A prospective phase I/II trial of the combination of ixazomib citrate, rituximab and dexamethasone in patients wit relapsed or rogressive Waldenström’s macroglobiulinemia. A HOVON / Greek Myeloma Study Group study

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON27880

Source
Nationaal Trial Register

Brief title
HOVON 124 WM

Health condition

Waldenström’s macroglobulinemia (WM)

Sponsors and support

Primary sponsor: Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON)
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Source(s) of monetary or material Support: Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON), Koningin Wilhelmina Fonds (KWF), Millennium a Takeda company, Roche.

Intervention

Outcome measures

Primary outcome

Phase I: to assess the recommended phase II dose for the combination of oral ixazomib citrate and dexamethasone in patients with WM.

Phase II: to assess the efficacy (overall response rate) of ixazomib citrate in combination with rituximab and dexamethasone

Secondary outcome

- To assess the safety of oral ixazomib citrate in combination with rituximab and dexamethasone, followed by rituximab maintenance for 2 years, with special emphasis on neurotoxicity, infections and the incidence of IgM flare requiring plasmapheresis

- To assess feasibility oral ixazomib citrate in combination with rituximab and dexamethasone, defined as percentage of patients who complete the full treatment course (at least 6 cycles of
induction treatment and 2 years of maintenance treatment)

- To assess the effect of 2 cycles of ixazomib citrate and dexamethasone (before rituximab is added) on M-protein levels

- To assess the improvement of response during rituximab maintenance

- To assess the effect of ixazomib citrate, rituximab and dexamethasone treatment on patient reported outcomes (quality of life (QoL))

- To perform an exploratory analysis of prognostic markers and markers of disease activity

- To study in vivo the effect of treatment with an oral proteasome inhibitor in sorted WM B cells and plasma cells from the bone marrow (exploratory analysis)

Study description

Background summary

Study phase:

Phase I/II

Study objective:

To establish the recommended phase II dose for the combination of oral ixazomib citrate, and dexamethasone in patients with WM.

In Phase II to assess the efficacy (overall response rate) of oral ixazomib citrate in combination with rituximab and dexamethasone.

Patient population:

Patients with relapsed or progressive WM, age >=18 years.

Study design:

Prospective, non-randomized, open label, phase I/II intergroup study

Duration of treatment:

Expected duration is 8 months of induction therapy, followed by 2 years of maintenance therapy.

All patients will be followed until 5 years after end of maintenance.

Study objective

The hypothesis is that treatment with the combination ixazomib citrate, rituximab and dexamethasone will be effective in patients with relapsed WM with good tolerability.

Study design

At entry, before the start of each induction cycle, before start of maintenance, during maintenance every 3 months, during follow-up every 3 months (for 5 years).

Intervention

All patients will receive 8 cycles of induction treatment with ixazomib citrate, rituximab (only cycles 3 to 8) and dexamethasone, followed by 2 years of maintenance treatment with

rituximab once every 3 months.
Phase I part: In the induction cycles in the phase I part of the study, ixazomib citrate, rituximab and dexamethasone are given using one dose level of ixazomib citrate (4 mg flat dose on day 1,8,15 of a 28-day schedule; cycle 1-8) with rituximab (375 mg/m2 i.v. on day 1, cycle 3 -8) and dexamethasone (20mg flat dose on day 1, 8, 15 and 22). If the dose of 4 mg is not feasible, 3+3 patients will be treated with an ixazomib dose of 3.0 mg. The goal of the phase I
part of the study is to establish the recommended phase II dose (R2PD) of ixazomib citrate given in combination with rituximab and dexamethasone for the phase II part of the study.

Phase II part: In the phase II part of the study, in the induction cycles ixazomib citrate is given at the RP2D in combination with rituximab and dexamethasone, followed by rituximab maintenance.

Contacts

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Eligibility criteria

Inclusion criteria

•A diagnosis of relapsed or progressive WM (lymphoplasmacytoid lymphoma in the bone marrow with an IgM M-protein)

•Age ≥ 18 years

•WHO 0-2

•Presence of an IgM M-protein in the serum (as demonstrated by SPEP and IF)

•Measurable disease (IgM M-protein > 10 g/l (1 g/dl))or, in case the M-protein is present but unquantifiable, total serum IgM level > 10 g/l (1 g/dl))

•Symptomatic disease (see appendix C)

•≥ 1 prior(s) lines of treatment

•Patients showing progressive disease under treatment with chemotherapy only (e.g. chlorambucil, CVP, fludarabine or fludarabine/cyclophosphamide) are allowed on study

•Platelets > 75x109/l. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment.

•ANC >1.0 x109/l

•Negative pregnancy test at study entry for women of childbearing potential

•A female patient is either post-menopausal for at least 1 year before the screening visit, or surgically sterile, or, if of childbearing potential, agrees to practice 2 effective methods of contraception at the same time, from the time of signing the informed consent until 12 months after the last dose of rituximab, or agrees to completely abstain from heterosexual intercourse. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)

•Male patients, even if surgically sterilized, (i.e., status post vasectomy) must agree to practice effective barrier contraception during the entire study period and through 90 days after the last dose of ixazomib and/or rituximab, or agree to completely abstain from heterosexual intercourse. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)

•Written informed consent

•Prior plasmapheresis in case of symptomatic hyperviscosity is allowed

Exclusion criteria

•Bortezomib refractory (no PR/CR after treatment with bortezomib, and/or progression within 6 months of treatment with bortezomib)

•Rituximab refractory (progressive disease during treatment or within 6 months after last administration of rituximab)

•Amyloidosis

•Peripheral neuropathy, grade 3 or higher, or grade 2 with pain on clinical examination during the screening period. For assessment of the peripheral neuropathy the neuropathy questionnaire tool must be used (see 10.4.2)

•Creatinine clearance <30 ml/min according to the Cockroft&Gault formula (see appendix I)

•Known HIV seropositivity

•Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or history of HBV infection (patients with serological evidence of current or past HBV exposure are excluded unless the serological findings are clearly due to vaccination)

•History of organ transplantation including allogeneic stem cell transplantation

•Known intolerance of rituximab and/or boron

•Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.

•Bing Neel syndrome, or other forms of central nervous system involvement, or severe neurological disorders

•Severe cardiac dysfunction (NYHA classification III-IV; see appendix H)

•Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months

•Severe pulmonary dysfunction (CTCAE grade III-IV)

•Significant hepatic dysfunction (defined as total bilirubin >1.5 ULN (unless caused by Gilbert syndrome) and/or transaminases ≥3 times upper limit of normal, unless caused by WM

•Active, uncontrolled infections requiring systemic antibiotic therapy or other serious infections within 14 days before study enrollment

•Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, hypertension)

•Diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and having any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if

they have undergone complete resection

•Major surgery within 14 days of enrollment

•Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administrations of the ixazomib citrate

•Systemic treatment, within 14 days before the first dose of ixazomib citrate, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John’s wort

•Breastfeeding

•Current participation in another therapeutic clinical trial (other study medication should have been stopped at least 4 weeks before registration in this trial) and throughout the duration of this trial.

•Failure to have fully recovered (i.e., □ Grade 1 toxicity) from the reversible effects of prior chemotherapy.

•Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib citrate including difficulty swallowing.

•Any psychological, familial, sociological and geographical condition potentially hampering compliance with the study protocol and follow-up schedule

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2014
Enrollment:	72
Type:	Actual

Ethics review

Positive opinion Date:	08-05-2015
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	NL5025
NTR-old	NTR5171
Other	: HOVON 124 WM 2013-002711-94

Study results

Summary results
none