Een fase 1-2 studie van everolimus en lage dosis orale cyclofosfamide bij patiënten met uitgezaaide niercelkanker.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21801

Source
Nationaal Trial Register

Brief title
Everolimus-LDcyclo

Health condition

Metastatic renal cell cancer.

Sponsors and support

Primary sponsor: VU University Medical Center
Source(s) of monetary or material Support: KWF
Novartis

Intervention

Outcome measures

Primary outcome

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.

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

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 pharmacokinetics 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.

Participating centers:

Academisch Ziekenhuis Maastricht, Antoni van Leeuwenhoek Ziekenhuis, Universitair Medisch Centrum Sint Radboud, Isala Klinieken, HagaZiekenhuis, Medisch Centrum Alkmaar, Medisch Centrum Leeuwarden, Sint Franciscus Gasthuis Rotterdam, Universitair Medisch Centrum Groningen, Spaarne Ziekenhuis Hoofddorp, Sint Antonius Ziekenhuis Nieuwegein.

Study objective

The addition of metronomic cyclophosphamide to standard 2nd line treatment with everolimus will improve progression free survival of patients at 4 months from the reported value of 50% to 70% in patients with mRCC.

Study design

Primary outcomes: 28 days up to 2 years;

Secondary outcomes: 2 years.

Intervention

Patients with mRCC will be treated with low-dose oral cyclophosphamide (8 different dose levels and schedules) in combination with fixed dose (10 mg) everolimus.

Dose levels of oral cyclophosphamide during the phase I part of the study are as follows:

0. No cyclophosphamide;

1. 50 mg cyclo; o.d., week on, week off;

2. 50 mg cyclo; o.d., continuous;

3. 50 mg cyclo; bid, week on, week off;

4. 50 mg cyclo; bid, continuous;

5. 100 mg cyclo; bid, week on, week off;

6. 100 mg cyclo; bid, continuous;

7. 150 mg cyclo; bid, week on, week off;

8. 150 mg cyclo; bid, continuous.

Patients will be enrolled in cohorts of 5 per dose level. The first 5 patients enrolled will be assigned to dose level 0. 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. At the final dose level recommended for the phase II study a minimum of 10 patients will be treated.

Contacts

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Eligibility criteria

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) ¡À 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 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. 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 when given for disorders such as rheumatoid arthritis, asthma, or adrenal

insufficiency. 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 type:	Interventional
Intervention model:	Parallel
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-10-2011
Enrollment:	96
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	22-09-2011
Application type:	First submission

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
NTR-new	NL2937
NTR-old	NTR3085
Other	METc VUmc : 11/016
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A