PROTOCOL SUMMARY NMSG#23/15

Study Title: A prospective phase 2 study to assess the minimal residual disease after ixazomib plus lenalidomide and dexamethasone (IRd) treatment for newly diagnosed transplant eligible myeloma patients

Phase: Phase 2

Number of Patients: 120

Study Objectives

Primary

- To investigate the protocol treatment efficacy based on serological and bone marrow analyses including minimal residual disease assessment by MFC and safety of IRd induction followed by ASCT, IRd consolidation and IR or R maintenance.

Secondary

- MRD-negativity at any time during study protocol treatment
- Safety
- Overall response rate (ORR)
- Progression-free survival (PFS) in both groups
- Improvement of responses and MRD negativity during maintenance in both groups
- Time to next treatment
- Quality of life
- Overall survival (OS)

Tertiary/Exploratory

- Exome and RNA sequencing of myeloma cells of high-risk patients, drug sensitivity and resistance testing of high-risk patients (translational part of the study with specific funding from Celgene)
- Comparison of MFC and molecular response of MRD-negative patients

Overview of Study Design:

This Nordic Myeloma Study Group 23/15 is a first line study for multiple myeloma (MM) patients eligible for high dose treatment (HDT) supported with autologous stem cell transplantation (ASCT). The main aim of this study is to assess the proportion of patients having a MFC-MRD < 0.01% (multiparameter flow cytometry- minimal residual disease < 0.01%), during the protocol treatment including four cycles of IRd induction, single ASCT, two IRd cycles as consolidation and risk stratified maintenance. The total proportion of patients reaching this response will be assessed after one year of maintenance.

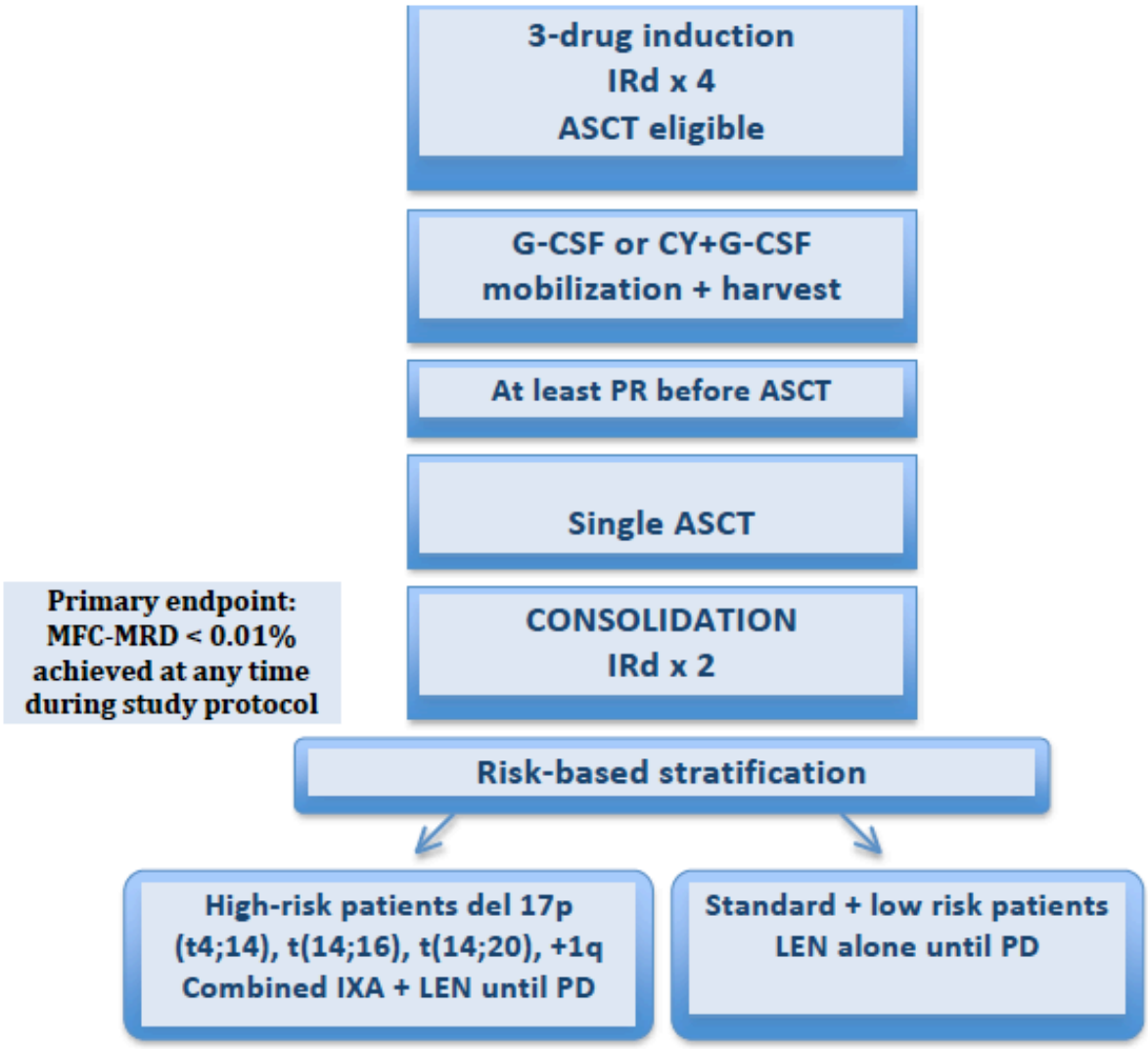
This is not a randomized study but we have the Finnish Myeloma Study-MM02 as a historical control with the design of lenalidomide plus bortezomib and dexamethasone

(RVD) + single ASCT + lenalidomide maintenance design (NCT01790737).
The present study is using more sensitive MFC method so in addition to the MRD < 0.01% level (comparable with previous MFC-MRD) the secondary end point is MFC-MRD negativity. We assume that treatment with 2nd generation proteasome inhibitor (PI), ixazomib, combined with lenalidomide and dexamethasone during induction and consolidation followed by maintenance will produce higher proportion of patients with low- or negative MRD load. Prolonged treatment with PIs is considered to be important for high-risk-patients, at least for t(4;14) and del17p patients[1] and the risk stratified maintenance phase is planned to answer the question whether the PFS of high-risk and standard-or low-risk patients will be comparable with this design.

Duration of Study:

Expected duration of treatment:

- induction 4-5 months
- stem cell mobilization, collection and ASCT with post-transplant supportive care 2 months
- consolidation 2 months, starting within 100 days after ASCT
- maintenance will be started one month after consolidation continuing until progression or toxicity
- The first analyses of the study will be done when the last patient has been two years on maintenance treatment. The treatment of each individual patient will continue until progression or excess toxicity.
- All patients will be followed until 10 years after registration


3-drug induction
IRd x 4
ASCT eligible
G-CSF or CY+G-CSF
mobilization + harvest
At least PR before ASCT
Single ASCT
CONSOLIDATION
IRd x 2
Primary endpoint:
MFC-MRD < 0.01%
achieved at any time
during study protocol
Risk-based stratification
High-risk patients del 17p
(t4;14), t(14;16), t(14;20), +1q
Combined IXA + LEN until PD
Standard + low risk patients
LEN alone until PD