An explorative and feasibility study of Venetoclax combined with Tamoxifen in patients with relapsed/refractory Diffuse Large B-cell Lymphoma

Published: 22-06-2021
Last updated: 04-04-2024

Primary objectives1. To assess the safety of Tam added to Ven. Venetoclax will be dosed at 800 mg once daily. After 2 days of venetoclax, tamoxifen will be orally administrated in a ramp-up phase (2 days 10mg, 2 days 20mg, to a final dose of 40 once...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON51061

Source
ToetsingOnline

Brief title
TamVen

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Large B-cell lymphoma, lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

Source(s) of monetary or material Support: UMCG Hematologie

Intervention

Keyword: relapsed/refractory Diffuse Large B-cell Lymphoma, Tamoxifen, Venetoclax

Outcome measures

Primary outcome

Descriptive analyses of safety and toxicity (using SAE grade 3 and 4 listing)

of tamoxifen and venetoclax

Secondary outcome

• To assess the effectivity of the combination Tam and Ven as measured by the

day + 28 and +90 response as measured by FDG PET CT scan.

• To assess the duration of response (DOR)

• To assess the progression free survival (PFS) after 3 months (after the first

dose of TAM)

• To assess the overall survival (OS) after 3 months

Study description

Background summary

This trial aims to asses safety of tamoxifen added to venetoclax in patients with Diffuse Large B-cell Lymphoma (DLBCL) who have no other treatment options.

The rationale for tamoxifen (Tam) and venetoclax (Ven) is based on pre-clinical and clinical data; 1) Single agent therapy of the selective estrogen receptor modulator Tam has been shown to be safe and might be effective in patients with B-cell lymphomas; 2) Studies from the Dutch cancer registry demonstrated that women with breast cancer (BC) who were treated with Tam had a significant lower incidence of DLBCL compared to women with breast cancer who were not treated with tamoxifen; 3) The BCL-2 inhibitor Ven is modestly effective as a single agent (overall response rate 18%, dose: 800-1200mg) and in combination with chemotherapy in patients with DLBCL (dose venetoclax 800mg); 4) Research in our

own lab showed that in malignant and normal lymphocytes, the estrogen receptor beta (ER) is expressed in the mitochondria of these cells. Ligation of ER* with tamoxifen results in BAD-independent (BCL-2 protein response) apoptosis. Subsequently, pre-clinical data in DLBCL cell lines demonstrated a synergistic cell killing effect of the combination Tam and Ven; 5) The combination of Tam (40 mg) and Ven (800 mg) was studied in patients with estrogen receptor alfa (ER) positive BC. This combination was effective and safe, with one important side-effect, a marked lymphopenia (but no other cytopenias), confirming that B-lymphocytes are a targeted by the combination of Tam and Ven.

Study objective

Primary objectives
1. To assess the safety of Tam added to Ven. Venetoclax will be dosed at 800 mg once daily. After 2 days of venetoclax, tamoxifen will be orally administrated in a ramp-up phase (2 days 10mg, 2 days 20mg, to a final dose of 40 once daily, see study scheme)

Secondary objectives
1. To assess efficacy of Tam added to Ven. An FDG PET / CT scan will be performed at day +28 and +90 of treatment.
2. To assess the duration of response (DOR)
3. To assess the progression free survival (PFS)
4. To assess the overall survival (OS)

Study design

This is a prospective, explorative feasibility trial.

Intervention

Patients in this study are treated with oral Ven (800 mg once daily) and oral Tam (starting with a ramp-up phase; 2 days 10mg, 2 days 20mg, and 40mg once daily). These doses are the approved doses for treatment of breast cancer (Tam) and the advised dose for the treatment of B-cell Non-Hodgkin Lymphoma (NHL)

Study burden and risks

The benefit of this study is to explore an oral treatment regimen in patients who have no other (curative) treatment options.
The burden and risks associated with participation mainly involves potential toxicity associated with the study drugs, e.g. tumor lysis syndrome. To that end patients will be hospitalized and monitored for at least 24 hrs after the first dose of venetoclax and after the addition of tamoxifen.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Patients of 18 years and older and under the age of 70 with a diagnosis of Diffuse Large B-cell lymphoma (according WHO 2016) and refractory after 2 lines of therapy for patients ineligible for CAR T-cell therapy and after CAR T-cell therapy (hence after 3rd line of therapy). Patients with relapsed/refractory DLBCL older than 70 years after at least 1 line of conventional chemotherapy or after CAR T-cell therapy.
• Written informed consent.
• No known allergy to Ven or Tam.

Exclusion criteria

• Eastern Cooperative Oncology Group (ECOG) performance status >2
• Absolute neutrophil count (ANC) <1,000/µL
• Platelet count <50,000/µL
• Absolute lymphocyte count <100/µL
• Primary and secondary CNS lymphoma
• Active systemic fungal, viral or bacterial infection
• CrCl <30 mL/min calculated according to the modified formula of Cockcroft and Gault or by direct urine collection
• Pregnant or breast-feeding woman

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	21-10-2021
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tamoxifen
Generic name:	Tamoxifen
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Venetoclax
Generic name:	Venetoclax

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-06-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-06-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2020-005515-51-NL
CCMO	NL76026.042.21
Other	NL9075