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Ixazomib citrate-thalidomide-low dose dexamethasone induction followed by maintenance therapy with ixazomib citrate or placebo in newly diagnosed multiple myeloma patients not eligible for autologous stem cell transplantation; a randomized phase II trial

PROTOCOL

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Synopsis

Rationale

Standard of care in Europe for the newly diagnosed elderly MM patient is melphalan-prednisone-bortezomib. Hematological toxicity and increased rate of second primary malignancies with alkylating agents justifies the investigation of a triplet combination therapy ommitting alkylating agents. A triplet combination without alkylating agents combining an IMiD (thalidomide or lenalidomide), a proteasome inhibitor (bortezomib) and corticosteroids have been found to be effective indeed. In view of a high incidence of peripheral neuropathy in the current protocol bortezomib will be replaced with the oral proteasome inhibitor ixazomib citrate. Importantly, this is an oral regimen, especially being convenient in an elderly population. The hypothesis is that the response rate will be superior, with less hematological and a lower incidence of neural toxicity as compared to standard therapy. In addition, a role for maintenance therapy with bortezomib has been suggested in non-head to head comparisons. Therefore, the efficacy of ixazomib citrate maintenance therapy will be investigated by randomizing maintenance treatment with ixazomib citrate versus placebo.

Study objectives

- To compare the efficacy determined as progression free survival between maintenance treatment with ixazomib citrate versus placebo
- To determine efficacy of induction therapy determined as stringent CR, CR, VGPR and PR
- To determine toxicity, polyneuropathy and hematological toxicity in specific, during induction and maintenance treatment with xazomib citrate or placebo
- To determine progression free survival and overall survival from registration
- To compare the efficacy between maintenance treatment with ixazomib citrate versus placebo determined as overall survival from randomization
- To determine the efficacy of maintenance therapy with ixazomib citrate determined as an increase in response during maintenance treatment with ixazomib citrate versus placebo
- To determine efficacy of induction therapy determined as time to response

- To determine feasibility, defined as discontinuation rate due to toxicity, during induction and maintenance treatment with ixazomib citrate or placebo
- To determine time to next treatment
- To determine PFS on second line therapy
- To determine Quality of Life during induction therapy and maintenance treatment with ixazomib citrate versus placebo
- To identify clinical, imaging-related and molecular prognostic markers prognostic and predictive for outcome and toxicity
- To determine second primary malignancies (SPM).

Study design

Prospective, multicenter, randomized double blind placebo controlled phase II

Patient population

Previously untreated symptomatic patients with MM age ≥ 66 years or patients ≤ 65 years and ineligible for high dose therapy and peripheral stem cell transplantation

Intervention

Following induction therapy half of the patients will receive 4 mg of ixazomib citrate capsules as a maintenance therapy until progression and the other half of patients will receive placebo capsules as a maintenance therapy until progression

Duration of treatment

Expected duration of induction treatment: 9 months

Maintenance therapy with ixazomib citrate or placebo will be given until progression

All patients will be followed 8 years after registration

Target number of patients

Approximately 142 patients will be registered in order to randomize 94 patients. See section 14.1 for detailed information.

Expected duration of accrual

18 months

Main study endpoints

Progression free survival from randomization

Response rate after induction treatment

Benefit and nature and extent of the burden and isks associated with participation

The benefit will be that patients will be treated with a proteasome inhibitor/IMiD/corticosteroid based induction regimen, that has been shown to result in the highest response rates when non-head to head compared to European standard proteasome inhibitor/alkylating agent/corticosteroid or IMiD/alkylating agent/corticosteroid based regimens. Moreover, the oral proteasome inhibitor ixazomib citrate has been shown to induce considerably less neuropathy as compared to bortezomib. The burden will be that following induction therapy, maintenance therapy will be given until progression. Although a benefit with respect to prolongation of PFS is expected, the extent is currently unknown. Patients may suffer from side effects, although these are generally mild with ixazomib citrate. Moreover, 50% of patients will receive a placebo. There are no additional procedures required as compared to standard care. Patients will only participate in Quality of Life studies.

Planned interim analysis and DSMB

One interim analysis is planned, primarily to describe adverse events observed during the ixazomib citrate-thalidomide - low dose dexamethasone induction therapy. This will be done when of the first 20 registered patients the data regarding cycles 1-4 are available. Results of the interim analysis will be presented confidentially to a DSMB. Only if the DSBM recommends that the study should be stopped or modified, the results will be made public to the principal investigators for further decisions