# A PHASE 3 RANDOMIZED, OPEN-LABEL TRIAL OF SELINEXOR, POMALIDOMIDE, AND DEXAMETHASONE (SPd) VERSUS ELOTUZUMAB, POMALIDOMIDE, AND DEXAMETHASONE (EloPd) IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA (RRMM)

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This study has been transitioned to CTIS with ID 2024-518304-53-00 check the CTIS register for the current data. The primary objective of the study is to compare the PFS of SPd versus EloPd in patients with MM who have received 1 to 4 prior anti-MM...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Haematopoietic neoplasms (excl leukaemias and lymphomas) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON56661

**Source**
ToetsingOnline

**Brief title**
EMN29

### Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

**Synonym**
Hematological malignancy, relapsed and refractory multiple myeloma

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Stichting European Myeloma Network (EMN)
**Source(s) of monetary or material Support:** opdrachtgever

## Intervention

**Keyword:** Multiple myeloma, Pomalidomide, Relapsed and refractory, Selinexor

## Outcome measures

### Primary outcome

Primary endpoint:

PFS, defined as time from date of randomization until the date of first

confirmed progressive disease (PD), per IMWG response criteria, or death due to

any cause, whichever occurs first.

### Secondary outcome

Key Secondary Efficacy Endpoints

• OOR, defined as any response >= PR (i.e., PR [partial response], VGPR [very

good partial response], CR ([complete response], or sCR [stringent complete

response])

• Overall survival (OS)

Additional Secondary Efficacy Endpoints

• Clinical benefit rate (CBR), defined as response >=minimal response (MR)

• Duration of response (DOR)

• Time to next treatment (TNT)

• Time to initial response (TTR)

• Time to best response (TTBR)

• Time to progression after first post-SPd/EloPd treatment or death (PFS2)

Safety and tolerability of study treatment will be evaluated based on AE reports, vital signs, clinical laboratory results, electrocardiogram (ECG) and physical examination findings, by means of the occurrence, nature, and severity of AEs as categorized by the CTCAE v5.0.

Patient-reported quality of life (QoL, as measured by the European Organisation for Research and Treatment of Cancer-Quality of Life (EORTC QLQ C30), EORTC-QLQ-MY20, and EQ-5D-5L instruments..

Selinexor and pomalidomide PK parameters, estimations of maximum plasma concentration, area under the concentration versus time curve (AUC), and apparent clearance, if feasible.

# Study description

**Background summary**

Pomalidomide and dexamethasone (Pd) is a commonly used backbone regimen in patients with relapsed or refractory multiple myeloma (RRMM) worldwide. There are several triplets based on Pd, including in combination with proteasome inhibitors (PIs), elotuzumab, and an anti-CD38 monoclonal antibody (mAb). However, the increasing use of anti-CD38 mAbs and PIs in the first or early relapse lines of therapy makes their subsequent use in combination with pomalidomide in RRMM less optimal in clinical practice, with data indicating limited efficacy with re-exposure. For patients who have been previously treated with an immunomodulatory drug (IMiD; e.g., lenalidomide), a PI, and an anti-CD38 mAb, there is a significant need for combinations with Pd that

utilize novel mechanisms of action to improve patient benefit.
This trial will evaluate the effect of the role of 2 drugs with novel mechanisms of action, selinexor and elotuzumab, in combination with Pd in patients with RRMM who have been previously treated with an IMiD, a PI, and an anti-CD38 mAb. Starting in protocol version 2.0, eligible patients must have received an anti-CD38 monoclonal antibody as part of the treatment regimen immediately prior to study enrollment.
Selinexor is a novel, oral nuclear exportin inhibitor approved by the European Medicines Agency (EMA) and by the US Food and Drug Administration (FDA) 1) in combination with dexamethasone is indicated for the treatment of adult patients with RRMM who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors (PIs), at least 2 IMiDs, and an anti-CD38 monoclonal antibody (mAb); and 2) in combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received at least 1 prior therapy. In addition, it has been approved by the US FDA for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.
Further evaluation of selinexor-based combinations was initiated to control MM as relapses are frequent and response to therapy declines as later lines are used. The current trial is based on results from studies KCP-330-017 (STOMP; NCT02343042) and XPORT-MM-028 (NCT04414475). As of 06 September 2022, a total of 95 patients received the SPd regimen. Dosing schedules ranged from 60 mg to 80 mg selinexor twice weekly (BIW) or 40 to 100 mg selinexor QW. Dexamethasone was dosed at 40 mg weekly, and pomalidomide was dosed 2 to 4 mg once daily (QD) on Days 1 through 21, administered in 28-day cycles (White 2021). Among patients with pomalidomide-naïve or non-refractory MM in STOMP (n=44), overall response rate (ORR) was 57% and median progression-free survival (mPFS) was 12.2 months. Two expansion cohorts dosed with selinexor either at 40 mg QW (SPd-40) or 60 mg QW (SPd-60) in combination with pomalidomide 4 mg once daily (QD) on Days 1 through 21 and dexamethasone 40 mg QW were enrolled. Preliminary data available at the inception of this study suggested that the SPd-60 regimen conferred higher response rates and deeper responses compared to SPd-40. However, Grade 1/2 AEs and dose modifications were more frequent in the SPd-60 cohort compared to SPd-40 (White 2021a). Initially and until protocol version 1.6, this study enrolled patients to 2 SPd cohorts, SPd-40 and SPd-60. By protocol version 2.0, sufficient follow-up data in patients treated with SPd-60 and SPd-40 in the STOMP and XPORT-MM-028 studies accumulated to identify SPd-40 as the optimal dose regimen of SPd based on benefit/risk assessment; thus, only the SPd-40 regimen will be compared to EloPd starting in protocol version 2.0.
The subset of patients in STOMP and XPORT-MM-028 who had received prior anti-CD38 mAb treatment was analyzed, with data indicating an overall response rate of 63.6%; the ORR was 62.5% for those patients who received the anti-CD38 mAb treatment in the line of therapy immediately prior to start of SPd. The mPFS seen in patients who received anti-CD38 mAb treatment prior to SPd-40 and SPd-60 were similar at 11.2 and 8.9 months, respectively (unpublished data).
Elotuzumab is a signaling lymphocytic activation molecule F7 (SLAMF7)-directed

immunostimulatory antibody indicated in combination with pomalidomide and dexamethasone (EloPd) for the treatment of adult patients with MM who have received at least 2 prior therapies, including lenalidomide and a PI. Elotuzumab induces natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity on SLAMF7-expressing myeloma cells and direct activation of NK cells. It may also facilitate macrophage-mediated killing of myeloma cells (Collins 2013, Balasa 2015, Kurdi 2018). Previous studies of the EloPd regimen in patients with at least 2 prior lines of therapy showed a mPFS of 10.3 months and ORR of 53% (Dimopoulos 2018). There are no prospective data on the outcome of treatment with EloPd in patients with prior therapy with an anti-CD38 mAb; however, retrospective studies have reported lower ORR and PFS with EloPd in patients previously exposed to daratumumab (Hoylman 2020, Becnel 2018).
There is a growing demand for combination therapy that minimizes clinic visits. SPd is an all-oral combination that should reduce patients* burden relative to other anti-MM treatment regimens that require a subcutaneous or intravenous (IV) infusion and frequent clinic visits. All other approved Pd-based triplet combinations require parenteral administration, entailing hospital/clinic visits.

**Study objective**

This study has been transitioned to CTIS with ID 2024-518304-53-00 check the CTIS register for the current data.

The primary objective of the study is to compare the PFS of SPd versus EloPd in patients with MM who have received 1 to 4 prior anti-MM lines of therapy and never received pomalidomide, selinexor, or elotuzumab. Patients must have had prior treatment with an IMiD (lenalidomide) and a PI in the past, and must have received treatment with an anti-CD38 mAb in the immediate line of therapy prior to start of study treatment. Additional objectives are to compare clinical efficacy and safety of SPd versus EloPd, to characterize the pharmacokinetics (PK) of selinexor and pomalidomide, and to evaluate potential exposure-response relationships for applicable efficacy and safety endpoints in patients treated with SPd.

**Study design**

This study is comprised of 2 parts:
• Part 1 included patients randomized to 3 arms: selinexor 40 mg QW in combination with Pd (SPd-40), selinexor 60 mg QW in combination with Pd (SPd-60), and elotuzumab in combination with Pd (EloPd), to confirm the optimal dose of selinexor for Part 2 of the study. Data from STOMP and XPORT-MM-028 confirmed the optimal selinexor regimen to be SPd-40; thus, starting in protocol version 2.0, the study will enroll patients under Part 2.
• Part 2 will include patients randomized in a 1:1 manner between the SPd-40

and EloPd arms until ~222 patients are included in the ITT population.
The final PFS will include patients from Part 2 as well as patients from the SPd-40 and EloPd arms from Part 1 who were treated with an anti-CD38 mAb in their immediate prior line of therapy.

**Intervention**

Please refer to tables 2 and 3 in the synopsis.

**Study burden and risks**

Please refer to appendix D of the ICF.

# Contacts

**Public**
Stichting European Myeloma Network (EMN)

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**Scientific**
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NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

There is no difference in the patient population enrolled in Part 1 or Part 2 of the study. 1. Relapsed or refractory MM per IMWG criteria with measurable disease as defined by at least 1 of the following: a. Serum M-protein >=0.5 g/dL (>=5 g/L) by serum protein electrophoresis (SPEP) or, for immunoglobulin (Ig) A or D myeloma, by quantitative serum IgA or IgD levels >=0.5 g/dL. b. Urinary M-protein excretion >=200 mg/24 hours. c. Serum free light chain (FLC) >=100 mg/L, provided that the FLC ratio is abnormal (normal FLC ratio: 0.26 to 1.65). 2. Received at least 1 and no more than 4 prior anti-MM lines of therapy. Induction therapy followed by stem cell transplant and consolidation/maintenance therapy will be considered as 1 line of therapy. 3. Prior therapy that includes >=2 consecutive cycles of lenalidomide and a proteasome inhibitor given alone or in combination.
4. Prior therapy with an anti-CD38 mAb as part of their immediate last line of therapy prior to study entry (Before protocol version 2.0 patients with any prior therapy with an anti-CD38 mAb were eligible for the study.) 5. Eastern Cooperative Oncology Group (ECOG) performance status of <=2. 6. Resolution of any clinically significant non-hematological toxicities (if any) from previous treatments to Grade <=1 by Cycle 1 Day 1 (C1D1). Patients with clinically significant Grade 2 neuropathy from previous treatments may be included. 7. Adequate hepatic function within 28 days prior to C1D1: a. Total bilirubin <2 × upper limit of normal (ULN) (except patients with Gilbert's syndrome who must have a total bilirubin of <3 × ULN) b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) <2.5 × ULN 8. Adequate renal function within 28 days prior to C1D1 (estimated creatinine clearance [CrCl] of >=15 mL/min (not requiring dialysis), calculated using the formula of Cockcroft and Gault or measured by 24-hour urine collection). 9. Adequate hematopoietic function within 7 days prior to C1D1 defined as absolute neutrophil count >=1.5 x 10^9/L, hemoglobin >=8.5 g/dL, and platelet count >=100 x 10^9/L (patients for whom <50% of bone marrow nucleated cells are plasma cells) or >=75 x 109/L (patients for whom >=50% of bone marrow nucleated cells are plasma cells) a. Patients receiving hematopoietic growth factor support, including erythropoietin, darbepoetin, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), and platelet stimulators (e.g., romiplostim, or eltrombopag) must have a 2-week interval between growth factor support and the Screening assessments. b. Patients must have: - At least a 2-week interval from the last red blood cell (RBC) transfusion prior to the Screening hemoglobin assessment, and - At least a 1-week interval from the last platelet transfusion prior to the Screening platelet assessment. However, patients may receive RBC and/or platelet transfusions as clinically indicated per institutional guidelines during the study. 10. Patients with active hepatitis B virus (HBV) are eligible if antiviral therapy for hepatitis B has been given for >8 weeks and viral load is <100 IU/mL. Patients with evidence of non-active HBV should be discussed with the Medical Monitor and should be monitored or receive prophylaxis at the discretion of the Investigator and

study site institutional guidelines 11. Patients with a history of hepatitis C virus (HCV) are eligible if they have received adequate curative anti-HCV treatment and HCV viral load is below the limit of quantification. 12. Patients with a history of human immunodeficiency virus (HIV) are eligible if they have CD4+ T cell counts >=350 ells/µcL, negative viral load, and no history of acquired immunodeficiency syndrome (AIDS)- defining opportunistic infections in the last year and should be on established antiretroviral therapy (ART) for at least 4 weeks.
13. Global (excluding Germany): Female patients of childbearing potential must have a negative serum pregnancy test within 10 to 14 days and a second negative serum test within 24 hours prior to the first dose of study treatment. Female patients of childbearing potential ho are sexually active must agree to use a barrier method in addition to highly effective methods of contraception throughout the study and for 90 days following the last dose of study treatment.
Germany only: Premenopausal female patients of childbearing potential must have a negative serum pregnancy test within 10 to 14 days and a second negative serum test within 24 hours prior to the first dose of study treatment. Premenopausal female patients of childbearing potential who are sexually active must agree to use a barrier method in addition to highly effective methods of contraception throughout the study and for 90 days following the last dose of study treatment.
Please refer to protocol for inclusion criteria #14 to 17.

## Exclusion criteria

There is no difference in the patient population enrolled in Part 1 or Part 2 of the study. This trial will enroll patients who meet all of the inclusion criteria and none of the exclusion criteria. Exclusion Criteria: 1. Smoldering MM. 2. Plasma cell leukemia. 3. Documented active systemic amyloid light chain amyloidosis. 4. Any history of central nervous system MM. 5. Prior treatment with: a. a selective inhibitor of nuclear export (SINE) compound, including selinexor. b. pomalidomide or elotuzumab. 6. Any concurrent medical condition or disease that is likely to interfere with study procedures. 7. Uncontrolled active infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to C1D1. Patients on prophylactic antibiotics or with a controlled infection within 1 week prior to C1D1 are acceptable. 8. Known intolerance, hypersensitivity, or contraindication to any of the study treatments. 9. Radiation, chemotherapy, or immunotherapy or any other anticancer therapy including investigational therapies and high dose dexamethasone (i.e., 40 mg daily for 4 days per week) <=2 weeks prior to C1D1. Patients on long-term glucocorticoids during Screening do not require a washout period, but must be able to tolerate the specified dexamethasone dose in this study. 10. Prior autologous stem cell transplantation <100 days or allogeneic stem cell transplantation <4 months prior to C1D1. 11. Major surgery within 4

weeks prior to C1D1. 12. Active graft versus host disease after allogeneic stem cell transplantation. 13. Pregnant or breastfeeding females. 14. In the opinion of the Investigator, patients who are below their ideal body weight and would be unduly impacted by changes in their weight. 15. Clinically significant cardiac disease, including: a. Myocardial infarction within 6 months before C1D1, or unstable or uncontrolled disease/condition related to or affecting cardiac function (e.g., unstable angina, congestive heart failure, New York Heart Association Class III-IV). b. Uncontrolled cardiac arrhythmia (CTCAE v. 5.0 Grade 2 or higher) or clinically significant electrocardiogram (ECG) abnormalities. c. Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF [APPENDIX 4]) >470 msec. 16. Any active gastrointestinal dysfunction interfering with the patient's ability to swallow tablets, or any active gastrointestinal dysfunction that could interfere with absorption of study treatment. 17. Any active, serious psychiatric, medical, or other conditions/situations that, in the opinion of the Investigator, could interfere with treatment, compliance, or the ability to give informed consent. 18. Contraindication to or inability to tolerate any of the required concomitant drugs such as dual antiemetics (Section 10.1.1 ), or supportive treatments. 19. Patients unwilling or unable to comply with the protocol.

# Study design

## Design

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|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 23-01-2024 |
| Enrollment: | 11 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Registration: | No |
| Product type: | Medicine |
| Brand name: | Dexa 4 mg inject JENAPHARM |
| Generic name: | dexamethasone |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Dexa 8 mg inject JENAPHARM |
| Generic name: | dexamethasone |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Empliciti |
| Generic name: | elotuzumab |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Imnovid |
| Generic name: | pomalidomide |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | selinexor |
| Generic name: | selinexor |
| Registration: | Yes - NL outside intended use |

# Ethics review

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|---|---|
| Approved WMO Date: | 21-02-2022 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 18-07-2022 |
| Application type: | First submission |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam |

| | |
|---|---|
| | (Rotterdam) |
| Approved WMO Date: | 16-02-2023 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 21-02-2024 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 19-04-2024 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 09-05-2024 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |
| Approved WMO Date: | 14-06-2024 |
| Application type: | Amendment |
| Review commission: | METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam) |

# 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 |
|---|---|
| EU-CTR | CTIS2024-518304-53-00 |
| EudraCT | EUCTR2021-001691-41-NL |
| ClinicalTrials.gov | NCT05028348 |
| CCMO | NL78293.078.22 |