



# **Outcomes of maintenance Treatment using lenalidomide or Bortezomib in Multiple Myeloma patients post Autologous Stem Cell Transplantation**

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا  
إلا ما علمتنا إنك أنت  
العليم العظيم

صدق الله العظيم

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## *List of Abbreviations*

Abb.	Full term
<b>AML</b> .....	Acute myeloid leukemia
<b>ASCT</b> .....	Autologous stem cell transplant
<b>Bort</b> .....	Bortezomib
<b>CALGB</b> .....	Cancer and leukemia group B
<b>CBC</b> .....	Complete blood count
<b>CR</b> .....	Complete remission
<b>CRAB</b> .....	C = calcium (elevated), R = renal failure, A = anemia, B = bone lesions
<b>CT</b> .....	Computerized tomography
<b>CyBorD</b> .....	Bortezomib intravenously, cyclophosphamide and dexamethasone
<b>EFS</b> .....	Event free survival
<b>EMD</b> .....	Extra medullary disease
<b>ESR</b> .....	Erythrocyte sedimentation rate
<b>FISH</b> .....	Fluorescence in situ hybridization
<b>FLC</b> .....	Free light chain
<b>GEP</b> .....	Gene expression profile
<b>GEP</b> .....	Gene expression profile
<b>HDC</b> .....	High-dose chemotherapy
<b>HMT</b> .....	Histone methyltransferase
<b>HU</b> .....	Hounsfield units
<b>IFN</b> .....	Interferons
<b>IMiDs</b> .....	Immunomodulatory drugs
<b>IMWG</b> .....	International myeloma working group
<b>KRD</b> .....	Carfilzomib, lenalidomide, and dexamethasone
<b>KRD</b> .....	Carfilzomib, lenalidomide, and dexamethasone
<b>LDH</b> .....	Lactate dehydrogenase

## *List of Abbreviations Cont...*

Abb.	Full term
<b>Len</b> .....	Lenalidomide
<b>MDS</b> .....	Myelodysplasia
<b>MGUS</b> .....	Monoclonal gammopathy of undetermined significance
<b>MM</b> .....	Multiple myeloma
<b>MRC</b> .....	Myeloma research council
<b>MRD</b> .....	Minimal residual disease
<b>MRI</b> .....	Magnetic resonance imaging
<b>mSMART</b> .....	Mayo Stratification for Myeloma and Risk-adapted Therapy
<b>NGS</b> .....	Next generation sequencing
<b>OS</b> .....	Overall survival
<b>PCL</b> .....	Plasma cell leukemia
<b>PD</b> .....	Pomalidomide plus low-dose dexamethasone
<b>PET</b> .....	Positron emission tomography
<b>PFS</b> .....	Progression free survival
<b>PFS</b> .....	Progression- free survival
<b>PIs</b> .....	Proteasome inhibitors
<b>RANKL</b> .....	Receptor activator for nuclear factor $\kappa$ B ligand
<b>Rd</b> .....	Lenalidomide plus dexamethasone
<b>S-2M</b> .....	Serum - 2-microglobulin
<b>sCR</b> .....	Stringent CR
<b>SCT</b> .....	Stem cell transplant
<b>SD</b> .....	Standard deviation
<b>SGOT</b> .....	Serum glutamic oxaloacetic transaminase
<b>SGPT</b> .....	Serum glutamic pyruvic transaminase
<b>SMM</b> .....	Smouldering multiple myeloma
<b>SPMs</b> .....	Second primary malignancies

## *List of Abbreviations Cont...*

Abb.	Full term
<b>SPSS</b> .....	Statistical Program for Social Science
<b>TD-PACE</b> .....	Thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide
<b>TRM</b> .....	Treatment related majority
<b>TTP</b> .....	Median time to progression
<b>VCD</b> .....	Bortezomib, cyclophosphamide, and dexamethasone
<b>VGPR</b> .....	Very good partial response
<b>VRD</b> .....	bortezomib, lenalidomide, and dexamethasone
<b>VTD</b> .....	Bortezomib, thalidomide, and dexamethasone
<b>WBC</b> .....	White blood celss

# INTRODUCTION

**M**ultiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. Myeloma is most frequently diagnosed among people aged 65 to 74 years, with the median age being 69 years (*Siegel et al., 2016*).

However, statistics also reveal that death rates have been falling an average 0.8% each year over the period of 2004 through 2013 due to availability of newer and more effective treatment options. Symptoms of the disease are bony aches, polyuria, gastrointestinal disturbances, rapid progress dehydration and renal impairment (*Siegel et al., 2016*).

Most patients have serum M-protein with or without associated urinary M-protein. In the Mayo Clinic review of 1027 patients newly diagnosed with MM, 20% of patients had secretory urinary M-proteins; however, 3% of patients had neither serum nor urine M-protein, and therefore had no secretory myeloma (*Kyle et al., 2003*).

Specific chromosomal abnormalities have been identified in patients with MM involving translocations, deletions, or amplifications. The three main translocations are the t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16)(q32;q23). Several studies have confirmed that patients with t(4;14) and

t(14;16) have a poor prognosis, while t(11;14) is believed to impart no increased risk (*Gertz et al., 2005*).

Recommends additional tests that may be useful under some circumstances. These include whole body MRI or whole body PET/CT scan (*Durie et al., 2002*).

Treatment of MM has been rapidly evolving because of the introduction of new classes of drugs, such as immunomodulatory drugs (IMiDs) (*Brenner et al., 2008; McCarthy et al., 2017*).

In addition, there is increasing understanding of the tumor biology, creating the rationale for new combinations of therapies and new drug development (*Anderson, 2011*).

Patients presenting with active (symptomatic) myeloma are initially treated with primary therapy and in selected patients, primary therapy is followed by high-dose chemotherapy with autologous stem cell support. The 3-drug regimens is preferred than the 2-drug regimens as it's based on improved response rates, depth of response, and rates of progression-free survival (PFS) and overall survival (OS) seen with 3-drug regimens in clinical trials. However, the panel notes that doublets could be used if a patient is elderly and/or frail and unable to tolerate a 3-drug regimen (*Anderson, 2011*).

The results have shown that primary therapy with bortezomib/ lenalidomide/dexamethasone is active and well

tolerated in all newly diagnosed patients with MM, transplant eligible as well as transplant ineligible (*Richardson et al., 2010*).

Autologous SCT results in high response rates and remains the standard of care after primary therapy for eligible patients. In 1996, results of the first randomized trial were reported; this trial demonstrated that autologous SCT is associated with statistically significant higher response rates and increased OS and EFS when compared with the response of similar patients treated with conventional therapy (*Attal et al., 1996*).

The response rates were evaluated after induction therapy and after autologous SCT. Taking into consideration patients who actually underwent the autologous SCT, the CR rates were increased from 35% pre-transplant to 57% post-transplant, in the group treated with bortezomib, thalidomide, and dexamethasone as induction therapy and from 14% to 40% in the group treated with thalidomide and dexamethasone as induction therapy (*Rosiñol et al., 2012*).

Maintenance therapy with lenalidomide was found to significantly reduce risk of disease progression or death after both single and tandem transplantation compared with no maintenance. Bortezomib as Maintenance Therapy after Autologous SCT, the results from the HOVON study show that maintenance with single- agent bortezomib after autologous SCT is well tolerated and is associated with improvement of ORR (*McCarthy et al., 2017*).