Phase 1-2 study of everolimus and low-dose oral cyclophosphamide in patients with metastatic renal cell cancer.

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Primary: Phase I part 1) Assessment of the recommended dosing and schedule for metronomic cyclophosphamide when administered in combination with fixed dose (10 mg) oral everolimus in patients with mRCC with respect to the selective induction of CD4+...

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

Summary

ID

NL-OMON43872

Source
ToetsingOnline

Brief title
Everolimus-LDcyclo

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Kidney cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Novartis,Novartis Oncology Nederland

Intervention

Keyword: Cyclophosphamide, Everolimus, Metastatic renal cell cancer

Outcome measures

Primary outcome

Primary objectives Phase I

1) Assessment of the recommended dosing and schedule for metronomic cyclophosphamide when administered in combination with fixed dose (10 mg) oral everolimus in patients with mRCC with respect to the selective induction of CD4+CD25+ regulatory T cell depletion.

2) Assessment of safety and tolerability for the combination of metronomic cyclophosphamide and fixed dose oral everolimus in patients with mRCC.

Primary objectives Phase II

1) To investigate the proportion of patients with mRCC receiving everolimus and metronomic cyclophosphamide that is alive and progression-free at 4 months.

2) Assessment of safety and tolerability for the combination of metronomic cyclophosphamide and fixed dose oral everolimus in patients with mRCC.

Secondary outcome

Secondary Objectives Phase I and II study

1) To assess the response rate, time to progression, and overall survival of the combination of metronomic cyclophosphamide and fixed dose oral everolimus in patients with mRCC.

2) Assessment of the immunological effects of combining metronomic cyclophosphamide with everolimus.

3) Assessment of the effect of the combination of metronomic cyclophosphamide and everolimus on selected angiogenesis parameters.

4) To assess whether intrapatient changes in thrombocyte numbers correlate with response rate and/or time to progression in patients using the combination of metronomic cyclophosphamide and fixed dose oral everolimus.

5) To asess the effects of the combination of metronomic cyclophosphamide and everolimus on tumor-infiltrating leukocytes, including CD4+CD25+FOXP3+ regulatory T cells.

6) To assess the effects of cyclophosphamide administration on the drug levels of everolimus.

Study description

Background summary

In the present phase 1-2 study we aim to determine whether depletion of Tregs using metronomic cyclophosphamide can enhance the antitumor efficacy of everolimus in patients with mRCC not amenable to or progressive after a VEGF-receptor tyrosine kinase inhibitor containing treatment regimen. In the phase 1 part of the study we will determine the optimal CD4+CD25+ regulatory T cell-depleting dose and schedule of metronomic oral cyclophosphamide when given in combination with a fixed dose (10 mg daily) of everolimus. In the phase 2 part of the study we will subsequently evaluate whether the number of patients who are cancer progression free at 4 months can be increased from 50% to 70% by adding metronomic cyclophosphamide (in the dose and schedule determined in the phase 1 part) to everolimus. In addition to efficacy, we will evaluate treatment toxicity to determine whether this combination strategy is feasible and safe.

Study objective

Primary:
Phase I part
1) Assessment of the recommended dosing and schedule for metronomic cyclophosphamide when administered in combination with fixed dose (10 mg) oral

everolimus in patients with mRCC with respect to the selective induction of CD4+CD25+ regulatory T cell depletion.
2) Assessment of safety and tolerability for the combination of metronomic cyclophosphamide and fixed dose oral everolimus in patients with mRCC.

Phase II part
1) To investigate the proportion of patients with mRCC receiving everolimus and metronomic cyclophosphamide that is progression-free at 4 months.
2) Assessment of safety and tolerability for the combination of metronomic cyclophosphamide and fixed dose oral everolimus in patients with mRCC.

Secondary:
1) To assess the response rate, time to progression, and overall survival of the combination of metronomic cyclophosphamide and fixed dose oral everolimus in patients with mRCC.
2) Assessment of the immunological effects of combining metronomic cyclophosphamide with everolimus.
3) Assessment of the effect of the combination of metronomic cyclophosphamide and everolimus on selected angiogenesis parameters.
4) To assess whether intrapatient changes in thrombocyte numbers correlate with response rate and/or time to progression in patients using the combination of metronomic cyclophosphamide and fixed dose oral everolimus.
5) To asess the effects of the combination of metronomic cyclophosphamide and everolimus on tumor-infiltrating leukocytes, including CD4+CD25+FOXP3+ regulatory T cells.
6) To assess the effects of cyclophosphamide administration on the drug levels of everolimus.

Study design

This is a phase I/II, national multi-center study of different doses and schedules of low-dose oral cyclophosphamide in combination with fixed dose everolimus in patients with mRCC not amenable to or progressive after a VEGF-receptor tyrosine kinase inhibitor containing treatment regimen.

Phase I part:
Patients will be enrolled in cohorts of 5 per dose level. The first 5 patients enrolled will be assigned to dose level 0 in order to assess immune and angiogenic effects caused by everolimus monotherapy. The second 5 patients enrolled will be assigned to dose level 1. If there are <=1 dose-limiting toxicities (DLTs) experienced by the first 5 patients in a cohort during the first 28 days after the first study treatment, further patients will be entered in the next dose level. Entry of patients into the expansion cohort will not occur until at least 28 days after the last patient in the escalation phase received his/her first study treatment. At the final dose level recommended for the phase II study a minimum of 10 patients will be treated.

Phase II part:
In the phase 2 part of the study up to 56 patients will be treated at the dose level that has been selected based on its capacity to most selectively deplete circulating Treg levels in the phase 1 part of the study. Based on data of patients with mRCC treated with everolimus monotherapy after previous treatment with sunitinib ± sorafenib, we aim to increase the number of patients who are alive and cancer progression free at 4 months from 50% to 70% by adding metronomic cyclophosphamide. In addition, we consider this increase meaningful as long as the combination treatment does not cause combination treatment related toxicity >= grade 3 in >= 30% of patients.

Intervention

Phase I part:
Cohorts of 5-10 patients will be treated with escalating doses of oral cyclophosphamide to determine the recommended safe dosing for the combination of everolimus plus cyclophosphamide in patients with metastatic renal cell cancer.

Phase II part:
In the phase II part of the study up to 56 patients will be treated at the dose level that has been selected based on its capacity to most selectively deplete circulating Treg levels in the phase I part of the study.

Study burden and risks

Common undesirable side effects of everolimus are: rash, hypercholesterolemia, and/or hypertriglyceridemia, stomatitis/oral mucositis, fatigue, headache, anorexia, non-infectious pneumonitis, nausea, vomiting, diarrhea, lung diseases, neutropenia, thrombocytopenia, and infections.

Common undesirable side effects of cyclophosphamide are: nausea/vomiting, anorexia, diarrhea, constipation, stomatitis, mucositis, hematological toxicity, pneumonitis, interstitial pneumonia, alopecia, pigment changes skin/nails, hyponatremia, allergy, dizziness, neutropenia and thrombocytopenia

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. Patients with histologically or cytologically confirmed clear-cell mRCC with progressive disease and not amenable to or progressive on or within 6 months of stopping treatment with a VEGF receptor tyrosine kinase inhibitor (sunitinib (or pazopanib) ± sorafenib).
2. Prior therapy with cytokines (i.e. IL-2, interferon) and/or VEGF-ligand inhibitors (i.e. bevacizumab) is permitted.
3. Patients with brain metastases are eligible if they have been stable for at least two months post-radiation therapy or surgery.
4. Aged 18 years or older.
5. No other current malignant disease, except for basal cell carcinoma of the skin.
6. WHO performance status 0-2.
7. Life expectancy of at least 12 weeks.
8. Adequate hematologic function: ANC >= 1.5 x 109/L, platelets >= 100 x 109/L, Hb >= 6.0 mmol/L.
9. Adequate hepatic function: serum bilirubin <= 1.5 x ULN, ALT and AST <= 2.5 x ULN (or <= 5 times ULN if liver metastases are present).
10. Adequate renal function: calculated creatinine clearance >= 50 ml/min.
11. Measurable or evaluable disease as defined by RECIST 1.1.
12. Patients with reproductive potential must use effective contraception. Female patients of child baring potential must have a negative pregnancy test.
13. Signed informed consent.

14. Able to receive oral medication.

Exclusion criteria

1. Patients currently receiving chemotherapy, immunotherapy, or radiotherapy or who have received these <= 4 weeks prior to visit 1. Radiotherapy on a non-target lesion is allowed >= 2 weeks prior to visit 1.The wash-out period for sunitinib or sorafenib is at least 2 weeks from the first dose of the study medication.
2. Known human immunodeficiency virus (HIV) or other major immunodeficiency.
3. Immunosuppressive agents within 3 weeks of study entry, except for low dose corticosteroids with a maximum daily dose of 10mg prednisone or equivalent. Topical or inhaled corticosteroids are permitted.
4. Patients with an active bleeding diathesis or on oral anti-vitamin K medication.
5. Patients with untreated CNS metastases with clinical symptoms or who have received treatment for CNS metastases within 2 months of study entry. Patients with treated CNS metastases, who are neurologically stable and off of corticosteroids for more than 2 months prior to study entry are eligible to enter the study.
6. Active infection or serious intercurrent illness, except asymptomatic bacteriuria.
7. Presence of unstable angina, recent myocardial infarction (within the previous 6 months), or use of ongoing maintenance therapy for life-threatening ventricular arrhythmia.
8. Macroscopic hematuria
9. Prior therapy with mTOR inhibitors.
10. Known hypersensitivity to everolimus or other rapamycins (sirolimus/temsirolimus) or to its excipients.
11. Pregnant or nursing women, or women who were of childbearing potential and who were not utilizing an effective contraceptive method. A woman of childbearing potential is defined as a female who is biologically capable of becoming pregnant. Men with partners of childbearing potential not using an effective method of contraception. (Use of effective contraceptives must continue for 3 months after the last dose of everolimus).
12. Presence of any significant central nervous system or psychiatric disorder(s) that would hamper the patient*s compliance.
13. Uncontrolled diabetes as defined by fasting serum glucose > 2 ULN, severely impaired lung function.
14. Cirrhosis/chronic active hepatitis/chronic persistent hepatitis, history of HCV infection (for hepatitis screening indications see section 3.3).
15. Drug or alcohol abuse.
16. Any other major illness that, in the investigator*s judgment, substantially increased the risk associated with the subject*s participation in the study.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-01-2012
Enrollment:	96
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	Everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Endoxan
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	28-01-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO Date:	05-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	30-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2010-024515-13-NL
CCMO	NL35150.029.11