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Inclusion and exclusion criteria:

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Newly diagnosed multiple myeloma as defined by the International Myeloma Working Group (IMWG) and eligible for high-dose therapy and ASCT.
2. Must be ≥18 and ≤75 years of age at the time of signing the informed consent.
3. Measurable disease as in serum as defined by the IMWG criteria; serum monoclonal paraprotein (M-protein) level ≥10 g/L or light chain multiple myeloma with involved serum immunoglobulin FLC >100 mg/L and abnormal serum immunoglobulin kappa lambda FLC ratio.
4. Voluntary written informed consent.
5. Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2. ECOG 3 can be enrolled if caused by myeloma.
6. Must be willing and able to adhere to the study protocol visit schedule and other protocol requirements.
7. Female of childbearing potential (FCBP) must have a confirmed negative serum pregnancy test within 10 to 14 days prior to inclusion.
8. FCBP and male subject who are sexually active with FCBP must agree to use highly effective concomitant methods of contraceptive during the study and for at least 28 days following the last study drug dose. Male subjects must use contraception and refrain from donating sperm for at least 28 days after the last dose of lenalidomide according to Pregnancy Prevention.

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

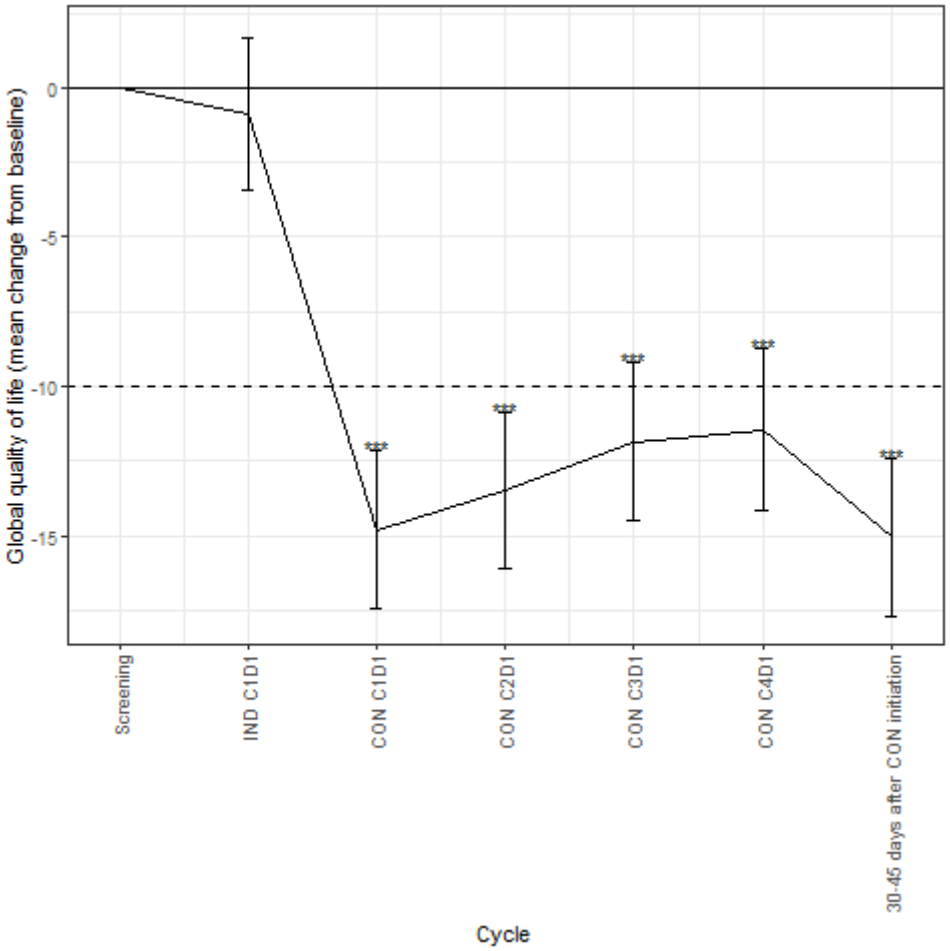
1. Received more than one cycle of induction treatment for multiple myeloma.
2. Ongoing or active systemic infection, active hepatitis B or C virus infection or known human immunodeficiency virus (HIV) positive
3. Concurrent medical or psychiatric condition or disease that is incompatible to HDM and ASCT or that will likely result in reduced study compliance and reduce ability to follow study procedures, or that in the opinion of the investigator, would constitute a hazard for participating in this study.
4. An active malignancy with a lower life expectancy than myeloma
5. Female patient who has a positive serum pregnancy test during the screening period.
6. Female patient who is lactating during the screening period but are not willing to stop lactating prior to the first treatment cycle starts.
7. Known allergies to any of the study medications, their analogues, or excipients in the various formulations of any agent.

Supplemental Table 1. REMNANT Modified IMWG response criteria

Two consecutive assessments are needed for confirmation of all response grades, except for bone marrow samples and imaging assessments. Plasmacytoma(s) measurement is determined by the sum of the products of the maximal perpendicular diameters of measured lesions.	
Response criteria	
MRD-negative	Complete response or better as defined below plus: • Absence of phenotypically aberrant clonal plasma cells by NGF Euroflow on bone marrow aspirates with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Stringent complete response	Complete response as defined below plus: • Absence of clonal cells in bone marrow by immunohistochemistry or negative 2-4 color flow cytometry
Complete response	• Negative immunofixation in the serum and a normal FLC ratio* • <5% PCs in bone marrow. • Disappearance of any soft tissue plasmacytomas.
Very good partial response	• ≥90% reduction in serum M-protein and a ≥90% decrease in the difference between involved and uninvolved FLC levels from baseline is required (if measurable at baseline). • ≥90% reduction in size of soft tissue plasmacytomas.
Partial response	• ≥50% reduction of serum M-protein and a ≥50% decrease in the difference between involved and uninvolved FLC levels from baseline is required (if measurable at baseline). • ≥ 50% reduction in size of any soft tissue plasmacytomas.
Stable disease	Not meeting criteria for CR, VGPR, PR or progressive disease.
Disease progression	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: • Serum M-protein (absolute increase must be ≥5 g/L) • Serum dFLC (absolute increase must be >100 mg/L) • Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis;

Abbreviations: MRD=minimal residual disease. NGF=next-generation flow. FLC=free light chain. PC=plasma cell. M-protein=monoclonal protein. SPD=sum of the products of the maximal perpendicular diameters of measured lesions. CR=complete response. VGPR=very good partial response. PR=partial response. dFLC=difference FLC.
*The FLC ratio is considered normal if both involved/uninvolved FLC are in the normal range and/or below normal range.

Supplemental Figure 1. Mean change in global health status/quality of life score



Mean change in global health status/quality of life score from screening to induction cycle 1 day 1 (IND C1D1), consolidation cycle 1 day 1 (CON C1D1) and so on, presented with 95% confidence intervals for each mean score. Threshold for clinical meaningful deterioration of <10 points is presented with a horizontal dashed line. Time points with clinical statistically significant (<0.001) and clinical meaningful deterioration in global health status/quality of life score are marked with asterisk (***).

Supplemental Table 2. Multi-Center Sites

Muli-Center Site	**Site Principal Investigator**	**Patient distribution**
Oslo University Hospital	Frida Bugge Askeland, MD Fredrik Schjesvold, MD	70
Stavanger University hospital	Einar Haukås, MD	47
Vestfold Hospital Trust	Magnus Moksnes, MD	39
Akershus University Hospital	Anette L. Eilertsen, MD	32
Haukeland University Hospital	Galina Tsykonova, MD	35
Hospital Oestfold, Kalnes	Birgitte Dahl Eiken, MD	32
University Hospital of North Norway	Nils Morten Leknes, MD	20
Sørlandet Hospital, Kristiansand	Jürgen Rolke, MD	26
Levanger Hospital	Vidar Stavseth, MD	16
Ålesund Hospital	Eivind Samstad, MD	13
Nordland Hospital, Bodø	Randi Fykse Hallstensen, MD	15
Førde Central Hospital	Damian Szatkowski, MD	5
St. Olav's Hospital	Tobias S. Slørdahl, MD	32