) Known cardiomyopathy and/or clinically significant abnormal ECG findings at Screening disqualifying the patient from nephrectomy and subsequent sunitinib treatment

6) Karnofsky performance status <70%
   For patients in **France** Karnofsky performance status ≤70%

7) National Cancer Institute (NCI) Common Terminology criteria for Adverse Events (CTCAE) Grade 3 hemorrhage within 28 days before Screening

8) Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication

9) Clinically significant gastrointestinal abnormalities

10) Uncontrolled hypertension, or uncontrolled diabetes mellitus

11) Pulmonary embolism within 12 months prior to Screening

12) Prior history of invasive cancer within 5 years before Screening, except for adequately treated *in situ* carcinomas or non-melanoma skin cancer

13) Ongoing infection that requires parenteral treatment with antibiotics

14) Active or latent virus disease (HIV, HBV and HCV)

15) ECOG performance status >2 after optimization of analgesics

16) Abnormal or clinically significant coagulation parameters at the discretion of the investigator, i.e.:
   - Prothrombin Time - International Normalized Ratio (PT-INR)
   - Activated Partial Thromboplastin Time (APTT)

   Patients being treated with anticoagulants are excluded if the coagulation parameters are outside the therapeutic intervals as described in the SmPC/USPI for the administered treatment

17) Known major adverse reaction/event in connection with previously made vaccination (e.g. asthma, anaphylaxis or other serious reaction)

18) Known hypersensitivity or allergy to sunitinib or to chemically related products or likely to be exacerbated by any component of the study products

19) Prior systemic antitumor therapy within 28 days before Screening Visit. However, local radiation therapy to any area except for the abdominal/retroperitoneal area including the kidney tumor is allowed

20) Exposure to other investigational products within 28 days prior to Screening Visit

21) Patients on anticoagulants for whom temporarily stop and start, supported by low molecular weight heparin (or other anticoagulation therapy at the discretion of the Investigator and/or per local standard of care) during vaccination and nephrectomy, is not an option

| **Name of the Sponsor/Company:** Immunicum AB (publ) | **Study Code:** IM-201 |
|---|---|
| **Name of Investigational Medicinal Product:** Intuvax | **EudraCT No.:** 2014-004510-28 |
| **Development Phase of the Study:** Phase II | **Trial under an IND:** IND No.: 17081 |

22) History of alcohol or substance abuse

23) Any reason that, in the opinion of the Investigator, contraindicates that the patient participates in the study

**EFFICACY AND SAFETY ENDPOINTS:**

Primary endpoints

- OS from randomization overall in mRCC patients and by each subgroup, i.e. in high-risk and in intermediate-risk mRCC patients
- 18-month survival rate from randomization overall in mRCC patients and by each subgroup, i.e. in high-risk and in intermediate-risk mRCC patients

Secondary endpoints

- Frequency and proportion of AEs including clinical significant changes in laboratory tests and vital signs from Screening
- PFS from start of sunitinib according to RECIST 1.1*
- Proportion of Objective Response Rate (ORR) from start of sunitinib treatment and duration of response in each subgroup*
- TTP from start of sunitinib treatment*
- Relative number of tumor infiltrating CD8+ T-cells in the resected primary tumor compared to relative number of infiltrating CD8+ T-cells in available diagnostic pre-biopsy (sample from either primary tumor or metastasis acceptable)

**Note*: For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, baseline for PFS, ORR and duration of response, and TTP is defined as the first imaging assessment after nephrectomy.

| **Name of the Sponsor/Company:**<br>Immunicum AB (publ) | **Study Code:**<br>IM-201 |
|---|---|
| **Name of Investigational Medicinal Product:**<br>Intuvax | **EudraCT No.:**<br>2014-004510-28 |
| **Development Phase of the Study:**<br>Phase II | **Trial under an IND:**<br>IND No.: 17081 |

[redacted]

**STATISTICAL METHODS:**

As this study is exploratory, sample size is not based on typical power calculation for confirming an efficacy as this would require either a too long follow-up or an unrealistic number of patients. Statistical hypothesis testing will be used but to be interpreted as exploratory analysis results. No adjustment for multiplicity will be done. All tests will be two-sided and type-1 error level is set to 0.05, i.e. significance level. Two primary endpoints are defined, each one in relation to the two primary objectives.

All patients will be followed for survival until date of death can be confirmed or up to 5 years after collection of the last patient's 18 months survival data, whichever comes first. Post-study survival data will be collected as described in *Section 11.3*. The primary analysis will be conducted based on the data collected at the entire study end. If the time point for the collection of post-study survival data at the entire study end, before DBL, differs with more than 2 months compared to the last patient's 18 months post randomization time point, then an additional collection of survival data will be conducted and the first follow-up analysis of post-study survival data will be done, as described in *Section 12.5*.

The primary endpoints will be evaluated and compared between treatment groups based on high-risk mRCC patients and intermediate-risk mRCC patients overall and by subgroups as part of the Full Analysis Set (FAS) population in the following way:

(i) OS

The primary endpoint median OS after randomization in high-risk and intermediate-risk mRCC patients will be calculated and compared overall and by subroup using the FAS in the following way:

Survival functions will be displayed graphically using Kaplan-Meier plots, and life table statistics will be produced including summaries of number of events and censored observations. Estimates of 25%, 50% (median) and 75% percentiles of time of survival with corresponding 95% confidence intervals will be calculated. Analysis where the survival functions will be compared between Intuvax+sunitinib, vs. sunitinib alone will be conducted using a log-rank test. Time to death in this analysis will be defined as the time from randomization until the event occurs.

In addition the primary efficacy endpoint will be evaluted using the Per Protocol Set (PPS).

(ii) 18-month survival rate

The primary endpoint 18-month survival rate after randomization in high-risk and intermediate-risk mRCC patients will be calculated and compared overall and by subgroup using life table statistics including summaries of number of events and censored observations and similar survival statistics as described for the analysis of OS above.

*NB:* Patients alive at the End-of-Study Visit will be followed for survival until date of death can be confirmed or for a maximum of 5 years after collection of the last patient's 18 months survival data, whichever comes first.

Lost to follow-up patients will be handled as censored observations if date of death cannot be found from medical records or databases (including public records).

**STUDY PERIOD:**

Start of inclusion: Q2 2015

Planned last patient last study visit or last patient's safety evaluation (up to 30 days after the last patient's last dose of an IMP), whichever occurs later: Q3 2019

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# 3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

## 3.1 List of Abbreviations

| | |
|---|---|
| AB plasma | Plasma from blood with blood-group AB |
| AE | Adverse Event |
| ALAT | Alanine Aminotransferase |
| ALP | Alkaline Phosphatase |
| APTT | Activated Partial Thromboplastin Time |
| ASA | Acetylsalicylic Acid |
| ASAT | Aspartate Aminotransferase |
| BP | Blood Pressure |
| CA | Competent Authority |
| Ca | Calcium |
| CD | Cluster of designation |
| CFR | Code of Federal Regulations |
| CNS | Central Nervous System |
| CR | Complete Response |
| Creat | Creatinine |
| CT | Computerized Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DC | Dendritic cell |
| DCR | Disease Control Rate |
| DLT | Dose Limiting Toxicity |
| DMSO | Dimethyl sulfoxide |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EEA | European Economic Area |
| EORTC | European Organisation for Research and Treatment of Cancer |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| GFR | Glomerular Filtration Rate |
| GGT | Gamma-Glutamyl Transferase |
| Gluc | Glucose |
| Hb | Hemoglobin |
| HBV | Hepatitis B Virus |

| | |
|---|---|
| HCC | Hepatocellular Carcinoma |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| HLA | Human Leukocyte Antigen |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IF-ANA | Anti-nuclear antibodies |
| IFN | Interferon |
| IL | Interleukin |
| IMP | Investigational Medicinal Product |
| IRB | Institutional Review Board |
| LLN | Lower Limit of Normal |
| LMWH | Low Molecular Weight Heparin |
| MHC | Major Histocompatibility Complex |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mRCC | Metastatic Renal Cell Carcinoma |
| MRI | Magnetic Resonance Imaging |
| Na | Sodium |
| NCI | National Cancer Institute |
| ORR | Objective Response Rate |
| OS | Overall Survival |
| PD | Progressive Disease |
| PFS | Progression Free Survival |
| PPS | Per Protocol Set |
| PR | Partial Response |
| PT-INR | Prothrombin Time - International Normalized Ratio |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| RBC | Red Blood Cells |
| RCC | Renal Cell Carcinoma |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Stable disease |
| SFU | Sunitinib Follow-Up |
| SmPC | Summary of Product Characteristics |

| | |
|---|---|
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TKI | Tyrosine Kinase Inhibitor |
| TSH | Thyroid-Stimulating Hormone |
| TTF | Time to Treatment Failure |
| TTP | Time to Progression |
| ULN | Upper Limit of Normal |
| USPI | United States Product Insert |
| WBC | White Blood Cell |
| WHO | World Health Organization |

### 3.2 Definition of Terms

*NB:* Detailed definitions of terms from the updated guideline Response Evaluation Criteria In Solid Tumors (RECIST v1.1) [1] are included in *Section 10.2.2.2* and detailed definitions for Dose Limiting Toxicity (DLT) based on Common Terminology Criteria for Adverse Events (CTCAE) grading [2] for specific AEs are presented in *Section 11.5*.

| | |
|---|---|
| Baseline | The date of randomization is defined as baseline for OS and 18-month survival rate.<br>The centrally assessed CT performed at the Sunitinib Start Visit is defined as CT baseline for evaluation of PFS, response rate and time to progression (TTP) after start of sunitinib in intermediate- and high-risk patients, *Section 10.2.2.1*, *Section 10.2.2.2*, and *Section 10.2.2.3. Note*: For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, baseline for PFS, ORR and duration of response, and TTP is defined as the first imaging assessment after nephrectomy.<br>The Screening Visit is defined as baseline for all other assessments than those listed above. |
| Competent Authority (CA) | A government body or government appointed body that has legal authority to approve or disapprove clinical studies |
| Eastern Cooperative Oncology Group (ECOG) criteria (also referred to as WHO or Zubrod) [3] | 0 Fully active, able to carry on all pre-disease performance without restriction<br>1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work<br>2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours<br>3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours<br>4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair<br>5 Dead |
| High-risk mRCC patient according to Heng criteria [4] | Patients fulfilling three (3) to six (6) of the following prognostic factors:<br>• Hemoglobin (Hb) less than the lower limit of normal (LLN)<br>• Corrected Calcium (Ca) greater than upper limit of normal (ULN)<br>• Karnofsky performance status less than 80%<br>• Time for diagnosis to treatment less than one (1) year<br>• Neutrophils greater than ULN<br>• Platelets greater than ULN |
| Intermediate-risk mRCC patient | One (1) or two (2) of the following prognostic factors:<br>• Hb less than the lower limit of normal (LLN) |

| | |
|---|---|
| according to Heng criteria [4] | • Corrected Ca greater than upper limit of normal (ULN)<br>• Karnofsky performance status less than 80%<br>• Time for diagnosis to treatment less than one (1) year<br>• Neutrophils greater than ULN<br>• Platelets greater than ULN |
| Karnofsky performance status [5] | 100% Normal; no complaints; no evidence of disease<br>90% Able to carry on normal activity; minor signs or symptoms of disease<br>80% Normal activity with effort; some signs or symptoms of disease<br>70% Cares for self; unable to carry on normal activity or to do active work<br>60% Requires occasional assistance, but is able to care for most of his personal needs<br>50% Requires considerable assistance and frequent medical care<br>40% Disabled; requires special care and assistance<br>30% Severely disabled; hospital admission is indicated although death not imminent<br>20% Very sick; hospital admission necessary; active supportive treatment necessary<br>10% Moribund; fatal processes progressing rapidly<br>0% Dead |

# 4 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

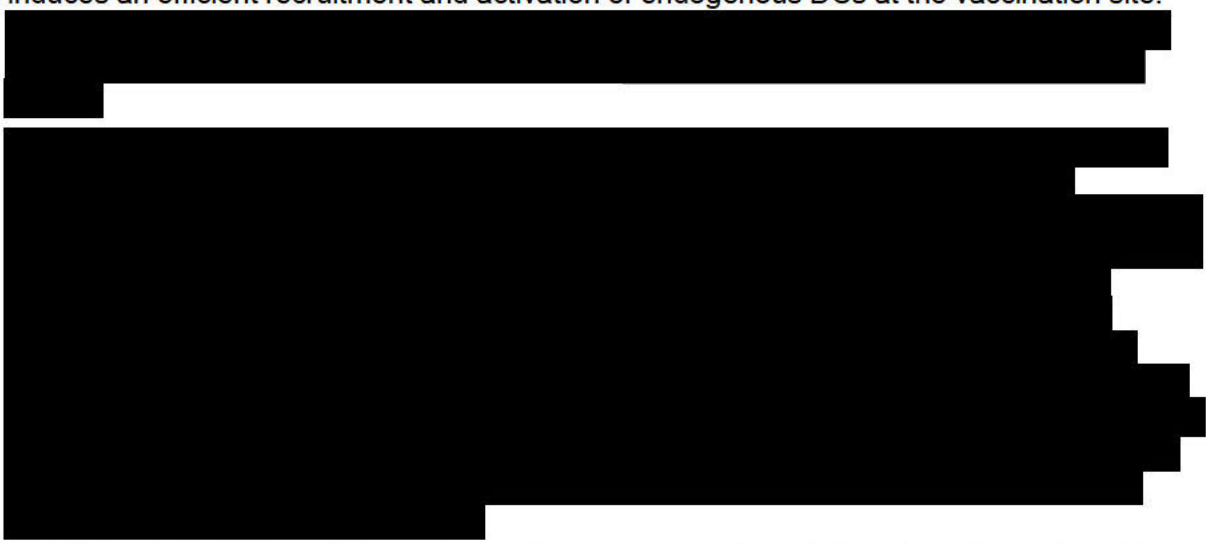
# 5 INTRODUCTION

## 5.1 Background

Renal cell carcinoma (RCC) is the most common form of kidney cancer and comprises 3% of all malignant tumors in adults [6]. Interleukin-2 (IL-2) was introduced as therapy for metastatic RCC (mRCC) over 20 years ago and systemic IL-2 or interferon-α (IFN-α) has remained the standard of care for patients with mRCC until recent years. Enhanced tumor biology understanding has resulted in the development of novel agents targeting angiogenesis and signal transduction pathways that has markedly improved treatment outcomes. Targeted agents such as tyrosine kinase inhibitors (TKIs), including sunitinib, pazopanib, sorafenib and axitinib are now considered standard treatments for mRCC [7]. Before their introduction, the median overall survival (OS) for patients with mRCC was around one (1) year, and only 10% of patients with mRCC survived past five (5) years. Following the introduction of targeted agents, a median OS of 43 months has set the new benchmark for patients belonging to the favorable Heng-risk group. However, treatment with targeted agents rarely achieves complete responses (CRs) and most patients develop resistance to therapy. Consequently, there is a growing interest in novel treatment approaches for mRCC such as immunotherapeutics.

The therapeutic vaccine developed by Immunicum AB, Intuvax, is composed of activated monocyte-derived dendritic cells (DCs) that have been stimulated with a combination of activating factors. As a result, at the time of vaccination a prominent and sustained production of desirable chemokines and DC-activating factors is achieved. Intuvax is manufactured from blood of healthy donors who are allogeneic in relation to the patient. This concept allows for patient-independent and large-scale production using standard methods. Therapeutic vaccination with Intuvax intratumorally does not involve co-administration of an antigen. Tumor antigens present within the injected target tumor tissue are expected to act as antigen source for recruited endogenous DCs.

The pre-clinical data obtained during development of Intuvax indicate that vaccination induces an efficient recruitment and activation of endogenous DCs at the vaccination site.



This is the third Intuvax-study in man and the second study in mRCC patients. A phase I/II study in hepatocellular carcinoma patients is ongoing. Twelve (12) patients were included during 2012-2013 at one (1) study site in Sweden in the first phase I study in patients with mRCC referred for nephrectomy. The diagnosis was based on radiological presentation. No pretreatment biopsies from the kidney(s) were collected. Patients with prior autoimmune disease, with ongoing immunosuppressive therapy, or any other active cancer were

excluded. The patients' metastatic load varied. Five (5) patients were in the high-risk group and seven (7) in the intermediate group, according to the Heng prognostic model [4]. The Intuvax injections were performed with the patient hospitalized three (3) days to ensure safe care, collection of vital signs and blood samples. The vaccinations were performed twice, 14 days apart, in all patients. Nephrectomy was performed two (2) weeks after the second vaccination. Three (3) different dose levels of DCs; 5 $x10^6$, 10 $x10^6$, and 20 $x10^6$, were administered.

No serious adverse events (SAEs) related to the vaccination were noted. Transient fever reactions with duration less than one (1) day and rash was noted in 5 out of 12 patients. All patients survived the postoperative three (3) month follow-up visit. No significant deviations in blood chemistry attributable to the vaccination procedure were noted. Accidental bile duct injury was inflicted in one (1) patient resulting in transient hepatic failure. The renal function was decreased after nephrectomy in all patients as expected but no further decrease was observed except for one (1) patient who developed progressive renal function deterioration due to a previously undetected plasma cell disorder/myeloma. There were no signs of any autoimmune reactions as measured by standard tests while a humoral donor-specific alloimmunization was seen in three (3) patients.

An increased number of tumor-specific lymphocytes were seen after vaccination in nine (9) patients indicating a systemic immune response. A dense infiltration of CD8+ T-cells was found in seven (7) nephrectomy specimens. Nephrectomy specimens with dense intratumoral T-cell infiltration exhibited only few and scattered CD8+ T-cells within the surrounding normal kidney parenchyma. These findings, together with the fact that the remaining renal function was not decreased more than anticipated, indicate that the observed cellular immune response was tumor specific and not directed towards normal renal structures. No correlation between Intuvax dose and intratumoral lymphocyte infiltration was observed. The degree of HLA-mismatch between vaccine-DCs and the patient was not correlating with degree of intratumoral CD8+ T-cell infiltration in this study.

The selected patient population had primary mRCC and consequently they can be considered as a poor prognostic group *per se*. In addition, unfavorable histology with sarcomatoid differentiation was more common than anticipated prior to study start; six (6) tumors presented sarcomatoid differentiation. Four (4) of these exhibited an extensive sarcomatoid differentiation (>20% of the tumor tissue), reflecting a highly unfavorable clinical presentation. All patients have progressed after nephrectomy and six (6) patients have received additional treatment with TKIs. The median OS in the subgroup of five (5) patients with high-risk/poor prognosis according to Heng criteria, of which four (4) patients have received additional TKI treatment, was 24.5 months. Additional treatments with surgery and radiotherapy have been given after progression to some patients.

In conclusion, the observed intratumoral infiltration of potentially cytotoxic CD8+ T-cells merit further studies in order to correlate this finding with clinical outcome. No correlation of DC dose and the immune response in the kidney could be identified. Circulating vaccine-DCs were transiently found in a minority of patients and usually in low numbers.

Fully mature allogeneic DCs have previously been tested in approximately 100 RCC patients using different administration routes [9,10,11,12,13]. These studies provide additional supporting safety information of the use of allogenic DC-based vaccines in treatment of RCC. Only mild AEs have been reported and no SAEs have been observed. The most commonly reported AEs in those studies were local reactions at the administration site (rash) and fever. No signs of autoimmunity have been observed.

## 5.2 Study Rationale

No curative treatment exists for mRCC, except in very few cases where a single metastasis can be surgically removed. General chemotherapy does not lead to remission and is therefore not used as regular treatment. Improved understanding of the underlying cellular mechanisms of the RCC pathogenesis has resulted in treatment evolvement from being predominantly based on cytokines (IFN-α2a and IL-2) to the use of targeted agents, such as sunitinib. However, complete and durable unmaintained remissions are rare, and obtained survival gain is limited. In addition, these interventions are associated with severe side effects and high costs. Consequently, there is a need for development of new therapies.

So far, no signs of tumor shrinkage related to Intuvax administration has been shown in Immunicum AB's clinical pilot studies in hepatocellular carcinoma (HCC) and mRCC. However, there are indications of extended OS suggesting that the tumor growth rate might be reduced as a result of Intuvax vaccination. Furthermore, post study case reports have shown objective tumor response in three (3) out of four (4) participating patients receiving sunitinib after tumor progression including one with Central Nervous System (CNS)-metastases and one with extensive sarcomatoid tumor differentiation. These two (2) cases of objective tumor responses are unexpected since both mRCC brain metastases as well as mRCC with extensive sarcomatoid tumor differentiation are known to be highly resistant to sunitinib treatment and therefore indicate that Intuvax followed by sunitinib may have a synergistic antitumor effect [14,15].

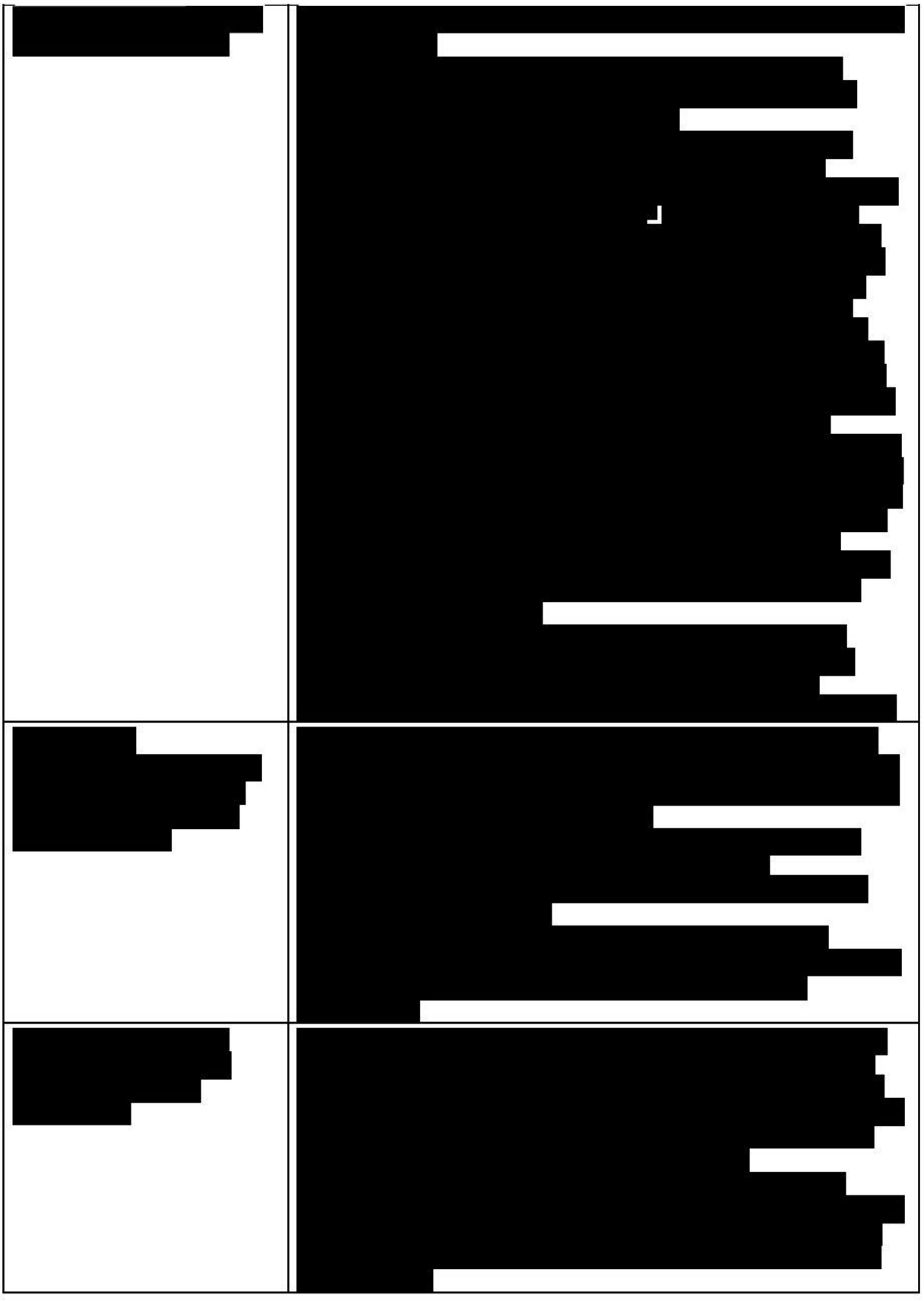
RCC is associated with immune dysfunction including shift from type 1 to type 2 T-cell cytokine response, increased numbers of myeloid-derived suppressor cells (MDSCs) and enhanced T regulatory (Treg) cell expression. It has been shown that sunitinib improves the immune suppression seen in the microenvironment of the tumor [16,17]. In a phase I/II clinical trial a positive effect of combining autologous DC immunotherapy with sunitinib was observed in advance stage mRCC patients [18]. A phase III study in a similar patient population is ongoing for further evaluation of the concept [19].

Immunicum AB's findings presented above together with the results reported in the literature on the use of autologous DCs in combination with sunitinib encourage Immunicum AB to further investigate the possibility of exploiting Intuvax vaccination when combined with sunitinib for the treatment of mRCC patients. It is postulated that Immunicum AB's allogenic DC vaccine will stimulate a more durable clinical and immunologic response in mRCC patients when used in a combined treatment setting.

## 5.3 Potential Risks and Benefits

[redacted]

[redacted]



**Clinical Risk/Benefit Assessment**

Treatment with Intuvax immunotherapy might potentially result in prolonged survival. The risk of serious immunologic reactions is expected to be low considering data from the supporting animal studies that have been performed and the completed phase I study in mRCC patients and the ongoing phase I study in HCC patients. The risk for a serious late immune reaction with secondary organ damage (most probably in the remaining kidney) is expected to be low considering the results from the same studies.

Intuvax-induced alloimmunization does not jeopardize future RBC transfusions, since RBC lack HLA antigen expression. Moreover, there is a very low risk that mRCC patients on sunitinib treatment will require platelet-transfusions or will be transplanted with an allogeneic organ. However, if severe thrombocytopenia occurs in patients that have developed HLA-antibodies due to prior Intuvax treatment, platelet transfusion can be conducted by selecting HLA-matched platelet donors. As treatment with Intuvax, followed by sunitinib, might prolong the survival in a patient population with poor prognosis, Immunicum believe the risk benefit overview is well balanced.

# 6 STUDY OBJECTIVES

## 6.1 Primary Objectives

The primary objectives are:

- To evaluate median OS from randomization in mRCC patients overall and by subgroup, i.e. in high-risk and in intermediate-risk patients separately, receiving two (2) vaccine doses of Intuvax pre-nephrectomy, followed by sunitinib initiated five (5) to eight (8) weeks post-nephrectomy and in non-vaccinated mRCC patients receiving sunitinib initiated five (5) to eight (8) weeks post-nephrectomy
- To evaluate 18-month survival rate from randomization in mRCC patients overall and by subgroup, i.e. in high-risk and in intermediate-risk patients separately, receiving two (2) vaccine doses of Intuvax pre-nephrectomy followed by sunitinib post-nephrectomy and in non-vaccinated patients receiving sunitinib post-nephrectomy

## 6.2 Secondary Objectives

The secondary objectives are:

- To evaluate safety and tolerability in high- and intermediate-risk mRCC patients receiving two (2) vaccine doses of Intuvax pre-nephrectomy followed by sunitinib post-nephrectomy and in non-vaccinated patients receiving sunitinib post-nephrectomy
- To evaluate PFS according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria from Sunitinib Start Visit in intermediate- and high-risk mRCC patients after receiving two (2) vaccine doses of Intuvax pre-nephrectomy followed by sunitinib post-nephrectomy and in non-vaccinated patients receiving sunitinib post-nephrectomy*
- To evaluate response and its duration according to RECIST 1.1 criteria from Sunitinib Start Visit in intermediate- and high-risk mRCC patients receiving two (2) vaccine doses of Intuvax pre-nephrectomy followed by sunitinib post-nephrectomy and in non-vaccinated patients receiving sunitinib post-nephrectomy*
- To evaluate time to progression (TTP) from Sunitinib Start Visit in intermediate- and high-risk mRCC patients receiving two (2) vaccine doses of Intuvax pre-nephrectomy followed by sunitinib post-nephrectomy and in non-vaccinated patients receiving sunitinib post-nephrectomy*
- To evaluate the number of infiltrating CD8+ T-cells in available diagnostic pre-biopsy (sample from either primary tumor or metastasis acceptable) and in the resected primary renal tumor in intermediate- and high-risk mRCC patients receiving two (2) vaccine doses of Intuvax pre-nephrectomy and in non-vaccinated patients

*_Note_: For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, baseline for PFS, ORR response and its duration, and TTP is defined as the first imaging assessment after nephrectomy.

## 6.3 [redacted]

[redacted]

# 7 INVESTIGATIONAL PLAN

## 7.1 Study Design and Plan-Description

The study is an open-label, randomized, controlled, two (2) armed, multicenter, phase II study. Intermediate- and high-risk mRCC patients according to Heng criteria are eligible for participation [4]. Stratified randomization based on Heng-risk categories applies. The patients are randomized in a consecutive order to one (1) of the following two (2) treatment arms when eligibility has been confirmed;

(i) Two (2) doses of Intuvax ($10x10^6$ DCs) administered intratumorally into the primary tumor 14 ±3 days apart followed by nephrectomy at least three (3) days after the second vaccine dose.

AND

Sunitinib treatment initiated five (5) to eight (8) weeks after nephrectomy, administered dose in accordance with the SmPC/USPI.

(ii) Sunitinib treatment initiated five (5) to eight (8) weeks after nephrectomy, administered dose in accordance with the SmPC/USPI.

The estimated number of patients to be randomized in the study is around 90. The patients will be randomized in a 2:1 (vaccine treatment arm [i]:control treatment arm [ii]) ratio. Stratification will be done at randomization for intermediate- and high-risk patients.

Patients randomized to treatment arm (i) are scheduled for 12 study visits and patients randomized to treatment arm (ii) are scheduled for 10 study visits during a study period of 78 weeks, see list below and *Figure 1*. In addition, all patients being exposed to any of the Investigational Medicinal Products (IMPs) will have a safety evaluation done for collection of SAEs up to 30 days after last dose of IMP administered in the study. The following visits apply for the two (2) patient populations:

- Screening Visit (Screening)
- Vaccination 1 Visit (Vacc1), applicable for patients randomized to treatment arm (i)
- Vaccination 2 Visit (Vacc2), applicable for patients randomized to treatment arm (i)
- Nephrectomy Visit (Nephrectomy)
- Sunitinib Start Visit (Sun-Start), five (5) to eight (8) weeks after Nephrectomy
- Sunitinib Follow-up Visits (SFU[6W] and SFU[12W]), every 6 weeks for 12 weeks or until locally CT-verified PD whichever occurs first
- Sunitinib Follow-up Visits (SFU[24W], SFU[36W], SFU[48W], and SFU[60W]), every 12 weeks until End-of study or until locally CT-verified PD whichever occurs first
- End-of-Study Visit (End-of-Study)

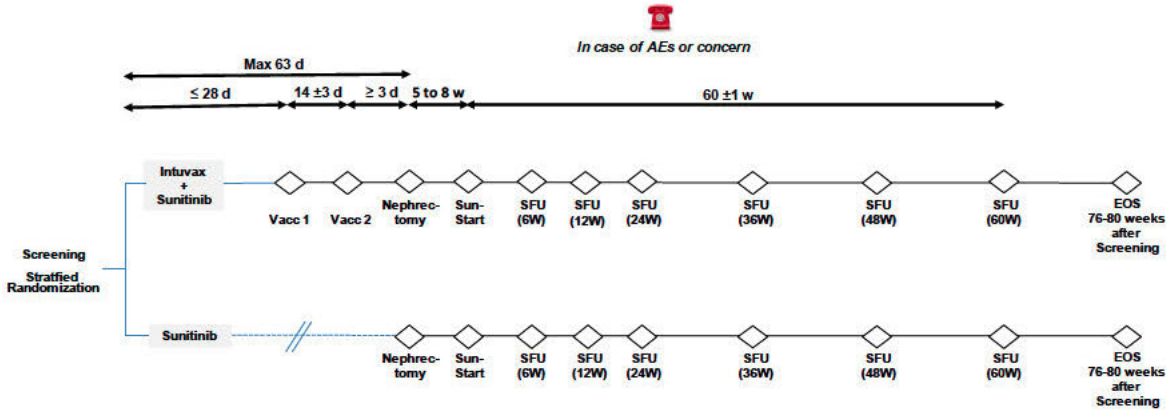
At the two (2) Vaccination Visits, the patients will be administered Intuvax ($10 x10^6$ DCs) intratumorally in the viable part of their primary tumor. Vaccine from the same batch (i.e. the same donor) will be used at both occasions. The patient will stay at the clinic at least four (4) hours after vaccination. Nephrectomy is done at least 3 days after the second vaccination and maximum 63 days after Screening. Sunitinib treatment is initiated five (5) to eight (8) weeks after nephrectomy, administered dose is in accordance with the SmPC/USPI.

All patients will be encouraged to contact the clinic in between study visits if they experience adverse events (AEs) or have any concerns. If follow-up of any symptoms is needed

between the planned visits, the patient will be scheduled for a visit as soon as possible and applicable assessments will be performed.

Post-study survival data (date of death) will be collected.

**Figure 1 Overall Study Design**




*Comment:* In addition to the visits included in the figure there will be a safety evaluation performed. Any SAE occuring up to 30 days after last dose of IMP administerered in the study will be collected from all patients being exposed to an IMP. Also post-study survival data (date of death) collection will continue on a yearly basis for a maximum of 5 years after collection of the last patient's 18 months survival data.

## 7.2 Study Procedures

### 7.2.1 Schedule of Study Events

The study assessments described in the sections below are presented in detail in *Section 10.2* (Efficacy assessments), *Section 10.4* (Demographic data and baseline characteristics) and *Section 10.5* (Safety assessments). Recording and reporting of AEs are described in detail in *Section 11* (Adverse Events).

The timing of all study events is presented in *Section 7.2.1.1* to *Section 7.2.1.9* and in *Table 2* (study flow chart), and *Table 3* (details on assessments in connection with vaccination for all patients randomized to Intuvax).

#### 7.2.1.1 Screening Visit

This visit is applicable for all patients.

*ACTIVITIES AND ASSESSMENTS:*

- Informed Consent, *Section 13.1.3*
- Demography, *Section 10.4.1*
- Medical and Surgical history, *Section 10.4.2*
- CT Scan to be done within 3 weeks from Screening Visit unless a CT scan has been performed in clinical routine within 6 weeks prior to Screening Visit, *Section 10.4.3*
- Brain imaging (preferably by contrast-enhanced) Magnetic Resonance Imaging (MRI) or CT to be done within 3 weeks from Screening Visit unless a CT scan has been performed in clinical routine within 6 weeks prior to Screening Visit, *Section 10.4.3*
- Prior Medication, *Section 10.4.4*
- Physical Examination, *Section 10.5.3*

- Vital Signs, *Section 10.5.4*
- ECG, *Section 10.4.5*
- Laboratory Safety Blood Assessments: Hematology, Clinical Chemistry including Glomerular Filtration Rate (GFR) based on Creatinine (Creat), Glucose (Gluc), Thyroid stimulating hormone (TSH), Thyroxine (free T4), and Prothrombin Time - International Normalized Ratio (PT-INR), Activated Partial Thromboplastin Time (APTT), and Pregnancy *Section 10.5.5*
- Laboratory Safety Urine Assessments, *Section 10.5.5*
- Additional Laboratory Blood Assessments: Serology (HIV, HBV, and HCV), *Section 10.4.6*, High resolution tissue typing of Human Leukocyte Antigens (HLA), *Section 10.4.7*
- ECOG score, *Section 10.2.3.1* and Karnofsky performance status, *Section 3.2*
- [redacted] *Section 10.2.3.2*
- Inclusion/Exclusion Criteria, *Section 8.2* and *Section 8.3*. To be checked when the results from all assessments made at Screening are available.
- Randomization, *Section 9.2*. To be done when eligibility has been confirmed.
- Confirmatory diagnostic biopsy in accordance with local routines prior to Vacc1 Visit, if required by local regulations and laws, *Section 9.2*.
- AEs, *Section 11.2*

A telephone contact will be made with the patient once randomization has been done in order to inform about which treatment the patient was allocated to and for scheduling the next study visit and a confirmatory biopsy if applicable.

Extra consent for vaccination for patients randomized to the vaccine arm, to be taken after randomization if required by local regulations.

#### 7.2.1.2 Vacc1 Visit (if applicable)

This visit is applicable only for patients randomized to Intuvax followed by sunitinib.

*TIME WINDOW:*
Vacc1 Visit to be done within 28 days after Screening

*ACTIVITIES AND ASSESSMENTS:*
Day before vaccination (optional):

The following assessments may be done the day before vaccination for logistical reasons:

- Laboratory Safety Blood Assessments: Hematology, Clinical Chemistry, PT-INR, and APTT, *Section 10.5.5*
- Pregnancy (either blood or urine), *Section 10.5.5*
- Laboratory Safety Urine Assessments, *Section 10.5.5*
- Physical Examination, *Section 10.5.3*
- ECOG performance status, *Section 10.2.3.1*
- AEs, *Section 11.2*

Day of vaccination (Pre-Vaccination):

*NB:* Absolute fasting for four (4) h prior to Intuvax administration applies.

- Concomitant Medication, *Section 10.4.4*
- Physical Examination unless done the day before, *Section 10.5.3*
- Vital Signs, *Section 10.5.4*
- Laboratory Safety Blood Assessments: Hematology, Clinical Chemistry, PT-INR, and APTT unless done the day before, *Section 10.5.5*
- Pregnancy (either blood or urine test) unless done the day before, *Section 10.5.5*
- Laboratory Safety Urine Assessments unless done the day before, *Section 10.5.5*
- Auto- and alloimmunization (baseline), *Section 10.5.6.1* and *Section 10.5.6.2*
- ECOG performance status unless done the day before, *Section 10.2.3.1*
- AEs, *Section 11.2*

Day of vaccination (Vaccination)

- Injection of Intuvax into the viable part of the renal tumor using CT or Ultrasound monitoring for confirmation of administration location, *Section 9.1.5*

Day of vaccination (Post-Vaccination)

- Vital Signs, *Section 10.5.4*
- AEs, *Section 11.2*
- Concomitant Medication, *Section 10.4.4*

#### 7.2.1.3 Vacc2 Visit (If applicable)

This visit is applicable only for patients randomized to Intuvax followed by sunitinib.

*TIME WINDOW:*
14 days (±3 days) after Vacc1 Visit

*ACTIVITIES AND ASSESSMENTS*
Exactly the same activities and assessments will be done at this visit as was done on Vacc1 Visit except for auto- and alloimmunization, *Section 7.2.1.2.*

#### 7.2.1.4 Nephrectomy Visit

This visit is applicable for all patients.

*TIME WINDOWS:*
At least 3 days after Vacc2 Visit and within 63 days from Screening Visit for patients randomized to Intuvax followed by sunitinib.

Within 63 days from Screening Visit for patients randomized to sunitinib only.

*ACTIVITIES AND ASSESSMENTS:*

Prior to Nephrectomy (may be done the day before vaccination for logistical reasons)

- Concomitant Medication, *Section 10.4.4*
- Laboratory Safety Blood Assessments:All patients: Hematology and Clinical Chemistry, for patients on anticoagulants: also PT-INR, and APTT, *Section 10.5.5*

- Laboratory Safety Urine Assessments, *Section 10.5.5*
- [redacted], *Section 10.2.3.2*
- AEs, *Section 11.2*

Nephrectomy and post Nephrectomy assessments

- Nephrectomy*, Section 9.1.1*
- Biopsies for central assessments of infiltrating CD8+ T-cells and immunohistology, *Section 10.2.2.4* and *Section 10.2.3.3*.
- AEs, *Section 11.2*
- Confirmation of mRCC diagnosis, *Section 10.4.2*

#### 7.2.1.5 Sun-Start Visit

This visit is applicable for all patients.

*TIME WINDOW:*
Five (5) to eight (8) weeks after Nephrectomy Visit

*NB:* The CT scan does not have to be done the very same day as the study visit. However, it has to be done within the above specified time window.

The laboratory safety blood and urine assessments do not have to be done the very same day as the study visit. However, it has to be done a maximum of 3 days prior to the visit.

*ACTIVITIES AND ASSESSMENTS*:

- CT Scan, *Section 10.4.3* including specification of target lesions *Section 10.2.2.2*
- Concomitant Medication, *Section 10.4.4*
- Physical Examination, *Section 10.5.3*
- Vital Signs, *Section 10.5.4*
- Laboratory Safety Blood Assessments: Hematology and Clinical Chemistry including GFR based on Creat, Gluc, TSH, and Thyroxine [free T4], *Section 10.5.5*
- Laboratory Safety Urine Assessments, *Section 10.5.5*
- Auto- and alloimmunization (only for patients treated with Intuvax), *Section 10.5.6.1* and *Section 10.5.6.2*
- ECOG performance status, *Section 10.2.3.1*
- [redacted] *Section 10.2.3.2*
- Start of sunitinib treatment. Dispense of sunitinib, *Section 9.1.4*
- AEs, *Section 11.2*

#### 7.2.1.6 SFU[6W], SFU[12W], SFU[24W], SFU[36W], SFU[48W], and SFU[60W]

These visits are applicable for all patients unless locally CT-verified PD occurs. In case of PD this visit should be considered the End-of-Study Visit.

If SFU[60W] is scheduled ≥76 weeks since Screening this visit should be considered the End-of-Study Visit, *Section 7.2.1.7*.

*TIME WINDOWS:*
SFU[6W]: 6 weeks (±7 days) after Sun-Start Visit
SFU[12W]: 12 weeks (±7 days) after Sun-Start Visit
SFU[24W]: 24 weeks (±7 days) after Sun-Start Visit
SFU[36W]: 36 weeks (±7 days) after Sun-Start Visit
SFU[48W]: 48 weeks (±7 days) after Sun-Start Visit
SFU[60W]: 60 weeks (±7 days) after Sun-Start Visit

*NB:* The CT/MRI scans do not have to be done the very same day as the corresponding study visits. However, each CT/MRI scan has to be done within the specified time window for the corresponding visit.

*ACTIVITIES AND ASSESSMENTS*:
The same activities and assessments will be done at these visits as was done on Sun-Start Visit except for auto- and alloimmunization, *Section 7.2.1.5.* In addition to dispense of sunitinib, the site personnel will collect unused and empty sunitinib packages (distributed at the previous visit) from the patient for drug accountability, *Section 9.1.4.*

#### 7.2.1.7 End of Study Visit

This visit is applicable for all patients.

*TIME WINDOW:*
78 ±2 weeks after Screening

*NB:* The CT/MRI scan does not have to be done the very same day as the study visit. However, it has to be done within the above specified time window.

*ACTIVITIES AND ASSESSMENTS*:
The same activities and assessments will be done at this visit as was done on SFU[6W] to SFU[60W] Visits, *Section 7.2.1.6.* No dispense of sunitinib will be done.

#### 7.2.1.8 Safety Evaluation 30 Days after Last Dose of Investigational Medicinal Product

The safety evaluation, i.e. collection of SAEs, as described in *Section 11.2* is applicable for all patients who have received any IMP.

*ACTIVITIES AND ASSESSMENTS*:
- SAEs, *Section 11.2*

#### 7.2.1.9 Extra Visits

Extra Visits are applicable for all patients if any symptoms need follow-up between planned visits.

*TIMING:*
The patient will be scheduled for a visit as soon as possible.

*ACTIVITIES AND ASSESSMENTS*:
- Concomitant Medication, *Section 10.4.4*
- Physical Examination, *Section 10.5.3*
- Vital Signs, *Section 10.5.4*

- Laboratory Safety Blood Assessments: Hematology and Clinical Chemistry. If the Extra Visit is scheduled after the Sun-Start Visit the assessments will also include GFR based on Creat, Gluc, TSH, and Thyroxine [free T4], *Section 10.5.5*
- Laboratory Safety Urine Assessments, *Section 10.5.5*
- ECOG performance status, *Section 10.2.3.1*
- AEs, *Section 11.2*
- Additional laboratory tests and other assessments as applicable to the discretion of the Investigator

#### 7.2.1.10 Post-Study Survival Information

This measure is applicable for all patients.

- Survival data, *Section 11.3*

### 7.2.2 Study Flow Charts

Detailed instructions on vital signs, AE collection, and blood sampling in connection to vaccination are shown in *Table 3*.

**Table 2 Study Flow Chart**

| **Visit** | **Screening**<br>**Day 1** | **Vacc1**<br>*Intuvax + sunitinib*[i]<br>**Day 2-28**<br>*sunitinib only:*<br>**N/A** | **Vacc2**<br>*Intuvax + sunitinib*[i]<br>**Day 16-42**<br>*sunitinib only:*<br>**N/A** | **Nephrectomy**<br>*Intuvax + sunitinib*[i]<br>**Day 19-63**<br>*sunitinib only:*<br>**Day 63 at the latest** | **Sun-Start**<br>**5 to 8 weeks after Nephr.**[j] | **SFU[6W]**<br>**6w ±7d after Sun-Start**<br>**SFU[12W]**<br>**12w ±7d after Sun-Start**<br>**SFU[24W]**<br>**24w ±7d after Sun-Start** | **SFU[36W]**<br>**36w ±7d after Sun-Start**<br>**SFU[48W]**<br>**48w ±7d after Sun-Start**<br>**SFU[60W]**[o]<br>**60w ±7d after Sun-Start** | **End-of-Study**<br>**78w ±2w after Screening** | **Safety Evaluation**<br>**Collection of SAEs up to 30 days after last dose of IMP** | **Extra visit**<br>**When needed** |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent | X | X[s] | | | | | | | | |
| Demography | X | | | | | | | | | |
| Medical and Surgical History | X | | | | | | | | | |
| CT/MRI scan[l] | X[m] | | | | X[t] | X[t] | | X[t] | | |
| Prior and/or Concomitant Medication | X | X | X | X[a] | X | X | | X | | X |
| Physical Examination | X | X | X | | X | X | | X | | X |
| Vital Signs[b] | X | X[c] | X[c] | | X | X | | X | | X |
| ECG | X | | | | | | | | | |
| Hematology and Clin. Chem. | X | X[d] | X[d] | X[a,d] | X[u] | X | | X | | X |
| GFR based on Creat, Gluc, TSH, and Thyroxine (free T4) | X | | | | X | X | | X | | X[n] |
| PT-INR | X | X[d] | X[d] | X[a,d] | | | | | | |
| APTT | X | X[d] | X[d] | X[a,d] | | | | | | |
| Pregnancy | X[e] | X[e] | X[e] | | | | | | | |
| Urinalyses | X | X[d] | X[d] | X[a] | X[u] | X | | X | | X |
| HIV/HBV/HCV and HLA | X | | | | | | | | | |

***Cont.*** **Table 2 Study Flow Chart**

| **Visit** | **Screening**<br>**Day 1** | **Vacc1**<br>*Intuvax + sunitinib*[:]<br>**Day 2-28**<br>*sunitinib only:*<br>**N/A** | **Vacc2**<br>*Intuvax + sunitinib*[:]<br>**Day 16-42**<br>*sunitinib only:*<br>**N/A** | **Nephrectomy**<br>*Intuvax + sunitinib*[:]<br>**Day 19-63**<br>*sunitinib only:*<br>**Day 63 at the latest** | **Sun-Start**<br>**5 to 8 weeks after Nephr.**[j] | **SFU[6W]** **6w ±7d after Sun-Start**<br>**SFU[12W]** **12w ±7d after Sun-Start**<br>**SFU[24W]** **24w ±7d after Sun-Start** | **SFU[36W]** **36w ±7d after Sun-Start**<br>**SFU[48W]** **48w ±7d after Sun-Start**<br>**SFU[60W]**[o] **60w ±7d after Sun-Start** | **End-of-Study**<br>**78w ±2w after Screening** | **Safety Evaluation**<br>**Collection of SAEs up to 30 days after last dose of IMP** | **Extra visit**<br>**When needed** |
|---|---|---|---|---|---|---|---|---|---|---|
| Auto- and Alloimmunization | | X[f] | | | X[f] | | | | | |
| ECOG performance | X | X[d] | X[d] | | X | X | | X | | X |
| Karnofsky performance | X | | | | | | | | | |
| [redacted] | X | | | X[a] | X | X | | X | | |
| Inclusion/Exclusion criteria | X[g] | | | | | | | | | |
| Randomization | X[g] | | | | | | | | | |
| Confirmatory diagnostic biopsy | X[p] | | | | | | | | | |
| Nephrectomy | | | | X | | | | | | |
| Biopsies (tumor x2, adjacent normal tissue) | | | | X | | | | | | |
| Administration of Intuvax[q] | | X[c] | X[c] | | | | | | | |
| Sunitinib dispense & return[h] | | | | | X[i] | X | | X[i] | | |
| AEs | X | X[c] | X[c] | X | X | X | | X[k] | X[v] | X |
| Diagnosis Confirmation[r] | | | | X | | | | | | |

a Assessment to be completed before nephrectomy and may be done the day before nephrectomy for logistical reasons
Locally analyzed Creatinine for patients included in the study before 28 August 2017 (if performed as part of clinical routine) to be recorded in eCRF

b Height only at Screening. Weight at all visits except for Vacc1 and Vacc2 Visits.

c See specific flow chart, *Table 3*, for detailed instructions on pre- and post-vaccination assessments.

d Physical examination, ECOG performance, and samples for safety lab and urinalyses may be taken the day before vaccination for logistical reasons
Locally analyzed results for Hb, WBC, platelets, PT-INR, and APTT need to be available before vaccination
Locally analyzed results for Hb, WBC, and clinical chemistry might need to be available prior to nephrectomy

Analysis of coagulation status at Nephrectomy is not necessary provided the patient is not on anticoagulant treatment. For patients on anticoagulants local sampling practice applies.

e Pregnancy test in blood at Screening, and in either blood or urine at Vacc1 and Vacc2 Visits. The pregnancy test result is needed prior to each vaccination.

f Samples for auto- and alloimmunization analyses will be collected prior to vaccination at Vacc1 Visit. Sampling at Sun-Start Visit only applicable for patients randomized to Intuvax.

g To be done when the results from all assessments made are available. Telephone contact with patient to inform about treatment and timing of next study visit.

h The prescribed dose to be in accordance with the SmPC/USPI including any dose adjustments.

i Return of sunitinib not applicable at Sun-Start Visit and Distribution not applicable at End-of-Study Visit. Standard of Care applies after End-of-Study.

j Start of sunitinib administration will be dependent on wound healing. The time window for initiation is five (5) to eight (8) weeks after Nephrectomy.

k Post-study collection of survival data.

l If CT cannot be used for some reason, MRI is acceptable. The same modality has to be used at all visits.

m CT scan to be done within 3 weeks before Screening unless a CT scan has been done in clinical routine within 6 weeks before Screening. Brain imaging (preferably by contrast-enhanced) MRI or CT to be done within 3 weeks before Screening Visit unless a CT scan has been performed in clinical routine within 6 weeks prior to Screening Visit

n To be done if Extra Visit is scheduled after Sun-Start Visit

o If SFU[60W] is scheduled ≥76 weeks since Screening this visit should be considered the End-of-Study Visit

p Confirmatory diagnostic biopsy in accordance with local routines prior to Vacc1 Visit, if required by local regulations and laws

q Absolute fasting for four (4) h prior to Intuvax administration applies

r Routine histology/Primary diagnosis is assessed locally

s Extra consent for vaccination for patients randomized to the vaccine arm, to be taken after randomization if required by local regulations

t The CT scan does not have to be done the very same day as the corresponding study visit. However, each CT scan has to be done within the specified time window for the corresponding visit

u The laboratory safety blood and urine assessments do not have to be done the very same day as the study visit. However, it has to be done within 3 days prior to the visit.

v SAEs only to be recorded and reported, see *Section 11.2*

**Table 3 Detailed Instructions on Assessments in Connection with Vaccination**

| Assessment | Pre-vaccination | Vaccination | Post-vaccination | | | | | |
|---|---|---|---|---|---|---|---|---|
| | > 2 h | 0 h | 15 min (±5 min) | 30 min (±10 min) | 60 min (±10 min) | 2 h (±10 min) | 3 h (±10 min) | 4 h (±20 min) |
| Intuvax injection | | X | | | | | | |
| BP | X | | X | X | X | X | X | X |
| HR | X | | X | X | X | X | X | X |
| Body temperature | X | | | X | X | X | X | X |
| AEs | X | | X | X | X | X | X | X |

### 7.3 Discussion of Study Design, Including the Choice of Control Groups

Intuvax is developed as an immune primer for cancer treatment that preferably should be combined with a drug that acts in synergy with Intuvax by inhibiting tumor-induced immunosuppression. In this study, Intuvax is given in combination with sunitinib, which like several other TKIs is known to inhibit myeloid-derived suppressor cells [25]. Based on current ESMO and NCCN guidelines [26, 27, 28] today's standard of care both in US and in the majority of the European countries involves initiation of systemic treatment with a TKI (including sunitinib or pazopanib) approximately 6 weeks post nephrectomy for all patients regardless of prognosis, i.e. poor (high risk) or intermediate. It is anticipated that all patients will benefit more from vaccination with Intuvax the sooner TKI treatment is initiated after performed nephrectomy.

Sunitinib alone was chosen as the active control for the study based on its documented positive impact on tumor response, PFS and OS in patients with mRCC. As discussed in *Section 5.2* it is hypothesized that sunitinib might contribute to an increased Intuvax efficacy.

### 7.4 Study Period

Expected timelines in the study:

Start of inclusion: Q2 2015

Planned last patient last study visit or last patient's safety evaluation (up to 30 days after the last patient's last dose of an IMP), whichever occurs later: Q3 2019

### 7.5 End of Study

The end of study is defined as the last patient last visit (LPLV) or the last patient's safety evaluation (up to 30 days after the last patient's last dose of an IMP), whichever occurs later.

# 8 SELECTION OF STUDY POPULATION

## 8.1 Number of Patients

The estimated number of patients to be randomized in the study is around 90. The patients will be randomized in a 2:1 (vaccination:control) ratio. Stratification will be done at randomization for intermediate- and high-risk patients, *Section 3.2*, and *Section 9.2*.

The choice of sample size is discussed in *Section 12.2*.

The study will be performed at approximately 25 sites in EU and approximately 5 sites in US. Competitive recruitment will apply.

## 8.2 Inclusion Criteria

The patients have to meet all of the following criteria to be eligible to enter the study:

1) Newly (<6 months) diagnosed RCC (histological/cytological verification is optional) with at least one (1) CT-verified metastasis ≥10 mm for which complete metastasectomy is not planned. US patients must have verified clear-cell tumor histology
2) Planned resection of primary tumor
3) Primary tumor diameter ≥40 mm
4) Candidate for first-line therapy with Sunitinib initiated five (5) to eight (8) weeks after nephrectomy
5) Female or male ≥18 years of age
6) Willing and able to provide informed consent
7) Adequate hematological parameters, i.e.:
   - B-Leukocyte count ≥4.5 x$10^9$/L
   - B-Platelet count ≥150 x$10^9$/L
   - B-Hemoglobin (Hb ≥90 g/L
8) Serum-creatinine and serum-bilirubin ≤1.5 × ULN. Serum-ALAT and serum-ASAT ≤2.5 × ULN (or ≤5 in case of liver metastases)
9) Female who has been post-menopausal for more than one (1) year or female of childbearing potential agreeing to use a highly efficient method of contraception (i.e. a method with less than 1% failure rate [e.g. sterilization, hormone implants, hormone injections, some intrauterine devices, or vasectomized partner or combined birth control pills]) from Screening until 90 days after last dose of Intuvax and/or until completed sunitinib treatment whichever occurs later. Female of childbearing potential must have a negative blood pregnancy test at Screening, and if randomized to vaccination a negative blood or urine pregnancy test within one (1) day before each dose of Intuvax) and must not be lactating.

   or

   Male agreeing to use condoms from Screening until 90 days after last dose of Intuvax and/or until completed sunitinib treatment whichever occurs later, or male having a female partner who is using a highly efficient method of contraception as described above.

### 8.3 Exclusion Criteria

Patients meeting any of the following criteria will not be permitted to enter the study:

1) Life expectancy less than 4 months
2) CNS metastasis that is symptomatic or progressing or untreated or that required current therapy (e.g. evidence of new or enlarging CNS metastasis or new neurological symptoms attributable to CNS metastases)
3) Active autoimmune disease which requires treatment with systemic immunosuppressive agents, e.g. inflammatory bowel disease, multiple sclerosis, sarcoidosis, psoriasis, autoimmune hemolytic anemia, rheumatoid arthritis, SLE, vasculitis, Sjögren's syndrome, scleroderma, autoimmune hepatitis, and other rheumatological diseases
4) Treatment with per oral systemic corticosteroids exceeding 10 mg/day within 7 days before Screening until Nephrectomy (inhaled, intranasal and local steroids acceptable irrespective of dose)
5) Known cardiomyopathy and/or clinically significant abnormal ECG findings at Screening disqualifying the patient from nephrectomy and subsequent sunitinib treatment
6) Karnofsky performance status <70%, *Section 3.2*
   For patients in **France** Karnofsky performance status ≤70%, *Section 3.2*
7) National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 hemorrhage within 28 days before Screening
8) Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication
9) Clinically significant gastrointestinal abnormalities
10) Uncontrolled hypertension or uncontrolled diabetes mellitus
11) Pulmonary embolism within 12 months prior to Screening
12) Prior history of invasive cancer within 5 years before Screening, except for adequately treated *in situ* carcinomas or non-melanoma skin cancer
13) Ongoing infection that requires parenteral treatment with antibiotics
14) Active or latent virus disease (HIV, HBV and HCV)
15) ECOG performance status >2 after optimization of analgesics, *Section 3.2*
16) Abnormal or clinically significant coagulation parameters at the discretion of the investigator, i.e.:
    - Prothrombin Time - International Normalized Ratio (PT-INR)
    - Activated Partial Thromboplastin Time (APTT)

    Patients being treated with anticoagulants are excluded if the coagulation parameters are outside the therapeutic intervals as described in the SmPC/USPI for the administered treatment
17) Known major adverse reaction/event in connection with previously made vaccination (e.g. asthma, anaphylaxis or other serious reaction)
18) Known hypersensitivity or allergy to sunitinib or to chemically related products or likely to be exacerbated by any component of the study products

19) Prior systemic antitumor therapy within 28 days before Screening Visit. However, local radiation therapy to any area except for the abdominal/retroperitoneal area including the kidney tumor is allowed
20) Exposure to other investigational products within 28 days prior to Screening Visit
21) Patients on anticoagulants for whom temporarily stop and start, supported by low molecular weight heparin (or other anticoagulation therapy at the discretion of the Investigator and/or per local standard of care) during vaccination and nephrectomy, is not an option
22) History of alcohol or substance abuse
23) Any reason that, in the opinion of the Investigator, contraindicates that the patient participates in the study

### 8.4 Restrictions

Intuvax: Treatment requires absolute fasting for a period of 4 hours prior to vaccination.

Sunitinib: Restrictions for treatment as in the SmPC/USPI for Sutent® (sunitinib), e.g. avoid concomitant administration of potent CYP3A4 inducers or inhibitors.

Nephrectomy: Same restrictions apply as in clinical routine.

### 8.5 Removal of Patients from Therapy or Assessment

Patients are free to discontinue their participation in the study at any time. Withdrawal from the study will not affect or prejudice the patient's further care or treatment. Patients may be withdrawn from study treatment and assessments at any time, if deemed necessary by the Investigator.

Patients who discontinue treatment with Intuvax and/or sunitinib for safety reasons (including DLT, see *Section 11.5*) or due to concomitant medication (*Section 9.6*) will not necessarily be considered withdrawn from the study unless there are other reasons for withdrawal. They should return for all following visits and assessments until PD.

Examples of reasons for withdrawal of patients from this study are:

- Progressive disease on sunitinib treatment
- Screening failure
- The decision of a patient to withdraw from the study (i.e. if the patient withdraws informed consent)
- Administration of concomitant medication prohibited by this protocol, *Section 9.6*
- Pregnancy
- Patient is lost to follow-up
- RCC diagnosis is not confirmed by histological findings from the biopsy collected at nephrectomy or, if applicable, from confirmatory pre-study treatment diagnostic biopsy

The reason and date the patient is withdrawn from the study and subsequent planned replacement therapy will be documented in the electronic case report form (eCRF).

All patients that have received IMP must have safety evaluations for 30 days after the last dose of IMP, *Section 11.2.*

If a patient is withdrawn from further assessments, the Investigator should attempt to complete all discharge procedures, i.e. End-of Study Visit. All AEs should be followed up according to *Section 11.2*.

If a patient is withdrawn from the study, all data collected until the time of withdrawal will be used in the analyses.

Survival data (including post-study survival data if applicable) will be collected and analyzed for all patients withdrawn from the study, *Section 11.3.*

Patients randomized to Intuvax who withdraw from the study before administration of the first dose of Intuvax will be considered screening failures. Patients randomized to sunitinib alone who withdraw from the study before any assessments made at the first visit following Screening will be considered screening failures.

Only patients considered screening failures will be replaced.

### 8.6 Premature Termination of the Study

The Investigator or the Sponsor may terminate this study prematurely for any reasonable cause. The Institutional Review Board(s) (IRBs)/Independent Ethics Committee(s) (IECs) and Competent Authorities (CAs) should be informed promptly.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study, or potential study patients
- A decision on the part of the Sponsor to suspend or discontinue development of Intuvax

If the CA obtains information that raises doubts about the safety or scientific validity of the clinical study, the CA can suspend or prohibit the study. Before the CA reaches its decision it shall, except where there is imminent risk, ask the Sponsor and/or the Investigator for their opinion, to be delivered within one week (Directive 2001/20/EC, Article 12, Section 1).

If the study is prematurely terminated or suspended for any reason, the Investigator/Institution should promptly inform the study patients and should assure appropriate therapy and follow-up for the patients.

### 8.7 Study Stopping Criteria

Study stopping criteria are defined as:

- Any death within 30 days of Intuvax administration that is not clearly attributable to surgery or disease progression
- Any CTCAE grade 4 autoimmune disorder
- Any toxicity that is unexpected, significant or unacceptable risk to the patients enrolled in the study, or potential study patients, *Section 8.6*

The identification of a study stopping criterion in a patient will result in the permanent discontinuation of Intuvax in this patient and the enrolment will be temporarily held until an appropriate evaluation of the cause of the toxicity has been determined and a correction action plan is established if needed.

The medical monitor should be notified immediately and the patient should be followed for safety as clinically indicated until the toxicity resolves and in the opinion of the investigator, no further follow-up regarding the toxicity is needed (minimum of at least 30 days after last dose of IMP).

# 9 TREATMENT OF PATIENTS

## 9.1 Investigational Medicinal Products

### 9.1.1 Treatment Regimens

Patients will be randomized to one (1) of the following two (2) treatment regimens:

(i) Two (2) doses of Intuvax ($10x10^6$ DCs) administered intratumorally into the primary tumor 14 ±3 days apart followed by nephrectomy and sunitinib initiated five (5) to eight (8) weeks after nephrectomy for all patients (administered dose in accordance with the SmPC/USPI)

(ii) Sunitinib initiated five (5) to eight (8) weeks after nephrectomy for all patients (administered dose in accordance with the SmPC/USPI)

Patients randomized to Intuvax will have their first vaccination within 28 days from Screening Visit.

All patients will have nephrectomy in accordance with local practice.

Patients randomized to sunitinib only will have nephrectomy done within 63 days from Screening.

Patients randomized to Intuvax will have nephrectomy done 3 days or later after the second vaccination and within 63 days from Screening. A patient randomized to Intuvax will have a 14 to 20 day delay of Nephrectomy as compared to if the patient had been randomized to sunitinib ony.

### 9.1.2 Identity of Investigational Medicinal Products

Intuvax

The Intuvax administered is a cryopreserved dendritic cell suspension containing $11.7x10^6$ viable and HLA class II expressing cells in 1 mL heat-inactivated AB plasma, supplemented with 10% dimethyl sulfoxide (DMSO). One (1) mL Intuvax is filled in vials which are stored at -150°C or below.

The IMP is thawed at the clinical site at the time for vaccination. No preparation of the IMP prior to vaccination is needed, *Section 9.1.4*.

Sunitinib

Marketed products of sunitinib will be used in this clinical study.

### 9.1.3 Packaging and Labelling of Investigational Medicinal Products

[redacted]

All manufacturing is performed in accordance with current Good Manufacturing Practice (cGMP) and with approved license for production of cell-based advanced therapeutic medicine products.

The labelling of the primary and secondary packaging of Intuvax and the supplement label for sunitinib will be according to US investigational labelling requirement per 21 Code of Federal Regulations (CFR) 312.6, EudraLex volume 4, Annex 13 Good manufacturing practices for Medicinal products for human and veterinary use and applicable local regulatory requirements.

[redacted], serves as central depot and manage supply of Intuvax to all local depots and participating sites.

### 9.1.4 Storage, Handling and Dispensing of Investigational Medicinal Products

Intuvax

Intuvax is transported and stored at -150 °C or below in a low temperature freezer or in liquid nitrogen. [redacted]

A study specific manual describing all details regarding handling, transport and preparation of the IMP will be available prior to study start.

In summary, Intuvax is delivered from the manufacturer to a central depot. The central depot will subsequently deliver the Intuvax to the local depot/pharmacy (or equivalent facility) where it will be stored until vaccination.

The responsible person at the central depot will arrange for Intuvax delivery to the concerned local depot/pharmacy (or equivalent facility) upon the receipt of a randomization alert from the Interactive Web Response System (IWRS). Minimum two (2) doses of vaccine from the same batch will be shipped to the pharmacy no later than the day before the patient's first vaccination. The pharmacy or delegated person is responsible for vaccine handling prior to administration.

The vaccine will be thawed at the clinical site and administrated without any additional preparation as soon as possible after complete thawing (but no later than 60 minutes from start of thawing), *Section 9.1.5*.

Sunitinib

Sunitinib is stored at room temperature in accordance with the SmPC/USPI and local clinical practice. The patients will receive the amount needed until next planned visit with a start at the Sunitinib Start Visit. The patients will be instructed on how to administer and store sunitinib. The patients will be asked to bring all unused and empty packaging to the clinic at the next planned visit. This procedure will be repeated at all following study visits.

### 9.1.5 Administration of Investigational Medicinal Products

Intuvax

After thawing, all suspension in the vial, e.g. one (1) mL is drawn and the injection needle is filled. The vaccination is done into the viable part of the renal tumor using CT or Ultrasound guidance and monitoring for confirmation of administration location. There is no need to flush the needle with saline since the dead space in the needle has been accounted for.

The total volume injected is recorded on a worksheet and in the eCRF at each Vaccination Visit.

The Intuvax administration must be done by a trained and qualified radiologist/urologist/ /surgeon using an antiseptic procedure in a facility equipped for invasive treatment.

Sunitinib

Per oral administration initiated five (5) to eight (8) weeks after nephrectomy for all patients Administered dose should be in accordance with the SmPC/USPI.

In case of unacceptable sunitinib side-effects the standard on/off schedule of 4 weeks on/ 2 weeks off (schedule 4/2) can be changed to 2 weeks on/1 week off (schedule 2/1). Retrospective data from patients treated with schedule 2/1 (50 mg/day) indicates superior PFS compared to those obtained with schedule 4/2. In addition, the reported safety profile and tolerance for schedule 2/1 justify its use in place of schedule 4/2 [29].

## 9.2 Method of Assigning Patients to Treatment Groups

At Screening the patient will be assigned a site specific screening number. This number will be generated automatically by Trial-on-Line, the electronic data capture (EDC) system used in the study. The screening number will be in the following format XX-YYYY. The letter XX is the site number and YYYY the consecutive patient number starting at 1001 at each site. The screening number will be used to identify the patient throughout trial participation.

Two (2) randomization lists are generated by [redacted] using a global randomization system. One (1) to be used for randomization of high-risk patients and one (1) to be used for randomization of intermediate-risk patients. One (1) copy of each randomization list is kept in a sealed envelope in a locked cabinet at [redacted] and one (1) copy is sent to the IWRS provider. Randomization codes will be strictly sequential within blocks as patients are eligible for randomization. The randomization code will not be available to any person involved in the conduct or evaluation of the trial before the trial database is locked.

When all results from the assessments made at Screening are available and the Investigator has confirmed eligibility and Heng-risk category for the patient the study coordinator will log into the IWRS and receive randomization and treatment information. The study nurse will make a telephone contact with the patient and inform about treatment and timing of next study visit. *NB:* If local regulations and laws require a confirmatory diagnostic biopsy before vaccination (i.e. systemic treatment) patients randomized to Intuvax will be booked for a biopsy collection visit prior to Vacc1 Visit. All participating US patients need a diagnostic pre-biopsy made at Screening in order to evaluate eligibility for sunitinib treatment following nephrectomy.

In case a patient randomized to Intuvax and sunitinib treatment withdraws prior to first dose of Intuvax or a patient randomized to sunitinib treatment only withdraws prior to any assessments made at the first visit following Screening they are considered screening failures, *Section 8.5*. A patient withdrawal contact will be performed via the IWRS allowing for additional patient inclusion until 90 patients have initiated study treatment.

If a patient is not given treatment according to the randomization list, no attempt should be made to remedy the error once IMP has been dispensed. [redacted] must be notified as soon as the error is discovered and the error must be adequately documented.

## 9.3 Selection of Doses in the Study

Intuvax

The Intuvax dose to be administered in this study consists of 10 x$10^6$ viable and HLA class II expressing DCs. The outcome of Immunicum AB's first-in-man study of Intuvax in RCC

patients (Protocol No.: IM-101 and EudraCT No.: 2011-002039-25) in which doses of 5 x$10^6$, 10 x$10^6$, and 20 x$10^6$ DCs have been administered formed the basis for the dose selection.

The same dose of Intuvax will be injected two (2) times with a 14 ±3 day interval into the viable part of the renal primary tumor during the period while the patient is awaiting nephrectomy. The patients will receive the vaccine cells from the same batch (i.e. the same donor) at both administrations. A survival of between 24 and 48 hours is expected for the injected DCs after the first vaccination and a considerably reduced survival after the second injection. On the other hand, the second administration triggers the inherent immune response memory initiated by the first administration. A 14 days period between dosing is suggested to avoid administration of a second dose to a patient with an exhausted immune system. This time-window also reflects the time between diagnosis and nephrectomy in routine care.

The suggested dose is also supported by the pre-clinical program on Intuvax that has been performed by Immunicum AB consisting of four (4) studies in rat. In order to mimic the human situation vaccine cells derived from circulating monocytes were used in the proof-of-concept study (VP10-14), the pilot-toxicology study (VP10-17), the toxicology study (VP10-43), and the biodistribution study (AB11-01). The toxicology study VP10-43 did not reveal any major changes in general health status, vital signs and laboratory parameters.

Sunitinib

The sunitinib dose to be administered in this study is in accordance with the SmPC/USPI from start of treatment.

**Duration of treatment**

Intuvax

Two (2) injections of Intuvax will be administered with 14 ±3 days interval followed by Nephrectomy in accordance with local routine at least 3 days after the second vaccination and maximum 63 days from Screening.

Sunitinib

Administration to be initiated five (5) to eight (8) weeks after nephrectomy for all patients. Treatment will continue until End-of-Study (78 ±2 weeks after Screening) unless terminated due to unacceptable side-effects or other reasons. For post study treatment see *Section 9.9*.

**Active control, dosage and mode of administration**

Sunitinib is the active control in this study, *Section 9.1.1*. Treatment (including dose adjustments etc.) will be in accordance with the SmPC/USPI from start of treatment.

## 9.4 Selection and Timing of Dose for Each Patient

The patients will be randomized to treatment when the results from all assessments made at Screening are available.

No time window between dosing of different patients applies in this study.

The time window between Intuvax doses for the individual patient is 14 ±3 days. If the individual patient experiences a DLT in connection with first vaccination, *Section 11.5* no second vaccination will be given to that patient.

## 9.5 Blinding

This is an open label study.

## 9.6 Prior and Concomitant Therapy

The following medications/therapies are prohibited during the study and within 28 days prior to Screening:

- Other investigational products
- Other systemic antitumor therapy.
- Local radiation therapy to any area except for the abdominal/retropertioneal area including the kidney tumor is allowed. The impact of any palliative radiotherapy administered on evaluable lesions must be discussed with the Medical Monitor and documented in the eCRF

The following medications are prohibited within 7 days prior to Screening Visit until Nephrectomy:

- Systemic per oral corticosteroids exceeding 10 mg/day. However, inhaled, intranasal and local (per cutaneous) steroids for treatment of skin disorders, chronic obstructive lung disease, asthma, or allergy are acceptable irrespective of dose.

Specific instructions in relation to the nephrectomy and Intuvax vaccinations:

- Concomitant oral antithrombotic, e.g. acetylsalicylic acid (ASA), withdrawal and re-start to be done according to local practice in connection with the nephrectomy and according to local practice for invasive examinations in connection with Intuvax vaccinations.
- Anticoagulants, local practice applies for start and stop of anticoagulant treatment and shift to/use of low molecular weight heparin treatment in connection with

nephrectomy and according to local practice for invasive examinations in connection with Intuvax vaccinations

Medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator as per local guidelines and Standard of Care. Whenever there is a medication available to prevent or alleviate a symptom it will be offered to the patient.

Patients who respond inadequately to sunitinib treatment and need to change systemic anti-cancer therapy should be scheduled for an End-of-Study Visit before being withdrawn from the study, *Section 8.5*. As described in *Section 11.2* safety evaluation must also be performed up to 30 days after the patient's last dose of IMP administered in the study.

The use of all medication by the patient must be recorded in the eCRF, *Section 10.4.4*.

In connection with the surgery various concomitant medications such as anesthesia, fluid substitution/blood substitution are part of clinical routine and these concomitant medications should not be recorded in the eCRF. Only concomitant medications not normally used in connection with the post-operative course after nephrectomy should be recorded in the eCRF.

## 9.7 Treatment Compliance

Intuvax

Administration will be done at the clinic by trained study personnel. Treatment compliance will be accomplished by documenting in record (i.e. the drug accountability, preparation, administration logs, the patients' eCRF and medical records) information on, but not limited to: the batch number of the IMP used, the time-point for preparation/thawing, the time-point for administration, if CT or Ultrasound was used for confirmation of administration location, and signatures of designated site staff preparing and administering the IMP.

Any deviations will be documented on the appropriate eCRF page.

Sunitinib

Patient compliance will be evaluated by unused tablet counts and check of empty packaging. Patients will be asked to return all unused and empty packaging material at the next clinic visit. The number of unused tablets will be counted upon return and recorded in the drug accountability log kept at the site. The sunitinib compliance including any deviations will be documented in the patients' eCRF.

## 9.8 Drug Accountability

Intuvax and sunitinib accountability, i.e. documentation of deliveries and return between the manufacturer, storage center, pharmacy, and/or the clinic shall be maintained.

It is the responsibility of the Investigator or trained designee to determine Intuvax and sunitinib accountability and complete the drug accountability log.

Drug accountability will be reviewed by the monitor during interim site visits and at the completion of the trial.

At the end of the study when overall drug accountability have been completed any unused IMP should be handled by the pharmacy according to instructions provided by the Sponsor.

A list of IMP, used, or returned must be prepared and signed by the Investigator or designee; an account must be given for any discrepancies.

Copies of all Drug Receipt Confirmations, Returned Clinical Supplies Reconciliation Forms and Drug Accountability Logs will be retained in the study file. These forms are subject to regulatory inspection at any time.

### 9.9 Post Study Treatment

Intuvax is an IMP under development and will consequently not be available for treatment of the patients after study completion.

Immunicum AB will pay the patients' sunitinib treatment during their participation in the study except for US patients who have health insurance that covers these costs as part of standard of care.

After end of study participation, patients will continue treatment in accordance with clinical praxis, i.e. as per local guidelines and Standard of Care.

# 10 STUDY ASSESSMENTS

## 10.1 Primary, Secondary, [redacted] Endpoints

Primary endpoints

- OS from randomization overall in mRCC patients and by each subgroup, i.e. in high-risk and in intermediate-risk mRCC patients
- 18-month survival rate from randomization overall in mRCC patients and by each subgroup, i.e. in high-risk and in intermediate-risk mRCC patients

Secondary endpoints

- Frequency and proportion of AEs including clinical significant changes in laboratory tests and vital signs from Screening
- PFS from start of sunitinib according to RECIST 1.1*
- Proportion of Objective Response Rate (ORR) from start of sunitinib treatment and duration of response in each subgroup*
- TTP from start of sunitinib treatment*
- Relative number of tumor infiltrating CD8+ T-cells in the resected primary tumor compared to relative number of infiltrating CD8+ T-cells in available diagnostic pre-biopsy (sample from either primary tumor or metastasis acceptable)

**Note:* For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, baseline for PFS, ORR and duration of response, and TTP is defined as the first imaging assessment after nephrectomy.

[redacted]

[redacted]

## 10.2 Efficacy Assessments

### 10.2.1 Primary Efficacy Variables and Assessments

#### 10.2.1.1 Overall Survival (OS)

OS is defined as time from randomization to death from any cause.

The OS reported from patients according to Heng criteria in the two (2) different treatment arms is a primary efficacy variable.

#### 10.2.1.2 Eighteen-(18)-Month Survival Rate

18-month survival rate is defined as the proportion of patients alive 18 months after randomization.

### 10.2.2 Secondary Efficacy Variables and Assessments

#### 10.2.2.1 Progression Free Survival (PFS) from Start of Sunitinib

PFS from start of sunitinib is defined as time from Sunitinib Start Visit to PD or death following sunitinib initiation from any cause, whichever occurred first. PFS from start of sunitinib will be evaluated per stratum and in total from the two (2) different treatment arms as a secondary efficacy variable.

Note: For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, sunitinib treatment did not have to be initiated at a fixed time point. For these patients, the first imaging assessment after nephrectomy will be used as baseline for evaluation of PFS, irrespective of whether or not the imaging assessment coincided with sunitinib treatment start. Further details will be provided in the Statistical Analysis Plan (SAP).

#### 10.2.2.2 Objective Response Rate and Duration of Response and Stable Disease from Start of Sunitinib

Evaluation of tumor response is based on centrally assessed CT scans, *Section 10.4.3*, according to the RECIST 1.1 guideline [1].

Definitions - RECIST v1.1

a) Measurable Disease

The presence of at least one (1) measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology. The same measurable and non-measurable lesions will be followed by RECIST v1.1. Disease progression will be determined using RECIST v1.1 criteria.

- Malignant lymph nodes
  To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness

recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

- Baseline documentation of "Target" and "Non-Target" lesions
  All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
  - ***Target lesions*.** 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. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
  - ***Non-target lesions*.** All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

b) Response Criteria

**Table 4 Target Lesions Evaluation Criteria**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. |
| Partial Response (PR) | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters |
| Progressive Disease (PD) | At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*NB*: the appearance of one or more new lesions is also considered progression). |
| Stable Disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study |

**Table 5 Non-Target Lesions Evaluation Criteria**

| | |
|---|---|
| Complete Response (CR) | Disappearance of all non-target lesions and normalization of tumor marker level |
| Progressive Disease (PD) | Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions[a] |

| | |
|---|---|
| Incomplete Response/ Stable Disease (SD) | Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits |

[a] Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the Investigator.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment Sunitinib until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of the measurement criteria.

**Table 6 Evaluation of Best Overall Response**

| Target Lesions | Non-Target Lesions | New Lesion | Overall response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Incomplete response/SD | No | PR |
| PR | Non-PD | No | PR |
| SD | Non-PD | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Note: For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, the first imaging assessment after nephrectomy will be used as baseline for evaluation of best overall response, irrespective of whether or not the imaging assessment coincided with sunitinib treatment start. Further details will be provided in the SAP.

Definitions for Response Evaluation

a) Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements do not need to be confirmed by repeat assessments after the criteria for response are first met.

b) Response rate

To be evaluated as the highest observed score of response during the study after randomisation in the ordinal categories of CR, PR, PD, SD and "Not evaluable". The response rate will be evaluated according to the Schedule of Study Events, *Section 7.2.1*.

c) Objective response

Is defined as the proportion of patients with CR and PR.

d) Disease control rate (DCR)

Also called Clinical Benefit Rate is defined as the proportion of subjects with CR or PR or Stable Disease (SD).

e) The duration of response and stable disease

The duration of response is calculated for only those patients who responded. It was the time from first objective response to first observed progression of disease or death if the death was due to disease progression (whichever comes first).

The duration of stable disease is calculated for only those patients who exhibited a best response of stable disease response as per RECIST v1.1. It is the time from first SD response to first observed progression of disease or death if the death was due to disease progression (whichever comes first).

The duration of response and stable disease will also be calculated for the patients who responded and/or had a best response of SD.

#### 10.2.2.3 Time to Progression (TTP) from Start of Sunitinib

TTP defined as time from Sunitinib Start Visit to date of first observed progression or date of death if the death was due to disease progression (whichever came first). Progressive disease is defined by RECIST v1.1 criteria and by clinical evaluation.

Note: For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, the first imaging assessment after nephrectomy will be used as baseline for evaluation of TTP, irrespective of whether or not the imaging assessment coincided with sunitinib treatment start. Further details will be provided in the SAP.

#### 10.2.2.4 Number of Infiltrating CD8+ T-Cells

At Nephrectomy two (2) separate biopsies from viable tumor tissue (10x10x5 mm) will be collected at least one (1) cm from each other from the resected renal tumor will be sent to [redacted], where they will be assessed centrally. The samples will be labelled with the patient's unique screening number, date and Tumor No. The study specific Laboratory Manual, which will be provided to all sites participating in this study will include full details on collection, handling and transport. All samples will be destroyed after analyses have been performed. Immunohistochemically stained sections of formalin-fixed, paraffin-embedded tissues will be analyzed.

The numbers of infiltrating CD8+ T-cells are evaluated per sample as follows: In the light microscope the area of the highest concentration of CD8+ T-cells are located. At this place an image is taken with the 10x objective. The position of the tissue section is then moved to an area just adjacent and a new photo is taken. This procedure is then repeated once more resulting in three (3) photos with the 10x objective adjacent to each other. The number of CD8+ T-cells are then manually counted from photo out-prints. Each photo covers 580x435 micrometer from the tissue section. From these figures the number of CD8+ T-cells/$mm^2$ are calculated. Two (2) different Investigators without prior knowledge of the patients' treatment assignment or clinical information will do these assessments. In case of discrepancy, the slides will be re-examined in order to reach consensus.

The median number of CD8+ T-cells from the six (2x3) counted areas per patient will be evaluated per stratum and in total from the two (2) treatment arms.

Additionally a part of the formalin-fixed and paraffin-embedded tumor tisssue prepared at [redacted], will be transported to the GLP compliant laboratory [redacted], where a validated automated quantification of intratumoral CD8+ T cells, using whole slide scanning instruments, will be performed. The immunohistochemistry

kit that will be used for revelation of CD8 staining at the Histalim Laboratory is a CE marked In Vitro Diagnostic Medical Device (IVD). The digitalization (Nanozoomer) of stained tissue slides follows 21 Code of Federal Regulations (CFR) part 11 guidelines. The tumoral area will be delineated by a trained operator and the surface of CD8 labeling percentage will be assessed in the delineated area. Finally, the analysis tool for semi-automated image quantification follows 21 CFR Part 11. All samples will be destroyed after analyses have been performed.

*NB.* For applicable patients one (1) pre-biopsy is taken for diagnostic purpose. If this is performed after consenting and before vaccination (for vaccine arm) this biopsy will be regarded as a baseline sample and will be analyzed as described above.

[redacted]

### 10.3 Drug Concentration Assessments - N/A

### 10.4 Demographic and Other Baseline Characteristics

#### 10.4.1 Demographic and Baseline Data

The following demographic and baseline data will be collected at the Screening Visit:

- Date of birth
- Sex
- Race (White, Asian, Black, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander)

Full information about the patients' Social Security Number and name is to remain confidential in the records of the respective Investigator.

### 10.4.2 Medical and Surgical History

*MEDICAL AND SURGICAL HISTORY (EXCLUDING MRCC)*
Clinical relevant past and present medical and surgical diagnoses non-related to RCC will be recorded at Screening in the eCRF. Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1.

*MEDICAL HISTORY (MRCC)*
The following medical history related to mRCC will be collected at Screening:

- Date of RCC diagnosis
- Primary tumor stage as defined by the American Joint Committee on Cancer's (AJCC's) TNM classification system [30]
- RCC symptoms including severity grading (NCI CTCAE version 4.0) [2]

The diagnosis of RCC will be confirmed by histopathological local assessment of tumor tissue after nephrectomy.

### 10.4.3 Efficacy Assessments by Imaging

The locally assessed CT scan in conjunction with screening is to verify patient eligibility. This scan will be performed within 3 weeks before the Screening Visit unless a CT scan has been done in clinical routine within 6 weeks prior to the Screening Visit.

Brain imaging: every subject must have had a MRI of the brain during the screening period unless a brain imaging by (preferably by contrast enhanced) MRI or CT was performed within the 6 weeks before randomization date. The MRI brain may be replaced by a CT brain if the subject does not tolerate the MRI procedure.

On study, MRI (preferably contrast-enhanced) of the brain (or contrast-enhanced CT if not possible otherwise) should only be performed on the indication of evocative neurological symptoms.

Tumor response will be evaluated by means of CT preferably, contrast enhanced of the chest, the upper and lower abdomen (including pelvis) and all other suspected sites of disease. The tumor response will be evaluated according to RECIST v1.1. [1] at baseline and for all repeated measurements according to the Schedule of Study Events, *Section 7.2.1*.

CT scan assessments will be done both by a local radiologist trained in the study protocol and by a central assessor at the designated imaging CRO, [redacted], without knowledge of the patients' treatment assignment and Heng-risk profile. Central assessments will form the basis for endpoint evaluations (PFS, ORR, TTP, TTF and tumor response rate). Central assessments will be done in accordance with a separate study-specific imaging protocol provided by [redacted].

A study specific instruction describing the handling, transferring, blinding, distribution, assessment, result processing, and filing of data will be handed out to all involved personnel.

CT scans performed at Sun-Start Visit five (5) to eight (8) weeks after nephrectomy will be used for evaluation of PFS from start of sunitinib, *Section 10.2.2.1*. Note: For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, the first imaging assessment (i.e. CT scan) after nephrectomy will be used.

CT scans performed at Sun-Start Visit five (5) to eight (8) weeks after nephrectomy will be used for evaluation of response rate from start of sunitinib, *Section 10.2.2.2*. Note: For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, the first imaging assessment (i.e. CT scan) after nephrectomy will be used.

Centrally assessed CT scans performed in conjunction with screening and at the first post-nephrectomy assessment will be used to assess tumor response rate between screening and the first imaging assessment (i.e. CT scan) post-nephrectomy.

The following information will be collected and used for the assessments if response is CR, PR, PD, SD, or “Not evaluable”:

- Date of Abdomen CT scan
- Date of Thorax CT scan
- Site of metastases (including specification of target and non-target lesions at Sun-Start Visit five (5) to eight (8) weeks after nephrectomy see *Section 10.2.2.2* and [1])
- Sum of the diameters for all target lesions, see *Section 10.2.2.2* and [1]
- New lesions, see *Section 10.2.2.2* and [1]

If CT cannot be used for some reason, MRI is acceptable. The same modality has to be used at all visits.

### 10.4.4 Prior and Concomitant Medication/Therapy

Prior medication/therapy is defined as medication/therapy administered prior to Screening Visit. All medication/therapy administered after Screening Visit are considered concomitant medication/therapy. Prior medication/therapy will be indicated as past or ongoing at Screening.

Prior medications taken within one (1) month prior to Screening and current ongoing treatment will be recorded at the Screening Visit on the concomitant medication page of the eCRF. Changes in concomitant medications will be recorded at all following visits throughout the study. For information on Concomitant Medication restrictions, see *Section 9.6*.

The following information will be collected and recorded in the eCRF: Drug name (product name), route, dose and units, frequency, indication, reference to AE if applicable, start date, end date or ongoing at the end of the study will be recorded.

Coding of prior and concomitant medications will be done using World Health Organization (WHO) Drug Dictionary.

### 10.4.5 Electrocardiogram (ECG)

A standard 12-lead electrocardiogram (ECG) recording will be performed according to local practice at Screening for identification of any heart failure. An overall interpretation of the ECG as “Normal” or “Abnormal” will be done. If an abnormal finding is considered clinical significant the patient will not qualify for participation in the study.

### 10.4.6 Serology

Blood samples for HIV, HBV and HCV will be collected and analyzed at Screening. Presence of any of these infections is an exclusion criterion.

The analyses will be performed by local laboratories. Sampling methods and procedures will be in accordance with local routine care. The Blood samples should be labelled with the patient's unique screening number.

### 10.4.7 Human Leukocyte Antigen (HLA)-typing

Blood samples will be taken at Screening for evaluating the patient's HLA type. HLA-A, HLA-B and HLA-DRB1 will be analyzed centrally by high resolution tissue typing assays at [redacted].

The blood samples collected should be labelled with the patient's unique screening number.

The study specific Laboratory Manual, which will be provided to all sites participating in this study, will include full details on blood sample collection, processing, storage, and shipping requirements. All samples will be destroyed after analyses have been performed.

## 10.5 Safety Assessments

### 10.5.1 Safety Variables

The following safety variables will be measured:

- AEs
- Physical Examination
- Vital Signs
- Laboratory Safety Assessments blood (hematology, clinical chemistry, and coagulation) and urine including pregnancy
- Other Safety Measurements (auto- and alloimmunization)

### 10.5.2 Adverse Events

AEs will be recorded during the study period from Screening Visit to the completion of the End-of-Study Visit.

SAEs will be recorded during the study period from Screening Visit to the completion of the End-of-Study Visit or up to 30 days after last dose of IMP administered in the study, whichever occurs later.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. The severity of AEs will be graded using the NCI CTCAE version 4.0 [2]. For further information of definitions and reporting of AEs and SAEs, see *Section 11* below.

Medical conditions or diseases present before Screening Visit are only considered AEs if they worsen after Screening Visit. Non-serious events occurring after signing the Informed Consent Form (ICF) but before any assessments made at the Screening Visit are recorded as Medical History in the eCRF.

### 10.5.3 Physical Examination

The timings of physical examinations are described in *Section 7.2.1* and *Table 2.* A physical examination in accordance with this protocol includes:

Skin, eye, ear, nose and throat, respiratory, cardiovascular, abdomen, lymphatic, and neurological/musculoskeletal (including reflexes)

The outcome of the assessments will be recorded as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”.

Clinically significant findings at Screening will be documented as Medical History. Clinically significant findings after Screening will be documented as AEs, *Section 10.5.2*.

### 10.5.4 Vital Signs

Vital signs will be monitored throughout the study as safety variables at the time points described in *Section 7.2.1* and in *Table 2*. In connection with vaccination and the 4-hour post-vaccination observation period, a detailed monitoring schedule applies, *Table 3*. The following assessments will be done and should be documented in the vital sign section of the eCRF:

- Supine systolic and diastolic blood pressure (mmHg), after 5 minutes lying down
- Supine heart rate (beats per minute), after 5 minutes lying down
- Body temperature (°C) (according to local practice)
- Height (cm), will be measured only at Screening Visit
- Weight (kg), will be measured at all visits except for Vacc1 and Vacc2 Visits

### 10.5.5 Laboratory Safety Assessments (Blood and Urine)

Blood and urine samples collected should be labelled with the patient’s unique screening number at all study visits. The study specific Laboratory Manual, which will be provided to all sites participating in this study, will include full details on blood sample collection, processing, storage, and shipping requirements (as applicable). All samples will be destroyed after analyses have been performed.

*BLOOD*

The centrally performed hematology and clinical chemistry analyses will be performed on serum samples by [redacted]

The coagulation (PT-INR and APTT) and pregnancy analyses will be performed by local laboratories in accordance with local routine.

In addition to the central analysis of Hb, WBC and platelets, local analysis will be made prior to the vaccinations. Following hospital practice locally analyzed results of Hb, WBC, platelets and clinical chemistry might be needed prior to Nephrectomy unless results from central analyses within 14 days prior to Nephrectomy are available and acceptable. Sampling methods and procedures will be in accordance with local routine for these analyses.

The timing of these assessments is described in *Section 7.2.1*, *Section 7.2.2*, and *Table 2*. At Vaccination Visits, blood samples will be collected prior to vaccination in connection with admission. If needed, for logistical reasons, these samples may be taken the day before vaccination. Also at Nephrectomy blood samples may be taken the day before for logistic reasons.

At least Hb, WBC, platelets, and coagulation status need to be available before vaccination and at least Hb, WBC, and clinical chemistry need to be available before nephrectomy. Analysis of coagulation status at Nephrectomy is not necessary provided the patient is not being treated with anticoagulants. For patients on anticoagulants local sampling practice applies.

The following laboratory safety parameters will be measured in blood*, Table 7:*

**Table 7 Laboratory Safety Parameters (Blood)**

| Category | Laboratory Parameter |
|---|---|
| Hematology (central analysis and additional local analysis of Hb, WBC and platelets at Nephrectomy and Vaccination Visits) | Hemoglobin (Hb), Red Blood Cells (RBC), White blood cells (WBC), Platelets, Neutrophils, Eosinophils, Basophils, Lymphocytes, and Monocytes |
| Clinical Chemistry (central analysis | C-Reactive Protein (CRP), Sodium (Na), Potassium (K), Creatinine[a], Albumin, corrected Calcium (Ca), Bilirubin, Lactate Dehydrogenase (LDH), Alkaline Phosphatase (ALP), Alanine Transaminase (ALAT), Gamma-Glutamyl Transferase (GGT), Aspartate Transaminase (ASAT), GFR based on Creatinine[b], Gluc[b], TSH[b], and Thyroxine (free T4)[b] |
| Coagulation (local analysis) | PT-INR[c] and APTT[c] |
| Pregnancy (local analysis) | human Chorionic Gonadotropin (hCG)[d] |

a Locally analyzed creatinine for patients included in the study before 28 August 2017 (if performed as part of clinical routine) to be recorded in the eCRF for Nephrectomy visit

b To be analyzed at Screening, Sun-Start Visit and at all following visits until end of study

c To be analyzed at Screening, Nephrectomy and Vaccination Visits

d To be analyzed in blood at Screening and in either blood or urine at vaccination visits, *Table 8*

The observed values for all categories except pregnancy will be recorded and assessed as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”.

Pregnancy testing in blood will be done to females of childbearing potential at Screening for patients randomized to Intuvax. At Vaccination Visits the pregnancy testing can be done either in blood or urine. The results will be recorded as “Negative” or “Positive”. A patient with a positive test at Screening should not be included in the study. A patient with a positive test at either of the Vaccination Visits should be withdrawn from further study treatment, *Section 11.7*.

*URINE*

The laboratory safety urinalyses will be performed centrally [redacted].

The timing of these assessments is described in *Section 7.2.1* and *Table 2*. At Vaccination Visits, urine samples will be collected prior to vaccination in connection with admission. If needed, for logistical reasons, these samples may be taken the day before vaccination.

The following laboratory safety parameters will be measured in urine*, Table 8:*

**Table 8 Laboratory Safety Parameters (Urine)**

| Category | Laboratory Parameter |
|---|---|
| Urinalysis (central analysis) | U-Microalbumin, U-Red blood cells, U-Glucose, and U-Nitrite |

| | |
|---|---|
| Pregnancy (local analysis) | Pregnancy dipstick[a] |

a To be analyzed in either blood or urine at Vaccination Visits and in blood at Screening

Unless pregnancy testing at Vaccination Visits is done in blood, urine analysis using dipsticks will be done to females of childbearing potential at Vaccination Visits for patients randomized to Intuvax. The results will be recorded as “Negative” or “Positive” and need to be available before vaccination. A patient with a positive test at either of the Vaccination Visits should be withdrawn from further study treatment, *Section 11.7*.

### 10.5.6 Other Safety Measurements

#### 10.5.6.1 Autoimmunization

Blood samples will be taken from patients randomized to Intuvax at Vacc1 (prior to vaccination) and Sun-Start Visits to evaluate potential autoimmune events by screening of autoantibodies against clinically relevant autoantigens:

- Anti-nuclear antibodies (IF-ANA) and kidney parenchyma-associated autoantigens (liver-kidney microsomal antigens and mitochondrial antigens).

The analyses will be performed by [redacted]. The blood samples collected should be labelled with the patient’s unique screening number at both study visits. The study specific Laboratory Manual, which will be provided to all sites participating in this study, will include full details on blood sample collection, processing, storage, and shipping requirements. All samples will be destroyed after analyses have been performed.

The IF-ANA results will be recorded and assessed as “Negative” or “Positive”. Additional assessment of “Weak” or “Strong” will be done for positive results on Homogenous, Speckled, Nucleolar, and Centromere patterns.

#### 10.5.6.2 Alloimmunization

Blood samples will be taken from patients randomized to Intuvax at Vacc1 (prior to vaccination) and Sun-Start Visits to evaluate potential vaccine-induced alloimmunization at the humoral level by screening of alloantibodies against HLA-A, B, C (HLA class I) and HLA-DR, DQ, DP (HLA class II) antigens.

The analyses will be performed by [redacted]. The blood samples collected should be labelled with the patient’s unique screening number at both study visits. The study specific Laboratory Manual, which will be provided to all sites participating in this study, will include full details on blood sample collection, processing, storage, and shipping requirements. All samples will be destroyed after analyses have been performed.

The results will be recorded and assessed as “Present” or “Not present”.

## 10.6 Appropriateness of Measurements

Standardized methods for measurements of efficacy and safety variables will be used.

# 11 ADVERSE EVENTS

## 11.1 Definitions

### 11.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

*Comment:* An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

### 11.1.2 Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

*Comment:* All AEs 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.

### 11.1.3 Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorized IMP or SmPC/USPI for an authorized product).

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

### 11.1.4 Serious Adverse Event

Any untoward medicinal occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

*Comments:* Life-threatening in the definition of a serious adverse event (SAE) or serious adverse reaction refers to an event in which the patient 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 was more severe.

Medical judgment should be exercised in deciding whether an AE/reaction is serious in other situations. Important AEs/reactions that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

## 11.2 Reporting of Adverse Events

Adverse event reporting and data management will be performed according to the following relevant guidelines:

- Directive 2001/20/EC (European Clinical Trial Directive),
- CPMP/ICH/E2A/377/95 (Clinical Safety Data Management: Definition and Standards for Expedited Reporting),
- CPMP/ICH/135/95 (GCP),
- 21 CFR 312.32 (FDA).

All study patients will be carefully monitored for the occurrence of AEs during the study period from Screening Visit to the completion of the End-of-Study Visit. SAEs will be collected until completion of the End-of-Study Visit or up to 30 days after last dose of IMP administered in the study, whichever occurs later.

All patients who received IMP who withdraw less than 1 month after IMP administration must have safety evaluations, defined as recording and reporting of any SAE, for 30 days after the last dose of Intuvax or Sunitinib. The Investigator will collect AEs with a non-leading question such as “have you experienced any new health problems or worsening of existing conditions” as well as reporting events directly observed or spontaneously volunteered by patients.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs including but not limited to events reported by the patient, or reported in answer to an open question by the Investigator or member of this team, which fall into any of the above definitions must be recorded as an AE in the eCRF and should include the following information:

- Brief description of the event (diagnosis)
- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding IMP
- Opinion on causality
- Seriousness
- Outcome

The general term “Progressive Disease” (PD) should not be used when reporting an AE. Instead, all symptoms, laboratory findings etc. including those that could be a reflection of PD should always be reported.

Severity describes the intensity of an event, and will be assessed using the NCI CTCAE version 4.0 [2]. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline. The term Grade refers to the severity of the AE. The following grades are used:

Grade 1 (Mild)

Asymptomatic or mild symptoms OR clinical or diagnostic observations only OR intervention not indicated.

Grade 2 (Moderate)

Minimal, local or noninvasive intervention indicated OR limiting age-appropriate instrumental Activities of Daily Living (ADL). (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)

Grade 3 (Severe or medically significant but not immediately life-threatening)

Hospitalization or prolongation of hospitalization indicated OR disabling OR limiting self-care ADL. (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)

Grade 4 (Life-threatening consequences)

Urgent intervention indicated.

Grade 5 (Death related to AE)

If an AE changes in severity, the worst severity should be reported.

**Causality**

Causality will be assessed as:

Probable

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the IMP, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible

A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the IMP, but which could also be explained by concurrent disease or other drugs or chemicals. Information on IMP withdrawal may be lacking or unclear.

Unlikely

A clinical event, including laboratory test abnormality, with a temporal relationship to IMP administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

**Follow-up of Patients after Adverse Events**

Any AE that is ongoing when the patient is withdrawn from the study should be followed up until the AE is resolved or the Investigator decides that the AE is stable and needs no further follow-up.

**Abnormal Laboratory Values/Vital Signs**

The reporting of abnormalities as both laboratory/vital signs findings and AEs should be avoided.

An asymptomatic abnormal laboratory/vital sign finding should only be reported as an AE if it is clinically significant, if it fulfils the criteria for an SAE or if it causes the patient to discontinue the study.

If an abnormal laboratory/vital sign value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory/vital sign result should be considered additional information.

**Safety Evaluation 30 Days after Last Dose of Investigational Medicinal Product**

All patients who have received IMP will have a safety evaluation, i.e., recording of SAEs for 30 days after last dose of IMP. The safety evaluation will be performed either as (i) a visit to

the clinic by the patient, (ii) a phone call to the patient by site personnel, or, if contact with the patient is not possible for any reason, (iii) as a review of the patient's medical records. All SAEs detected during the safety evaluation will be recorded in the eCRF and reported to [redacted] Drug Safety in accordance with the procedure presented in *Section 11.3*.

### 11.3 Reporting of Serious Adverse Events

The Investigator is responsible for ensuring that all SAEs are reported to the Sponsor immediately, but in any event no later than 24 hours of any site staff becoming aware of the event. Initial reports should be followed as soon as possible by detailed written reports. The initial and follow-up reports should identify patients by unique code numbers assigned in the study. The patient's names, personal identification numbers, and/or addresses must not be included. The following information is **mandatory** for the initial report:

- Patient study ID
- Study treatment (blinded, if applicable)
- Start date (time, if relevant) of the study treatment
- Brief description of the event (diagnosis)
- Start date (time, if relevant) of the event
- Seriousness criteria
- Causality assessment

For reported deaths, the Investigator should supply the Sponsor and the IRB/IEC (if applicable) with any additional requested information (e.g. autopsy reports and terminal medical reports).

Detailed instructions describing the procedure of reporting SAEs including Suspected Unexpected Serious Adverse Reactions (SUSARs), *Section 11.4*, will be distributed to the site and all involved parties at the Sponsor and [redacted] prior to study start.

As a principle, all SAEs must be documented and medically assessed by the Investigator and the outcome described in the AE section of the eCRF.

#### Follow-up of Post-Study Survival Information

Sites having patients who are still alive after the entire study has ended will be asked to seek survival information in medical records or databases (including public records).

The patient's survival information after the patient's End-of-study Visit will be reported to the safety database only, i.e. will not be included in the clinical database. A survival report form should be used for such reporting.

Post-study survival information will be collected as follows:

- Collection of survival data for the individual patient; at the 18 months post randomization time point
- A complete collection for all applicable patients; at the time of study end (*Section 7.5*)
- A complete collection for all applicable patients; at the last patient's 18 months post randomization time point and thereafter yearly up to 5 years

Updated information on median OS, will be reported to the authorities/IRBs/IECs as addendum(s) to the Clinical Study Report and also as part of the development safety update reports (DSURs).

**SAE REPORTING CONTACT DETAILS**

[redacted]

## 11.4 SAE and SUSAR Reporting to CAs, IRBs/IECs, and Investigators

The Sponsor is responsible for informing all concerned CAs, IRB/IECs, and all clinical study investigators utilizing Intuvax of any individual case reports of SAEs that are determined to be reportable by the Sponsor (i.e. SUSARs). For a SUSAR that is fatal or life-threatening, this should be reported as soon as possible and not later than 7 days after the Sponsor was first advised, for any other SUSAR this should be within 15 days. In addition to SUSARs, the Sponsor is also responsible for reporting any unanticipated events that may place other patients or the study at risk.

The Investigator will ensure that all relevant information is provided to the Sponsor to allow the Sponsor to meet their obligations to report the SUSAR to the CAs and IRBs/IECs. Furthermore, it is the responsibility of the Investigator to comply with any applicable site-specific requirements related to the reporting of SAEs (other than SUSARs) involving his/her patients to the IRB/IEC that approved the trial. The Sponsor must obtain adequate documentation showing that the IRB/IEC was properly and promptly notified as required.

## 11.5 Dose Limiting Toxicity (DLT)

The following AEs are classified as DLTs:

- Any AE of CTCAE grade 3 or higher (except for fever CTCAE grade 4 as this is an expected sign of immunologic response after vaccination), and assessed as possibly or probably related to Intuvax within the interval between the first vaccination and the subsequent one (i.e. the DLT observation period)
- Any autoimmune reaction CTCAE grade 3 or higher probably or possibly related to Intuvax within the interval between the first vaccination and the subsequent one.

If a patient experiences an AE that is qualified as DLT after first vaccination the second dose of vaccine will not be administered to the patient, *Section 8.5*.

All DLTs, irrespectively of seriousness, must be reported to the CRO using the same procedures and in the same timelines as is applicable for SAEs.

A DLT should be reported as an AE assessed as possibly or probably related to Intuvax as applicable. If a DLT fulfils any criterion for an SAE it should be reported as such.

### 11.6 Precautions/Overdose

Preparedness for anaphylaxis treatment in connection with vaccination is required. No antidote for Intuvax is available. In the event of overdose symptomatic management is indicated.

### 11.7 Pregnancy

Contraception is to be used from Screening until 90 days after last dose of Intuvax and/or until completed sunitinib treatment whichever occurs later.

Female patients will be instructed to notify the Investigator immediately if they become pregnant during the study. Male patients will be instructed to notify the Investigator immediately if their partner becomes pregnant. Pregnant patients will be withdrawn from further study treatment. The patients will also be instructed to report pregnancies discovered after the last visit, if they believe that conception occurred during their participation in the study.

A pregnancy as such is not an AE, unless there is a possibility that the IMP has interfered with the efficiency of any contraceptive measures. However, the Investigator should report pregnancies according to the procedures and timelines described for reporting of SAEs (*Section 11.3*). The pregnancy report form should be used instead of the SAE form.

The pregnant patient or partner will be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE. The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as an SAE.

# 12 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 12.1 Statistical and Analytical Plans

A separate SAP, which will provide the technical details of the statistical analysis outlined below, will be prepared and approved before study data analysis, including any interim analysis.

### 12.1.1 Data Sets to be Analyzed

The analysis population sets, which will be defined separately by stratum, are defined as follows:

**Full analysis set (FAS):** All patients randomized being evaluable for any high or intermediate stratum related efficacy endpoint.

**Per protocol set (PPS):** All patients randomized to Intuvax who had both doses of Intuvax administered or subject randomized to sunitinib alone, both having the nephrectomy and who continued the trial without any major protocol violations that could interfere with the objectives of this study.

Analyses of primary endpoints related to each stratum will be repeated using the PPS.

Subgroups will furthermore be defined separately by stratum, as patients exposed to at least one dose of sunitinib and having following evaluable PFS.

**Safety set:** All randomized patients who have at least one (1) assessment made at Screening.

Safety summaries will be performed on the safety set.

### 12.1.2 Definitions

For definitions used for endpoint evaluation, see *Section 10.2.1* and *Section 10.2.2*.

### 12.1.3 Statistical Issues

As this study is exploratory, sample size is not based on typical power calculation for confirming an efficacy as this would require either a too long follow-up or an unrealistic number of patients. Statistical hypothesis testing will be used but to be interpreted as exploratory analysis results. No adjustment for multiplicity will be done. All tests will be two-sided and type-1 error level is set to 0.05, i.e. significance level.

Handling of missing data will be described in detail in the SAP.

### 12.1.4 Summary Statistics

In general, data will be summarized by means of summary statistics. Continuous data will be presented with the number of observations, mean value, standard deviation, minimum, Q1, median, Q3 and maximum value. Categorical data will be presented as counts and percentages. Visit related data will be summarized up until and including the Nephrectomy Visit. Following this visit, visit related data may in addition be summarized, if applicable, based on results being re-allocated defined based on time intervals or as last available observation. Details for this will be specified in the SAP.

All individual patient data will be listed.

### 12.1.5 Primary Efficacy Analyses

Two primary endpoints are defined, each one in relation to the two primary objectives. As this trial is not powered to detect a statistical significant difference between treatment groups, *Section 12.2*, the statistical analyses described below should be considered exploratory. No adjustments for multiple testing will be done.

All patients will be followed for survival until date of death can be confirmed or up to 5 years after collection of the last patient's 18 months survival data, whichever comes first. Post-study survival data will be collected as described in *Section 11.3*. The primary analysis will be conducted based on the data collected at the entire study end. If the time point for the collection of post-study survival data at the entire study end, before DBL, differs with more than 2 months compared to the last patient's 18 months post randomization time point, then an additional collection of survival data will be conducted and the first follow-up analysis of post-study survival data will be done, as described in *Section 12.5*.

OS

The primary endpoint median OS after randomization in high-risk and intermediate-risk mRCC patients will be calculated and compared overall and by subgroup using the FAS in the following way:

Survival functions will be displayed graphically using Kaplan-Meier plots, and life table statistics will be produced including summaries of number of events and censored observations. Estimates of 25%, 50% (median) and 75% percentiles of time of survival with corresponding 95% confidence intervals will be calculated. Analysis where the survival functions will be compared between Intuvax+sunitinib, *vs.* sunitinib alone will be conducted using a log-rank test. Time to death in this analysis will be defined as the time from randomization until the event occurs.

In addition the primary efficacy endpoint will be evaluated using the PPS.

18-month survival rate

The primary endpoint 18-month survival rate after randomization in high-risk and intermediate-risk mRCC patients will be calculated and compared overall and by subgroup using life table statistics including summaries of number of events and censored observations and similar survival statistics as described for the analysis of OS above.

*NB:* Patients alive at the End-of-Study Visit will be followed for survival until date of death can be confirmed or for a maximum of 5 years after collection of the last patient's 18 months survival data, whichever comes first.

Lost to follow-up patients will be handled as censored observations if date of death cannot be found from medical records or databases (including public records).

### 12.1.6 Secondary Efficacy Analyses

Secondary efficacy endpoints will be presented descriptively by stratum (High-/Intermediate-risk mRCC patients) as stated explicitly for each endpoint below. Further analyses may be defined in the SAP, if appropriate. All secondary endpoints will be evaluated using the FAS. In addition, the PPS will be used.

PFS from start of sunitinib in intermediate and high-risk mRCC patients

The PFS analysis will be based on the subgroup of patients from FAS that actually had been exposed to at least one dose of sunitinib. PFS will be evaluated using similar survival statistics as described for the analysis of the primary endpoint.

Note: For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, sunitinib treatment did not have to be initiated at a fixed time point. For these patients, the first imaging assessment after nephrectomy will be used as baseline for evaluation of PFS, irrespective of whether or not the imaging assessment coincided with sunitinib treatment start. Further details will be provided in the SAP.

All other secondary endpoints defined as a time-to-event endpoint will be analyzed using the same statistical approach.

Response rate from Sunitinib Start Visit

Evaluation of response rate, based on CT and according to the RECIST 1.1 guideline, from Sunitinib Start Visit will be based on the subpopulation from FAS who have been exposed to at least one dose of sunitinib. Number of patients with CR, PR, PD, and SD after start of sunitinib will be summarized as described in *Section 12.1.4* for categorical data, using the underlying ordinal scale.

ORR including DCR will be summarized descriptively. Waterfall charts will be used to display the response distribution, details for this will be provided in the SAP. Between group comparison of the proportions will be done using Cochran Mantel Haenzel test including stratum on high-risk and intermediate-risk groups as a fixed factor.

Note: For intermediate-risk patients included in the trial according to protocol versions before version Final 4.0, the first imaging assessment after nephrectomy will be used as baseline for evaluation of ORR, irrespective of whether or not the imaging assessment coincided with sunitinib treatment start. Further details will be provided in the SAP.

Number of infiltrating CD8+ T-cells

The patient median number of CD8+ T-cells based on the counts, as evaluated by Micromorph, from the three (3) areas with most abundant positively stained cells, from the two (2) primary tumor biopsies, and from available diagnostic biopsies (either primary tumor or metastasis), and the patient's tumor area expressing CD8 from the two (2) primary tumor biopsies, as evaluated by Histalim, will be evaluated for the treatment arms per stratum and in total using summary statistics, as described for continuous data in *Section 12.1.4*.

### 12.1.8 Pharmacokinetic Analysis - N/A

### 12.1.9 Demographic and Other Baseline Characteristics

A patient disposition will be made including number of patients randomized, exposed to trial drug and completing, or withdrawal from trial (including reason for withdrawal). The number of patients in each analysis set will be included. The patient disposition will be made separately by stratum and overall.

Demographic, medical surgical history and other baseline data will be presented using summary statistics based on the safety set overall and split by stratum.

### 12.1.10 Exposure to Treatment

All details collected in relation to the Intuvax vaccination will be listed and tabulated if applicable. Nephrectomy data will be listed. Exposure data for sunitinib use will be listed per treatment group and stratum.

### 12.1.11 Concomitant Treatment

Concomitant medication and concomitant therapy will be summarized as number of patients being treated with each type of medication/therapy classified according to ATC level 3 and WHO Drug Dictionary preferred term. The safety set will be used for this presentation.

### 12.1.12 Adverse Events

Analyses of AEs will be based on the Safety set. AEs will be coded using MedDRA.

The total number of AEs will be summarized including the number of patients with at least one (1) AE, the total number of AEs, the number of unique AEs per treatment group and in total. The number of AEs per severity (CTCAE) and relation to trial drug will also be included and summarized per treatment group and in total. SAEs will be summarized in a similar manner.

The number of patients and the number of AEs will be tabulated by MedDRA system organ class and preferred term. AEs will also be tabulated versus worst severity and worst relationship to treatment. In this table, patients with AEs will be identified by their patient number.

AEs occurring during the 4 hours following the Intuvax vaccination will in addition be summarized separately.

Pretreatment events occurring between first assessment at Screening and first Intuvax dose (for vaccinated patients) and between first assessment at Screening and Nephrectomy (for unvaccinated patients) will in addition be summarized separately.

All AEs summaries will be made overall and separately by stratum.

### 12.1.13 Other Safety Assessments

<u>Physical Examination</u>

Physical examination data will be summarized by visit and treatment group as described in *Section 12.1.4.*

Vital Signs

Vital signs will be summarized by visit and treatment group, together with changes from Screening as described in *Section 12.1.4*.

Vital signs assessed during vaccination, will be summarized both by nominal time point and as change from the pre-vaccination at each post-vaccination time point.

Laboratory Safety Assessments

For laboratory data, summary statistics will be produced for observed values and for changes from screening to each visit as described in *Section 12.1.4*. In addition, the number of abnormal and clinically significant observations will be tabulated for each treatment group by visit. Abnormal values will be flagged in listings.

Shift tables will show the number of patients who changed from below, within or above the reference range at Screening to below, within or above the reference range at each time of assessment.

## 12.2 Determination of Sample Size

This is a proof of concept study and the number of patients chosen is based on practical considerations and not on a formal statistical power calculation. With around 90 patients randomized 2:1 to vaccination and control, it is expected that 18-month survival rate for high-risk and intermediate-risk mRCC patients overall can be adequately estimated for exploratory purposes but not to confirm the findings as statistical significant.

## 12.3 Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

Any deviation(s) from the original SAP will be described and justified in a protocol amendment and/or in a revised SAP and/or in the final report, as appropriate.

## 12.4 Interim Analysis

An interim analysis is not planned for in this study.

## 12.5 Follow-up Analysis of Post-Study Survival Data

Survival data will be analyzed post-study end as described in *Section 12.1.5* and *Section 12.1.6* and presented as addendum(s) to the final study report. Time-point(s) for analysis will be confirmed when considered justified by Immunicum AB and the Coordinating Investigator.

# 13 INVESTIGATOR/SPONSOR RESPONSIBILITIES

## 13.1 Ethics

### 13.1.1 Institutional Review Boards/Independent Ethics Committees and Competent Authorities

This protocol and any amendments will be submitted to concerned competent authorities (CAs) and properly constituted IRBs/IECs, in accordance with the International Conference on Harmonisation (ICH) guidelines, the applicable European Directives, the applicable sections of the US CFR, and/or other national and local legal requirements, for favorable opinion of the study. Favorable opinions must be obtained in writing before the first patient can be recruited. In addition to the protocol and any amendments the IRBs/IECs will review and approve any advertisements used for recruitment, as well as the informed consent documents, their updates (if any), and any other written materials given to the patients.

### 13.1.2 Ethical Conduct of the Study

The study will be conducted in compliance with the protocol, the applicable European Directives, US CFR sections that address clinical research studies, and/or other national and local legal requirements, ICH E6 good clinical practice (GCP) and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

### 13.1.3 Patient Information and Consent

All patients will receive written and verbal information regarding the study at a prior interview. This information will emphasize that participation in the study is voluntary and that the patient may withdraw from the study at any time and for any reason. All patients will be given the opportunity to ask questions about the study and will be given sufficient time to decide whether to participate in the study.

Before any study-related procedures the ICF will be signed and personally dated by the patient (or their legally acceptable representative and/or witness, as applicable) and by the person who conducted the informed consent discussion. Local regulations and laws regulate who is authorized to conduct the informed consent procedure.

The consent includes information that data will be recorded, collected, processed and protected in accordance with the European General Data Protection Regulation (2016/679) (GDPR).

The patient information includes information that the patients have the right to request access to their personal study data and the right to request rectification of any data that is not correct and/or complete. Furthermore, that Immunicum AB or designee personnel whose responsibilities require access to personal data agree to keep the identity of each patient confidential.

A copy of the patient information including the signed consent form will be provided to the patient.

Extra consent for vaccination for patients randomized to the vaccine arm, to be taken after randomization if required by local regulations.

## 13.2 Patient Records and Source Data

The origin of source data in the study will be further specified for each study site in a separate document (“Origin of Source Data”).

It is the responsibility of the Investigator to record essential information in the medical records in accordance with national regulations and requirements. The following information should be included as a minimum:

- A statement that the patient is in a clinical study
- The identity of the study e.g. Study code
- Patient unique screening number and/or patient number
- That informed consent was obtained and the date
- Diagnose and date of diagnosis
- Dates of all visits during the study period
- Any information relating to AEs
- All treatments and medications prescribed/administered (including dosage)
- Date of study termination
- Patient health service identification number

The Investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. eCRFs will be monitored on a regular basis.

### 13.3 Access to Source Data and Documentation

The Investigator should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate regulatory agencies, and the IRB/IEC, if required.

### 13.4 Monitoring

Immunicum AB is responsible for selecting qualified clinical trial centers to participate in this clinical trial. Site management and monitoring is delegated to [redacted] and these activities are specified in detail in the Study Monitoring Manual.

The monitor will visit the study site to ensure that the study is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements and any study specific documents such as monitoring manual and eCRF completion guidelines.

Monitoring visits will be conducted to confirm that e.g.:

- The investigational team is adhering to the study protocol
- Informed consent has been obtained from all participants
- AEs have been reported as required
- Data are being accurately recorded in the eCRFs
- IMP is being stored correctly and drug accountability is being performed on an on-going basis
- Facilities are, and remain, acceptable throughout the study

- The Investigator and the site are receiving sufficient information and support throughout the study

Moreover, during monitoring visits the data recorded in the eCRFs, source documents and other study-related records will be compared against each other in order to ensure accurate data that reflect the actual existence of the patient in the study i.e. source data verification.

### 13.5 Training of Study Personnel

The Investigator will maintain records of all individuals involved in the trial (medical, nursing and other personnel) and complete a delegation list to clarify roles and responsibilities. With the support from the designated CRO [redacted] and Immunicum AB the Investigator will ensure that appropriate training relevant to the trial is given to the personnel involved in the trial, and that any new information of relevance to the conduct of the trial is forwarded to the persons involved.

### 13.6 Data Management

Data management and handling of data will be conducted according to the study specific Data Management Plan, ICH guidelines and [redacted] standard operating procedures (SOPs).

An eCRF system will be used to capture data from the study. Data entry will be performed by the study site personnel. Validation and data queries will be handled by the [redacted] Data Management Team. The data will be subjected to validation according to [redacted] SOPs in order to ensure accuracy in the collected eCRF data.

Changes to the data in the eCRF will be made at the site by delegated study site personnel. The eCRF will have an audit trail with appropriate functionality for data capture, tracking and documentation of any queries or changes. Electronic signatures will be used to lock the data and identify the person entering or changing the data.

Before database closure a reconciliation will be performed between the SAEs entered in the safety database and the study database. After database closure, the database will be exported as SAS® data sets.

Any deviations, i.e. discrepancies and additions from the process defined in the Data Management Plan, will be described in a study specific Data Management Report.

### 13.7 Quality Assurance and Audit

Audits or inspections, including source data verification, may be performed by representatives of [redacted], the Sponsor, a CA and/or an IRB/IEC.

### 13.8 Record Retention

The Investigator/Institution should maintain essential documents (as defined in ICH E6 GCP, Section 8) as required by the applicable regulatory requirement(s). The Investigator/Institution should take measures to prevent accidental or premature destruction of the documents.

Essential documents should be retained according to applicable regulatory requirements of the country(ies) where the product is approved, and/or where the Sponsor intends to apply for approval.

It is the responsibility of the Sponsor to inform the Investigator/Institution in writing as to when the documents no longer need to be retained.

### 13.9 Protocol Deviations

Deviations to the study protocol will be documented in a Protocol Deviation Log.

The classification of patients into protocol deviators will be made during a meeting before database lock. The classification will be mutually agreed between the Sponsor and [redacted] before breaking the randomization codes. Listings will indicate the allocation of patients by analysis set and the number of patients per analysis set will be recorded in the clinical study report.

Any Serious Breaches that substantially affect the integrity or the safety of the patients or the scientific validity of the study will be reported to the relevant authorities in accordance with local regulatory requirements.

### 13.10 Protocol Amendments

If the study protocol needs to be substantially amended, the amendment must be approved by the CA and/or the IRB/IEC, as appropriate, before implementation, except for an amendment resulting from an immediate hazard to the patients. Approval must also be obtained for updates to the written Patient Information and ICF, when applicable.

If an amendment to the study protocol substantially alters the trial design, or increases the potential risk to the patients, the patient information has to be updated and written informed consent must be obtained again for currently enrolled patients. The updated patient information and informed consent must be provided to additional patients prior to their entry into the trial.

### 13.11 Insurance

The Sponsor must provide insurance or must indemnify (legal and financial coverage) the Investigator/the institution against claims arising from the study, except for claims that arise from malpractice, negligence or non-compliance with the protocol.

### 13.12 Report and Publication

After completion of the study, a clinical study report will be prepared according to the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3) by [redacted] in close collaboration with the Investigator and the Sponsor. Post-study survival data will be amended to the report.

All publications and presentations must be based upon the clinical study report.

All information supplied by the Sponsor in connection with this study will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the performance of this study.

If an Investigator wishes to publish results from this clinical study, written permission to publish must be obtained from the Sponsor in advance. As some of the information regarding the IMP and development activities at the Sponsor may be of a strictly confidential nature, the Sponsor must first review any publication manuscript prior to their submission to journals, meetings or conferences. The time for review should not exceed three (3) months after receipt of manuscript.

The Sponsor may choose to publish or present data from this study. If an Investigator is offered authorship, he/she will be asked to critically review the article for important intellectual content and approve the version to be published. The Sponsor has the right to use the results for registration and internal presentation and for promotion of the Sponsor's commercial interests.

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## 15 SIGNATURES

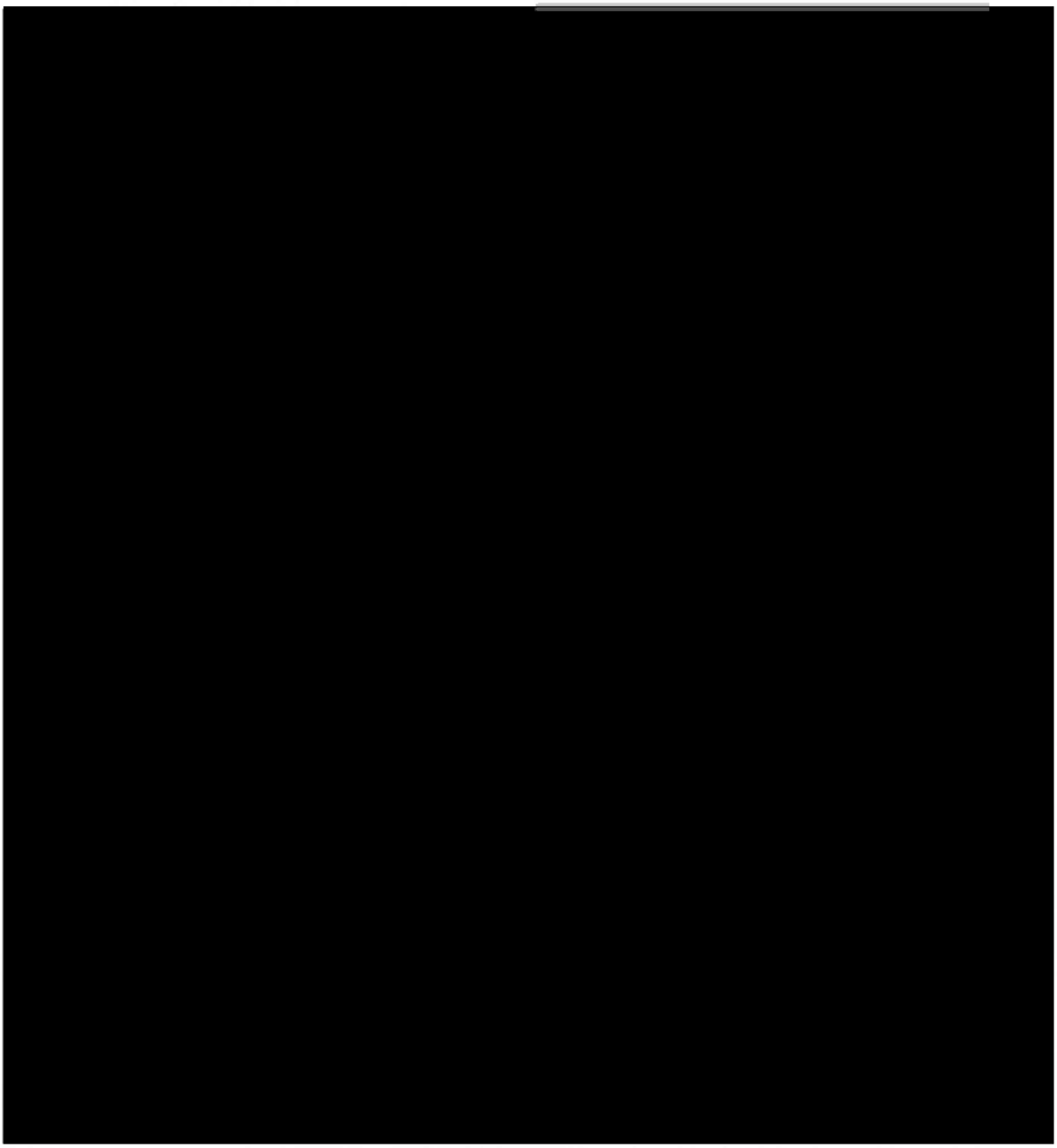
This Clinical Study Protocol is approved by:

SPONSOR'S STUDY DIRECTOR:

COORDINATING INVESTIGATOR:

## 15 SIGNATURES

This Clinical Study Protocol is approved by:



PROJECT MANAGER:

[redacted]

BIOSTATISTICIAN:

[redacted]

STUDY PROTOCOL AUTHOR:

[redacted]

PROJECT MANAGER:

[redacted]

BIOSTATISTICIAN:

[redacted]

STUDY PROTOCOL AUTHOR:

[redacted]

# 16 CLINICAL STUDY PROTOCOL AGREEMENT FORM

## 16.1 Clinical Study Protocol Agreement Form

I have read the clinical study protocol entitled: "*An open-label, randomized, controlled, multicenter, phase II study evaluating safety and efficacy of intratumorally administered Intuvax pre-nephrectomy followed by Sunitinib post-nephrectomy, compared to Sunitinib post-nephrectomy in metastatic renal cell carcinoma patients*" and verified that it contains all necessary information for conducting the study.

I hereby confirm that:

- I have carefully read and understood this clinical study protocol
- My staff and I will conduct the study according to the study protocol and will comply with its requirements, including ethical and safety considerations.

I understand that, should the Sponsor decide to prematurely terminate or suspend the study for whatever reason, such decision will be communicated to me in writing. Conversely, if I decide to withdraw from execution of the study I will immediately communicate such a decision to the Sponsor.

I agree not to publish any part of the results of the study carried out under this clinical study protocol without consulting the Sponsor.

_____

Principal Investigator: _____

Study Site: _____

Date: _____

Signature: _____

# 17 APPENDICES

[redacted]