A randomized, controlled Phase III study investigating IMA901 multipeptide cancer vaccine in patients receiving sunitinib as first-line therapy for advanced/metastatic renal cell-carcinoma.

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The primary objective of the present phase III study is to investigate whether IMA901 can prolong overall survival in patients with metastatic and/or locally advanced renal cell carcinoma (RCC) when added to standard first-line therapy with...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON36272

Source
ToetsingOnline

Brief title
IMA901 in patients receiving sunitinib for advanced/metastatic RCC

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
kidney cancer, renal cell carcinoma

Research involving

Human

Sponsors and support

Primary sponsor: immatics biotechnologies, GmbH
Source(s) of monetary or material Support: immatics biotechnologies GmbH;tubingen;Duitsland

Intervention

Keyword: cancer vaccine, multipeptide, renal cell-carcinoma

Outcome measures

Primary outcome

• Overall survival (OS), comparing patients receiving or not vaccination

therapy with IMA901 in addition to first-line therapy with sunitinib

Secondary outcome

• Overall survival in patients who are positive for the prospectively defined

primary biomarker signature (identified as being predictive for improved

clinical outcome in IMA901-vaccinated patients in the previous phase II study).

• Progression-free survival (PFS) using RECIST 1.1, based on the centrally

reviewed tumor images.

• Best tumor response according to RECIST 1.1, based on the centrally reviewed

tumor images.

• Safety and tolerability of IMA901 (and the immunomodulators GM-CSF and

cyclophosphamide) when added to first-line therapy with sunitinib.

• Cellular immunomonitoring (in a subset of patients recruited at pre-selected

centers):

o Description of T-cell responses to peptides contained in IMA901 (percentage

of immune responders),

o Analysis of other immune cell populations that may influence T-cell responses such as regulatory T cells (Tregs), myeloid-derived suppressor cells etc.

Secondary endpoints include a subgroup analysis of overall survival in patients who are positive for a prospectively defined primary biomarker signature (identified as being predictive for improved clinical outcome in IMA901-vaccinated patients in the previous phase II study; see section 8.2.3 of the study protocol for a detailed description of the primary biomarker signature), PFS, best overall response, cellular immunomonitoring in a subset of patients, and safety. The primary biomarker signature is described in Section 8.2.3 of the study protocol. Safety analysis will be based on adverse events (AEs), physical examinations, vital signs, hematology, clinical chemistry, urinalysis and ECG changes.
Further endpoints include subgroup analyses of overall survival in patients who are positive for further prospectively defined biomarkers (identified in the previous phase II study), and exploratory screening of new biomarkers (to be investigated in patients* blood and paraffin sections from tumor tissue) to predict better clinical outcome as response to vaccination with IMA901.
Biomarker sets will not be used for patient selection in this study.

Study description

Background summary

RCC accounts for approximately 3% of adult malignancies and is characterised by the lack of early warning signs, diverse symptoms and resistance to radiation

and chemotherapy. The longterm survival for patients with metastatic RCC remains modest with the current therapies available. In addition there are a number of toxicities associated with the current therapies. Thus the management of patients with mRCC remains a challenge and there is still high medical need for better treatment options.
IMA901 is a vaccine with a new mechanism of action which involves stimulating an immune response that is directed towards specific targets that are functionally important for the tumour. Studies so far with IMA901 have shown promising survival data and a favourable safety profile. In order to strengthen and maintain the immune response,
IMA901 will be given along with the immunomodulators GMCSF and lowdose cyclophosphamide. The coadministration with these immunomodulators has shown encouraging results and a good tolerability in previous studies.
Combining existing therapies is difficult due to their toxicities. However given the good safety profile of IMA901, combining IMA901 with an existing therapy could be a new therapy option. Preclinical studies investigating IMA901 in combination with sunitinib show that the combined therapy is feasible and the effects of IMA901 might be further enhanced by the stimulation of the immune system that results from sunitinib treatment.
This study will investigate the efficacy and safety of IMA901 given on top of sunitinib in patients with RCC, with the hope that it will lead to an increase in overall survival of these patients.

Study objective

The primary objective of the present phase III study is to investigate whether IMA901 can prolong overall survival in patients with metastatic and/or locally advanced renal cell carcinoma (RCC) when added to standard first-line therapy with sunitinib.
Secondary objectives include a subgroup analysis of overall survival in patients who are positive for a prospectively defined primary biomarker signature, the investigation of progression-free survival, best tumor response, safety, and immunological parameters (in a subset of patients).
Further objectives are additional biomarker analyses.

Study design

This is a multicenter, open-label, randomized phase III study to investigate whether IMA901 can prolong overall survival in patients with metastatic and/or locally advanced RCC when added to standard first-line therapy with sunitinib (primary endpoint).

* Screening (Visits A and B):
Informed consent will be obtained from patients for HLA typing (screening 1, Visit A). HLA-A*02-positive patients will then again be requested to give a separate informed consent to the remaining screening examinations (Screening 2,

Visit B) and participation in the study. All screening examinations (screening 1 and 2) must be completed (i.e. the results of the screening examinations [except for biomarker and immunomonitoring analysis] must be available) before start of sunitinib therapy.

* Start of sunitinib therapy:
Patients fulfilling all eligibility criteria will enter study IMA901-301 and start sunitinib first-line therapy according to the label (50 mg orally once daily, 4 weeks on treatment followed by 2 weeks off). One complete sunitinib cycle is defined as 42 days.
Patients eligible for continued sunitinib treatment (i.e. no clinical disease progression, no adverse events preventing further treatment after the first 4 weeks on sunitinib) will be randomized at Visit C which must take place 3 to 10 days before Visit D (see below).

* Randomization (Visit C):
At Visit C patients will be randomized at a ratio of 3:2 to the vaccination arm (Arm 1) and the control arm (Arm 2) and will receive further treatment as follows:
o Arm 1 (vaccination arm): 10 vaccinations with IMA901 plus GM-CSF. Cyclophosphamide will be administered once prior to the first vaccination. Continued sunitinib therapy.
o Arm 2 (control arm): Continued sunitinib therapy.
Randomization will be stratified according to risk group (favorable vs. intermediate), region (US vs. CEE vs. WEE vs. Asia) and prior nephrectomy (yes vs. no).

* Low-dose CY administration (Visit D):
At Visit D a single i.v. infusion of 300 mg/m2 cyclophosphamide (CY) will be given to patients in Arm 1 (vaccination arm). Visit D must be performed between days 31 and 36 of the first sunitinib cycle (i.e. within days 3 and 8 of the off-phase of the first sunitinib cycle) and 3 ± 1 days before the first vaccination (Visit 1) based on the following rationale: Vaccinations 1 to 3 (to be administered on 3 consecutive days = Visits 1 to 3) are considered to be highly relevant for immunological priming and are thus given during days with presumed low systemic concentrations of sunitinib in order to minimize the risk of interference with the initial T cell expansion, which is between days 33 and 42 of the first sunitinib cycle (i.e. between days 5 and 14 of the sunitinib off-phase). The first vaccination shall not be given before day 33 of the first sunitinib cycle (i.e. day 5 of the sunitinib off-phase) because by then the sunitinib plasma levels have decreased to approx. 25% of steady state concentration (t1/2=40 to 60h).

* Vaccination schedule (starting with Visit 1):
Patients in Arm 1 (vaccination arm) will start vaccination therapy 3 ± 1 days after Visit D with an intradermal (i.d.) injection of GM-CSF followed by an i.d. injection of IMA901. Patients will receive 6 vaccinations in the first 3

weeks (induction period, Visits 1 to 6) and then 4 more vaccinations at 3 weekly intervals (maintenance period, Visits 7 to 10).

* Study completion:
An individual patient is considered to have "completed" the study, if
• He/she has completed all scheduled visits.
• He/she experiences documented disease progression (as per RECIST 1.1. and/or clinical progression) or dies.
• He/she experiences adverse event(s) that in the opinion of the investigator require a permanent stop of sunitinib first-line therapy or a transient stop for more than 6 weeks.

Patients who for other reasons leave the study are considered as "prematurely withdrawn".
In any of the above mentioned cases, the investigator should aim to perform a formal End of Study (EOS) Visit.

Intervention

Patients will be randomized at a ratio of 3:2 to the vaccination arm (Arm 1) and the control arm (Arm 2) and will receive further treatment as follows:
o Arm 1 (vaccination arm): 10 vaccinations with IMA901 plus GM-CSF. Cyclophosphamide (single i.v. infusion of 300 mg/m2) will be administered once prior to the first vaccination. Continued sunitinib therapy.
o Arm 2 (control arm): Continued sunitinib therapy.

Study burden and risks

It is anticipated that patients be in the study for a maximum period of about 25 months which includes the following periods:
Screening period - maximum of 4 weeks - 2 visits
Pre-vaccination period - 5 weeks - 1 visit
Treatment (vaccination) period - 4 months - Vaccination group: 11 visits; Control group 6 visits
Follow-up period for tumor assessment - maximum of 19 months

Tumor assessments:
CT or MRI of the chest, abdomen and pelvis are scheduled in both study arms at screening (Visit B), at Visit 7 (within the off-phase of the second sunitinib cycle) and then at day 28 of every second sunitinib cycle, i.e. every 12 weeks (Visits 11 to 18/EOS) until all patients had the chance to complete Visit 14 (i.e., no remaining patient is non-progressive and still on-study before Visit 14).
CT or MRI of the brain is mandatory at screening (Visit B) and thereafter will only be performed if clinically indicated.
In patients with known or suspected bone metastases, imaging of bone lesions

(e.g., bone scan or X-ray or CT or MRI) will be performed at screening and if clinically indicated thereafter.

Safety assessments:
Safety assessments will be performed on a regular basis in both study arms and will comprise continuous AE reporting, physical examinations and assessment of vital signs, hematology, clinical chemistry and urinalysis. Up to the end of the vaccination period safety assessments will be done at screening (Visit B), at Visit D, then at 3-weekly intervals (Visits 6 and 7) followed by a 6-weeks interval (Visits 9) and a 5-weeks interval (Visit 11). During the follow-up period for PFS, safety will be assessed every 12 weeks (Visits 12 to 18/EOS).
A thyroid function test (TFT) will be performed at screening (Visit B), at Visit D, at Visits 7 and 11 and then every 12 weeks (Visits 12 to 18/EOS). AE reporting will continue during the follow-up period for PFS (Visits 12 to 18/EOS).
A 12-lead ECG will be performed in both study arms at screening (Visit B) and Visit 18/EOS.
Pregnancy testing will be performed according to applicable legislation. At the very least, women of child bearing potential must undergo a pregnancy test during screening, after the vaccination period (Visit 11) and at Visit 18/EOS.
The Karnofsky performance status will be documented in both study arms at screening (Visit B) and then at Visits D, 7 and 11 to 18/EOS.
Concomitant medication (documentation starting with Visit B) and details of sunitinib therapy will be documented in both study arms at all study visits.

Biomarker analysis:
Serum biomarkers will be analyzed in all patients in both study arms. Blood samples for biomarker assessment will be collected at screening (Visit B) and during the study (Visits D as well as 7, 9, 11 and 18/EOS).
In addition, tumor biomarkers will be analyzed in a purely exploratory fashion in both study arms, where paraffin sections or blocks from tumor tissue are available. For the collection of paraffin sections or blocks separate informed consents will be requested as this analysis is optional.

Immunomonitoring (subset of patients only):
In a subset of patients recruited at pre-selected centers specialized cellular immunomonitoring will be performed (T-cell responses to peptides contained in IMA901 and analysis of other immune cell populations that may influence T-cell responses such as Tregs, myeloid-derived suppressor cells etc.). Pre-sunitinib baseline blood samples to analyze cellular biomarkers, the potential influence of sunitinib on immune parameters and to allow immunological baseline comparison between the study arms will be taken at Visit B from patients in both study arms. Further blood samples for immunogenicity analysis will be taken only from patients in the vaccination arm (Arm 1) at Visits D, 5, 6, 7 and 9 (3 ± 1 days before and 2, 3, 6 and 12 weeks after the first vaccination).
One additional blood sample for hematology analysis (needed for immunomonitoring) will be taken from patients in the vaccination arm (Arm 1) at

Visit 5 at preselected sites where immunomonitoring is performed. The goal is to have evaluable immune data from approximately 80 patients randomized to the vaccination arm (Arm 1).

Follow-up for overall survival
After the interventional study period (including e.g. blood drawings, study medication, tumor assessments) all patients (including pre-maturely withdrawn patients unless they have withdrawn consent for overall survival follow-up) will be followed for survival (primary endpoint), subsequent anti-tumor therapy (or continued sunitinib therapy if applicable) and signs of autoimmunity every 3 months for a maximum of 8 years.

Risks in connection with this study are possible side effects of IMA901, GM-CSF or Cyclophosphamide, those of taking blood and radiation exposure due to CT imaging

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Aged at least 18 years.
2. HLA type: HLA-A*02-positive
3. Metastatic and/or locally advanced RCC with clear cell histology
4. Measurable and/or non-measurable tumor lesions as per RECIST 1.1 based on the local assessment.
5. Patients who are candidates for a first-line therapy with sunitinib.
6. Favorable or intermediate risk according to the 6-score risk criteria in patients treated with VEGF-targeted agents according to Heng [Heng et al. 2009].
7. Able to understand the nature of the study and give written informed consent.
8. Willingness and ability to comply with the study protocol for the duration of the study.
9. Female patients who are post menopausal (no menstrual period for a minimum of 1 year), or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or practice an medically acceptable methods of birth control
10. Male patients willing to use contraception (condoms with spermicidal jellies or cream) upon study entry and during the course of the study or have undergone vasectomy.

Exclusion criteria

1. Prior systemic therapy for metastatic disease.
2. History of or current brain metastases.
3. Abnormal >= CTC Grade 3 laboratory values at Screening 2
4. Metastatic second malignancy.
5. Localized second malignancy expected to influence the patient*s life span.
6. Patients with a history or evidence of systemic autoimmune disease
7. Known active hepatitis B or C infection.
8. Known HIV infection.
9. Active infections requiring oral or intravenous antibiotics.
10. Any other known infection with a biological agent that can cause a severe disease and poses a severe danger to lab personnel working on patients* blood or tissue.
11. Received study drug within any clinical study (including approved and experimental drugs) within 4 weeks before sunitinib start.
12. Serious intercurrent illness, which according to the investigator, poses an undue risk for the patient when participating in the trial,
13. Less than 12 months since any of the following:
• Myocardial infarction,
• Severe or unstable angina,
• Coronary or peripheral artery bypass graft,
• Cerebrovascular event incl. transient ischemic attack,
• Pulmonary embolism / deep vein thrombosis (DVT).
14. Pregnancy or breastfeeding.

15. Any condition which in the judgment of the investigator would place the patient at undue risk or interfere with the results of the study.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-04-2012
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	IMA901

Ethics review

Approved WMO

Date:	14-04-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	09-08-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-08-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-10-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-11-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-08-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-12-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-11-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-022459-45-NL
ClinicalTrials.gov	NCT01265901
CCMO	NL35225.000.11