

# Neoadjuvant propranolol in angiosarcoma patients

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To determine the clinical and histologic response of propranolol monotherapy in patients with angiosarcoma.

<b>Ethische beoordeling</b>	Niet van toepassing
<b>Status</b>	Werving nog niet gestart
<b>Type aandoening</b>	-
<b>Onderzoekstype</b>	Interventie onderzoek

## Samenvatting

### ID

NL-OMON23603

### Bron

Nationaal Trial Register

### Verkorte titel

PropAngio

### Aandoening

Angiosarcoma

## Ondersteuning

**Primaire sponsor:** The Netherlands Cancer Institute Antoni van Leeuwenhoek ziekenhuis

**Overige ondersteuning:** Anticancer Fund

## Onderzoeksproduct en/of interventie

## Uitkomstmaten

### Primaire uitkomstmaten

The primary endpoint is the clinical response according to RECIST 1.1 criteria. If propranolol leads to a response in  $\geq 3$  out of 14 patients, this treatment modality is highly interesting and should be tested further in a randomized trial. If propranolol leads to a

response in  $\geq 3$  out of 14 patients, this treatment modality is highly interesting and should be tested further in a randomized trial. A response is defined as CR, PR, or SD with an improvement in clinical characteristics, like thickness, erythema, necrosis or edema of the inflicted area.

## Toelichting onderzoek

### Achtergrond van het onderzoek

#### Rationale:

Propranolol hydrochloride, a  $\beta$ -blocker, has recently been repurposed against a benign vascular tumor called hemangioma with 88% complete or near complete resolution of the treated lesions. Also, several small case reports/series have suggested that propranolol could be repurposed to treat locally advanced or metastatic angiosarcoma. These patients were treated with propranolol, in combination with various chemotherapy regimens, such as cyclophosphamide and vinblastine. Preclinical studies have demonstrated synergy between propranolol in combination with vinblastine in in vitro angiosarcoma models. A reduction in proliferation index of angiosarcoma has also been reported in response to propranolol monotherapy in one patient.

In terms of safety in cancer patients, propranolol has been or is being used in more than 20 clinical oncology trials, including one clinical trial in advanced angiosarcoma in combination with cyclophosphamide (NCT02732678) with no major safety concerns when cardiovascular monitoring is performed (i.e. dose adapted to blood pressure and heart rate).

Since there is few data available regarding the activity and mechanism of action of propranolol as a single agent for angiosarcoma, both in the primary and metastatic setting, our goal is to evaluate the activity in a window study in angiosarcoma patients in a neoadjuvant setting before they proceed with the standard anti-cancer treatment.

The goal of this neoadjuvant window of opportunity study is therefore to prospectively evaluate the activity of propranolol in the clinical setting as monotherapy, where the neoadjuvant setting provides a good opportunity to rapidly evaluate both the clinical response and histological response, without a significant delay in anti-cancer treatment.

#### Objectives:

The primary objective is to determine the clinical response of propranolol monotherapy in patients with angiosarcoma. The secondary endpoint is to assess the histologic response of propranolol monotherapy in patients with angiosarcoma.

#### Study design:

Single-arm neoadjuvant window of opportunity phase II study to explore the activity of propranolol monotherapy in angiosarcoma.

#### Treatment:

Propranolol monotherapy 40-80 mg BID or TID if tolerated.

#### Treatment plan\*:

Dose escalation of propranolol before standard anti-cancer treatment Propranolol (tablet, 40 mg)

Day 1 – Day 7 1 x 40 mg, 2x/day

Day 8 – Day 14 2 x 40 mg, 2x/day

Day 15 – Day of surgery or biopsy 2 x 40 mg, 3x/day

Tapering of propranolol post- surgery/biopsy Propranolol (tablet, 40 mg)

Day 1 post-surgery/biopsy - Day 7 post-surgery/biopsy 2 x 40 mg, 2x/day

Day 8 post-surgery/biopsy - Day 14 post-surgery/biopsy 1 x 40 mg, 2x/day

\*Propranolol will be increased to the next dose level if heart rate is >60, systolic blood pressure (BP) is >110 and previous dose is well tolerated.

#### Duration/schedule:

When patients are diagnosed, standard anti-cancer treatment must be scheduled within 6 weeks. Since propranolol treatment can start immediately after the diagnosis and will be continued until the day the patient starts with the standard anti-cancer treatment, this is a so-called window of opportunity study. The duration of study treatment will be 3-6 weeks.

### **Doel van het onderzoek**

To determine the clinical and histologic response of propranolol monotherapy in patients with angiosarcoma.

### **Onderzoeksopzet**

The primary and secondary endpoints will be determined after 3-6 weeks of study treatment.

### **Onderzoeksproduct en/of interventie**

propranolol monotherapy

## **Contactpersonen**

### **Publiek**

NKI-AvL

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### **Wetenschappelijk**

NKI-AvL

Alaa Embaby

## Deelname eisen

### Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- o Histological proof of angiosarcoma
- o Patients with primary, recurrent and metastasised disease are eligible;
- o Patients with a window of at least 3 weeks before surgery or systemic therapy;
- o Age  $\geq 18$  years;
- o Able and willing to give written informed consent;
- o WHO performance status of 0, 1 or 2;
- o Evaluable disease according to RECIST 1.1 criteria; radiologic visible disease is not obligated
- o Minimal acceptable safety laboratory values
- o ANC of  $\geq 1.5 \times 10^9 /L$
- o Platelet count of  $\geq 100 \times 10^9 /L$
- o Hepatic function as defined by serum bilirubin  $\leq 1.5 \times ULN$ , ASAT and ALAT  $\leq 2.5 \times ULN$
- o Renal function as defined by serum creatinine  $\leq 1.5 \times ULN$  or creatinine clearance  $\geq 50$  mL/min (by Cockcroft-Gault formula);
- o At least one tumor lesion accessible to safely biopsy per clinical judgement of the treating physician

### Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- o Contraindication for propranolol therapy, like severe hypotension or bradycardia, sick-sinus syndrome, second or third grade heart block, cardiogenic shock, untreated heart failure, severe peripheral vascular disease asthma or other obstructive lung diseases, untreated pheochromocytoma, metabolic acidosis, prolonged fasting.
- o Current treatment with  $\beta$ -blockade therapy.
- o Any anticancer treatment within 30 days prior to receiving the first dose of investigational treatment; with the exception of hormonal therapy for breast cancer.
- o Concurrent treatment with an anticancer therapy: with the exception of hormonal therapy for breast cancer.
- o Patients with known alcoholism, drug addiction and/or psychiatric or physiological condition which in the opinion of the investigator would impair study compliance;
- o Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications;

- o Pregnancy;
- o Legal incapacity.

## Onderzoeksopzet

### Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blinding:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

### Deelname

Nederland	
Status:	Werving nog niet gestart
(Verwachte) startdatum:	25-10-2019
Aantal proefpersonen:	14
Type:	Verwachte startdatum

### Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

**Wordt de data na het onderzoek gedeeld:** Ja

#### Toelichting

All essential documents (including patient files, the Investigator Study File, CRFs and electronic study data), data management and statistical files will be kept for 15 years. Results of the study will be published in an international journal, independently of the results.

## Ethische beoordeling

Niet van toepassing	
Soort:	Niet van toepassing

## Registraties

## Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 49514

Bron: ToetsingOnline

Titel:

## Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

## In overige registers

Register	ID
NTR-new	NL8118
CCMO	NL71090.031.19
OMON	NL-OMON49514

## Resultaten