A Phase II study of Selinexor (KPT-330) combined with bortezomib and dexamethasone (SVd) for induction and consolidation for patients with progressive or refractory Multiple Myeloma.

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In this protocol we will study the value of selinexor as the third agent based on its unique mechanism of action and reported synergy with bortezomib in patients with progressive or refractory MM.

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON25937

Bron
NTR

Verkorte titel
The Selvedex trial

Aandoening

Multiple Myeloma
Multipel Myeloom
Progressive or Refractory
Progressief of refractair
safety and tolerability of selinexor

Ondersteuning

Primaire sponsor: Erasmus University Medical Center
Overige ondersteuning: Karyopharm Therapeutics

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Part I: Evaluate the safety and tolerability of selinexor at 3 different dose levels in combination with bortezomib/dexamethasone & determine the recommended dose level (RDL) of selinexor for Part II

Part II: Evaluate the efficacy of the combination of selinexor, bortezomib and dexamethasone (SVd) for induction and consolidation in subjects with
progressive or refractory multiple myeloma (MM). This objective will be investigated after 4 induction cycles and after 8 cycles.

Toelichting onderzoek

Achtergrond van het onderzoek

Standard regimens in multiple myeloma are 4 – 6 induction cycles of induction therapy (bortezomib/dexamethasone)
followed by High Dose melphalon (HDM) and autologous stem cell transplantation (ASCT). Preferably a third agent is
added to the bortezomib/dexamethasone. In this protocol we will study the value of selinexor as the third agent based on
its unique mechanism of action and reported synergy with bortezomib in patients with progressive or refractory MM.

Doel van het onderzoek

In this protocol we will study the value of selinexor as the third agent based on its unique mechanism of action and reported synergy with bortezomib in patients with progressive or refractory MM.

Onderzoeksopzet

Expected durations of therapies:

- Induction therapy 4 months

- Transplantation and recovery 2 – 4 months

- Consolidation therapy 4 months

- All patients will be followed until a maximum of 5 years after registration.

Onderzoeksproduct en/of interventie

The following treatments will apply:

Patients who have not previously received an autologous transplant and who are eligible for ASCT will be treated with 4 cycles of selinexor, bortezomib and
dexamethasone. After induction they will receive High Dose Melphalan (HDM) and unde rgo an Autologous Stem Cell
Transplantation (ASCT). Stem cell harvest will be performed using high-dose Cyclophosphamide and standard G-CSF. Following hematologic recovery, these
patients will receive 4 cycles of consolidation treatment with selinexor, bortezomib and dexamethasone.

Patients who have previously received an autologous transplant or who are transplant ineligible will be treated with 4 cycles of selinexor, bortezomib and dexamethasone followed by 4 cycles of consolidation treatment with selinexor, bortezomib and dexamethasone.
In Part I of the study, the maximum tolerated dose (MTD) or highest administered dose of selinexor when combined with bortezomib & dexamethasone will be determined in 6 patients per dose level. A maximum of 3 dose levels will be evaluated.

Escalation to a higher dose level is allowed if 0 or 1 dose limiting toxicity (DLT) is experienced in a dose level. Dose
escalation stops as soon as at least 2 patients in a dose level experience a DLT.

Part II of the study will be performed at the highest dose level where 0 or 1 DLT have occurred.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- The subject must understand and voluntarily sign an informed consent document prior to any study related assessments/procedures are conducted.

- Age ≥ 18 years at the time of signing the informed consent form.

- Able to adhere to the study visit schedule and other protocol requirements.

- Documented diagnosis of multiple myeloma and measurable disease (serum M-protein ≥ 5 g/L or urine M-protein ≥ 200 mg/24 hours or abnormal FLC ratio with involved free light chain (FLC) > 100 mg/L);

- Documented progression as per the IMWG uniform response criteria (Durie, 2006) during or after the anti-myeloma regimen; or never achieved a response better than PD after at least 2 cycles of their previous anti-myeloma regimen.

- At least one prior anti-myeloma regimen. Induction therapy followed by autologous stem cell transplant (ASCT) and consolidation/ maintenance will be considered as one regimen.

- Normal renal function with a Creatinine Clearance > 30mL/min according to the Modification of Diet in Renal Disease (MDRD) equation for estimation of Glomerular Filtration Rate (GFR)

- WHO performance status score of 0, 1 or 2 (see Appendix B).

- Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm

with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

- All subjects must agree to refrain from donating blood while on study drug and for 28 days after discontinuation from this study treatment.

- All subjects must agree not to share medication.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- Prior resistance/refractory disease to bortezomib

- Systemic AL amyloidosis

- Non secretory myeloma

- Known CNS involvement

- Absolute neutrophil count (ANC) <1.0 x 109/L, unless related to MM.

- Platelet count < 50 x 109/L.

- Corrected serum calcium > 14 mg/dL (> 3.5 mmol/L).

- Hemoglobin < 8 g/dL (< 4.9 mmol/L; prior RBC transfusion or recombinant human erythropoietin use is permitted).

- Significant hepatic dysfunction (Serum SGOT/AST or SGPT/ALT > 3.0 x upper limit of normal (ULN) or serum total bilirubin > 2 x ULN unless due to inheritable syndrome such as Gilbert’s)

- Prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years. Exceptions include the following:

o Basal or squamous cell carcinoma of the skin.

o Carcinoma in situ of the cervix or breast.

o Incidental histological finding of prostate cancer (TNM stage of T1a or T1b).

- Hypersensitivity to bortezomib or dexamethasone (this includes ≥ Grade 3 rash during prior bortezomib therapy).

- Peripheral neuropathy ≥ Grade 2 at time of registration.

- Subjects who received an allogeneic bone marrow or allogeneic peripheral blood stem cell transplant less than 12 months prior to initiation of study treatment

- Congestive heart failure (NY Heart Association Class III or IV) (see appendix C).

- Myocardial infarction within 12 months prior to starting study treatment

- Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris.

- Subjects who received any of the following within the last 14 days of initiation of study treatment:

o Major surgery (kyphoplasty is not considered major surgery).

o Use of any anti-myeloma drug therapy at the time of registration in the trial.

- Use of any investigational agents within 28 days or five half-lives (whichever is longer) of treatment.

- Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent
the subjects from signing the informed consent form.

- Any active uncontrolled infections

- Pregnant or breastfeeding females.

- Known human immunodeficiency virus (HIV) positivity, active infectious hepatitis A, B or C or
chronic hepatitis B or C.

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

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Enkelblind

Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-11-2014
Aantal proefpersonen:	49
Type:	Verwachte startdatum

Ethische beoordeling

Positief advies

Datum:	29-10-2014
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL4724
NTR-old	NTR4869
Ander register	: EMC-MM-KPT-330-001

Resultaten