Pilot study of everolimus in the treatment of advanced malignancies in patients with Peutz-Jeghers syndrome

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To determine the efficacy (as measured by objective tumor response) of single agent everolimus in the treatment of advanced malignancies or high risk polyps of patients known with PJS .

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON36695

Source
ToetsingOnline

Brief title
EVAMP

Condition

- Other condition
- Chromosomal abnormalities, gene alterations and gene variants
- Miscellaneous and site unspecified neoplasms benign

Synonym
Cancer, inherited development of polyps

Health condition

Peutz-Jeghers syndroom

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Novartis,Novartis Pharma B.V.

Intervention

Keyword: advanced cancer, Everolimus, mTOR-inhibition, Peutz-Jeghers

Outcome measures

Primary outcome

To determine the efficacy(as measured by objective tumor response) of single agent everolimus in the treatment of advanced malignancies or high risk polyps of patients known with PJS

Secondary outcome

*To determine the overall survival of patients treated with everolimus in patients with advanced malignancies in PJS.

*To evaluate the time to progression

*To evaluate the toxicity profile of everolimus in PJS patients

*To determine the association between drug levels of everolimus and objective clinical response

*To determine the influence of everolimus on the proliferation signaling mTOR pathway and its downstream targets in the tumor and blood prior and during treatment with the use of established biomarkers.

Study description

Background summary

Peutz-Jeghers syndrome is a rare cancer predisposition syndrome characterized by the development of gastrointestinal polyps and mucocutaneous pigmentation abnormalities.
The syndrome was first described in 1921 by the Dutch physician Dr Johannes Peutz working in The Hague. The syndrome was further characterized by Dr. Harold Jeghers in 1949, who recognized that *a single pleiotropic gene was responsible for both characteristics, the polyps and the spots.* PJS is an autosomal dominant cancer-prone gastrointestinal polyposis disorder. The disorder presents in 1 per 50,000 to 1 per 200,000 newborns. Due to the rarity of the syndrome, clinical accounts of pedigrees afflicted by the syndrome are rare, and accurate documentation of the increased cancer-risk is therefore complex. Based on large cohort studies, patients are estimated to display an 18-fold increased cancer risk over the normal population.
Most patients with Peutz-Jehgers disease have an inherited LKB1 mutation leading to aberrant m-TOR activity. Their risk to develop malignancies or intestinal polyps is probably related to this constitutive mTOR signaling. The most common type of malignancies are: pancreatic, gastrointestinal, colorectal, ovarian, and breast carcinomas. Even though in this group of patients active surveillance is performed regularly, there still is a high incidence of advanced disease.
Everolimus is an oral selective m-TOR inhibitor. Although aberrant mTOR activity is probably related to pre-malignant lesions in Peutz-Jeghers syndrome (PJS), the role in established cancer in unknown, till recently. In a recent case of a patient with PJS suffering of advanced pancreatic cancer we observed at our institution, an impressive response to oral treatment with everolimus monotherapy. Therefore mTOR inhibition might be a potential anti-cancer treatment in Peutz-Jeghers related malignancies and needs confirmation in a larger patient cohort.

Study objective

To determine the efficacy (as measured by objective tumor response) of single agent everolimus in the treatment of advanced malignancies or high risk polyps of patients known with PJS .

Study design

Phase II non randomized, open label, multiple centre study . In this pilot study we will treat all patients known with PJS and diagnosed with advanced malignancies or high risk polyps with everolimus 10mg daily. Pharmacokinetic/dynamic studies will be performed as well.

Intervention

Treatment with everolimus 10mg daily until disease progression or occurance of

unacceptable toxicity. For cohort 2 treatment of a maximum of 12 months.

Study burden and risks

The use of low-dose everolimus hasbeen applied for many years in the treatment of kidney and heart transplants. Since recently, everolimus has also been approved for the treatment of renal cell carcinoma with very limited side effects.
Therefore the burden for the patient by everolimus is very low, especially compared with standard therapy for advanced malignancies, which is usually the combined use of chemotherapy. The study-related examinations are similar to standard systemic treatment of advanced malignancies and therefore provide no increased risk to the participating patients. Patients can choose whether they wish to participate in additional investigations like endoscopies and tumorbiopsies. The risks of these voluntary investigations are considerably small. Patients with high risk polyps will have endoscopic examinations or a magnetic resonance bowel enteroclysis performed after 12 months instead of once every two years.

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

Two cohorts of PJS patients will be included.
Cohort 1: Advanced malignancy
Cohort 2: High risk polyps
*Known Peutz-Jeghers disease (with LKB1 mutation)
*Advanced malignancy of any tumor type, not suitable for surgery at the time of study enter
*No concurrent systemic anti cancer treatment
*No prior treatment with m-TOR inhibitor
*Prior malignancies or concurrent second malignancies are allowed
*Prior systemic therapy is permitted with a washout time of at least 4 weeks
*Cytological or histological confirmed carcinoma
*Metastatic or non-resectable disease
*Patients with clinically and/or radiographically documented measurable lesion according to RECIST criteria: X-ray, physical exam > 20 mm; Spiral CT scan > 10 mm; Non-spiral CT scan > 20 mm
*ECOG/ WHO performance 0-2
*Age > 18 years
*Life expectancy > 3 months
*Adequate renal function (defined as creatinine < 150 *mol/L)
*Adequate liver function (bilirubin < 1.5 times upper limit of normal, ALAT or ASAT < 5.0 times upper limit of normal in case of liver metastases and < 2.5 the upper limit of normal in absence of liver metastases
*Adequate bone marrow function (WBC > 3.0 x 10 9/L, platelets > 100 x 10 9/L) E.
Specific inclusion criteria for cohort 1:
1. Cytological or histological confirmed carcinoma
2. Metastatic or non-resectable disease
3. Patients with clinically and/or radiographically documented measurable lesion according to RECIST criteria:
a. X-ray, physical exam > 20 mm
b. Spiral CT scan > 10 mm
c. Non-spiral CT scan > 20 mm
Specific inclusion criteria for cohort 2:
1. Known high risk polyps (definition see page 19)
2. Ability to undergo endoscopies

Exclusion criteria

*Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
*Patients who are pregnant or lactating
*Patients who are of childbearing potential who do not agree to use a reliable contraceptive method throughout the study
*Patients who do have serious concomitant systemic disorder that would compromise the safety of the patient, at the discretion of the investigator
*Patients who are not willing to sign the Signed informed consent according to ICH/GCP, IRB approval obtained prior to treatment
*Patients who do have uncontrolled symptomatic hyperglycaemia
* Symptomatic PJ-polyps, defined as polyps likely to be responsible/causal for the abdominal symptoms the patient presents with.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-09-2012
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	everolimus

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-12-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-09-2011
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	EUCTR2010-020451-32-NL
ClinicalTrials.gov	NCT01178151
CCMO	NL33427.018.10