Clinical trials in multiple myeloma

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Klinische trials in multipel myeloom

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. A.L. Bredenoord

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 6 maart 2024 om 13.00 uur

door

Ruth Wester

geboren te Hengelo (OV)

ISBN: 978-94-6361-959-2
Layout: Egied Simons
Cover: Egied Simons
Printing: Optima Grafische Communicatie

The work described in this thesis was performed at the Department of Hematology at the Erasmus Medical Center, Rotterdam, the Netherlands.

Printing of this thesis was financially supported by the Erasmus University Rotterdam.

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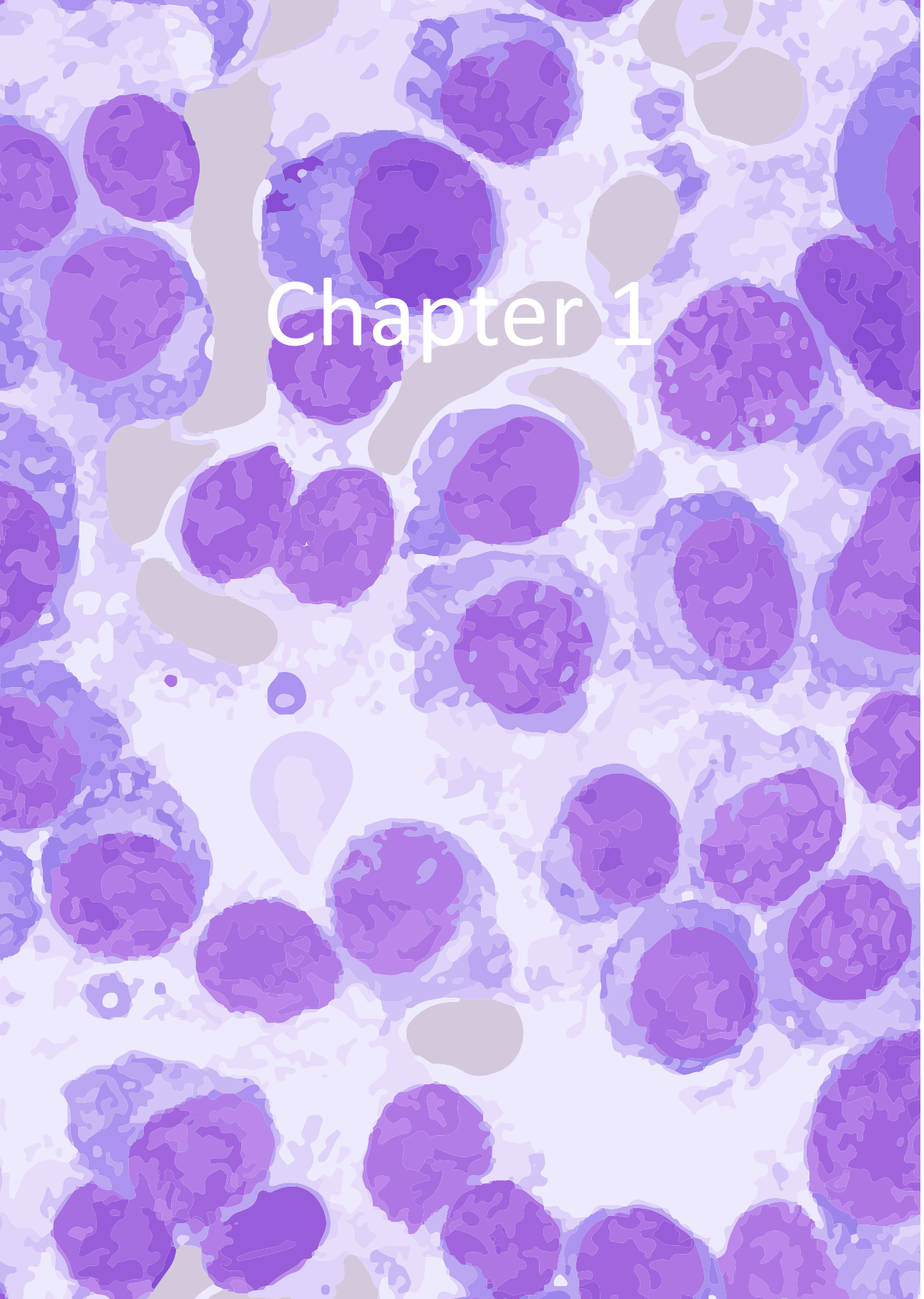
CONTENTS

PART I

General introduction, rationale and outline of the thesis



Chapter 1

Introduction

Table 1. IMWG diagnostic criteria for MGUS, SMM and MM[6]

Monoclonal gammopathy of undetermined significance
- Serum monoclonal protein < 30g/l and
- Clonal bone marrow plasma cells <10% and
- Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder

Smoldering multiple myeloma
- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60% and
- Absence of CRAB criteria or amyloidosis

Multiple myeloma
- Clonal bone marrow plasma cells ≥10% or biopsy-proven plasmacytoma and any of the following myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >177 µmol/L (>2 mg/dL)
    - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT
  - Any one or more of the following biomarkers predictive of fast progression:
    - Clonal bone marrow plasma cell percentage ≥60%
    - Involved: uninvolved serum free light chain ratio ≥100
    - >1 focal lesions on MRI studies

1.1 MULTIPLE MYELOMA

Multiple myeloma (MM) is a malignant plasma cell disorder and accounts for 1% of all malignancies and 10% of hematological malignancies. The annual incidence worldwide is approximately six per 100.000 and increases progressively with age, with a median presentation of 70 years. The incidence is higher in African Americans than in Caucasians.[1] The annual incidence in the Netherlands is approximately 7 per 100.000.[2]

Multiple myeloma is characterized by the clonal proliferation of malignant plasma cells in the bone marrow. These malignant plasma cells secrete a monoclonal protein (M-protein). This protein can be detected in serum and/or urine. The M-protein consists of a heavy chain, most commonly IgG or IgA and rarely IgM, IgD or IgE and a light chain (kappa or lambda). In 14% of patients the M-protein consists only of light chains and approximately 2% of patients with MM are characterized by the absence of detectable M-protein (non-secretory MM).[3]

Typical organ damage caused by the malignant plasma cell clone includes osteolytic bone lesions, renal failure, anemia, and hypercalcemia. These features are the result of the accumulation of myeloma (plasma) cells in tissues and due to the production of cytokines by the myeloma (plasma) cells.[4]

Moreover, due to immunodeficiency, caused by clonal expansion of myeloma (plasma) cells producing one aberrant immunoglobulin together with impaired production of functional normal immunoglobulins, recurrent infections are common in patients with MM.

The median overall survival (OS) has significantly improved during the last decades due to the introduction of novel therapeutic agents, i.e. high dose melphalan (HDM) followed by autologous stem cell transplantation (ASCT), immune modulating agents (IMiDs), proteasome inhibitors (PI), monoclonal antibodies and most recently chimeric antigen receptor T (CAR-T) cell therapy and treatment with bispecific T-cell engagers (BiTEs).[5]

1.1.1. Diagnosis

The diagnosis of symptomatic MM requires the presence of an M-protein, monoclonal plasma cells in the bone marrow and the presence of end organ damage, also specified by the CRAB criteria (hypercalcemia, renal failure, anemia and bone lesions). The International Myeloma Working Group (IMWG) developed criteria for MM and other plasma cell dyscrasias, as shown by Table 1.[6]

1.2 BIOLOGY OF MULTIPLE MYELOMA AND PREMALIGNANT CONDITIONS

MM evolves from a premalignant stage known as monoclonal gammopathy of undetermined significance (MGUS), progresses to smoldering multiple myeloma (SMM) and eventually to symptomatic MM.[7, 8] MGUS is present in 1% of patients older than 50 years and increases to 3% in patients older than 70 years. It is characterized by the presence of a serum M-protein less than 30 g/L, <10% monoclonal plasma cells in the bone marrow and absence of CRAB criteria (Table 1). The risk of progression of MGUS to MM is approximately 1% per year.

SMM is characterized by a higher tumor burden presenting with an M-protein of more than 30 g/L and/or clonal bone marrow myeloma (plasma) cells >10%, however without end organ damage (CRAB) or myeloma defining events (Table 1). The risk of progression to MM is approximately 10% per year and decreases after five years to 3% per year.[9, 10]

No definitive causative factors have been found for the development of MGUS/SMM/MM, however factors such as age, race, hereditary factors, history of autoimmune disease, history of inflammatory conditions and exposure to toxins were found to be possibly related. [11, 12]

Important initiating events involved in development of clonal plasma cell proliferation in MGUS include primary immunoglobulin heavy chain (IgH) translocations with potential oncogenes in other chromosomes (involvement of 5 recurrent chromosomal partners; 4p16, 6p21, 11q13, 16q23, 20q11) and hyperdiploidy.[12] As a result of secondary genetic alterations MGUS progresses to SMM and eventually MM and hereafter plasma cell leukemia. In plasma cell leukemia the malignant clone is not confined to the bone marrow and expands rapidly to a leukemic phase.[13] Extramedullary disease (EMD) occurs when myeloma (plasma) cells reside outside of the bone marrow and grow independent of the bone marrow microenvironment. It is characterized by the development of plasmacytomas in soft tissue due to hematogenous spread of myeloma (plasma) cells. Patients with EMD often have a poor prognosis.[14]

The bone marrow microenvironment facilitates the growth and proliferation of myeloma (plasma) cells and other hematopoietic cells. Plasma cells in MM are dependent on the microenvironment for their growth and proliferation by interaction of myeloma cells with components of this microenvironment, including bone marrow stromal cells (BMSC), osteoblasts, osteoclasts, endothelial cells and cells of the immune system including T-cells and myeloid-derived suppressor cells (MDSC).[15-17]

1.3 PROGNOSTIC FACTORS

During the last decades several staging systems predicting prognosis in MM have been developed. In 1975 the Durie-Salmon staging system was developed. This tool stratifies patients into three risk groups, low/intermediate/high, based on tumor burden, as well as M-protein, hemoglobin, serum calcium and osteolytic lesions.[18]

In 2005, the international staging system (ISS) stratified newly diagnosed MM(NDMM) patients into 3 risk categories using β2-microglobulin and serum albumin levels demonstrating a median survival of 62 months, 44 months and 29 months for stage I, II and III respectively. [19-21].

Adding LDH and cytogenetic abnormalities (CA) to the ISS staging system resulted in the revised international staging system (R-ISS). [22, 23] R-ISS stage I includes ISS stage I, no high risk CA, and normal LDH. High risk cytogenetics include del17p, t(4;14) and t(14;16). R-ISS stage III includes ISS stage III with high-risk CA and/or high LDH levels; R-ISS stage II includes all the other conditions. The median survival was 82%, 62% and 40% at 5 years for stage I, II and III respectively. Recently the R2-ISS was developed, to improve risk stratification by adding 1qgain/amplification, which had proven to be a poor prognostic factor.[24] A value was assigned to each risk feature according to their OS impact (ISS-III 1.5, ISS-II 1, del(17p) 1, high LDH 1, t(4;14) 1, and 1q+ 0.5 points).[25] The prognostic value of each single baseline risk feature was analyzed in an additive fashion, including 1q gain/amplification in the risk calculation. An additive scoring system based on top features predicting PFS and OS was developed and validated. Based on the total additive score four subgroups were defined; Low (score=0) with a median PFS of 68 months, Low-intermediate (score=0.5-1) with a median PFS of 45.5 months, High-intermediate (score=1.5-2.5) with a median PFS of 30.2 months and high (score=3-5) with a median PFS of 19.9 months.

Furthermore, some clinical factors are strong indicators for a poor prognosis; existence of extramedullary disease, renal failure at presentation, high level of circulating myeloma (plasma) cells and plasma cell leukemia have a negative impact on prognosis. [7, 26-28] In current practice, patients with NDMM with adverse cytogenetic risk factors have an indication for a tandem autologous stem cell transplantation.[29]

1.4 TREATMENT AND TARGETS OF THERAPY

Before the introduction of melphalan (an alkylating agent) the median survival of patients with MM was approximately 17 months. [30] The median survival improved to 30 months with the introduction of melphalan and prednisone (MP). [31, 32] In 5% of patients a complete response (CR) was achieved. In the years after introduction of MP as treatment for MM, no further improvement of survival was achieved. In 1983 treatment with HDM followed by autologous stem cell transplantation (ASCT) was introduced.[33] Hereby inducing higher response rates and an improvement in PFS. The median survival increased to approximately 5 years. [34] Treatment with combinations of chemotherapy using vincristine, adriamycin and dexamethasone (VAD) was also widely used. This led to rapid responses. However, survival was similar to other strategies. [35]

At present, HDM followed by ASCT is still the standard of care in first-line treatment of patients with NDMM. Survival has been greatly improved by the introduction of IMiDs, PI's and monoclonal antibodies.[36-38] (Figure 2.) Moreover, trials are ongoing using CAR-T cell therapy and bispecific antibodies (BITEs) with promising results in improving response and survival.[39-43]

The IMWG developed response criteria to evaluate the effectiveness of treatment in patients with MM. [44] Table 2 shows the definitions of the different responses.

Response evaluation is based on serum levels of M-protein and free light chains (FLC), urinary levels of M-protein and the amount of monoclonal plasma cells in the bone marrow. During treatment, response evaluation is performed after each treatment cycle. During follow-up, response is evaluated less frequently depending on clinical symptoms and the course of M-protein or FLC in serum and/or urine.

Table 2. IMWG criteria for response [44]

Response	IMWG criteria
sCR[1]	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
CR[2]	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow
VGPR[3]	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or > 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR[4]	>50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by >90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable, a > 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, > 50% reduction in myeloma (plasma) cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was > 30% In addition to the above listed criteria, if present at baseline, a > 50% reduction in the size of soft tissue plasmacytomas is also required
No change/ stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive disease	Increase of > 25% from lowest response value in any one or more of the following: Serum M-component and/or (the absolute increase must be > 0.5 g/dL) Urine M-component and/or (the absolute increase must be > 200 mg/24 h) Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL Bone marrow plasma cell percentage; the absolute percentage must be > 10% Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features). It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice Development of new soft tissue plasmacytomas or bone lesions Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] Decrease in hemoglobin of > 2 g/dL [1.25 mmol/L] Rise in serum creatinine by 2 mg/dL or more [177 mmol/L or more]
Relapse from CR	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of > 5% plasma cells in the bone marrow Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)

[1]stringent complete response; [2]complete response; [3]very good partial response; [4]partial response

1.4.1 Immunomodulatory drugs (IMiDs)

The introduction of IMiDs has changed the landscape for patients with MM. IMiDs such as thalidomide and lenalidomide have improved PFS and OS in NDMM. [36, 37] IMiDs have anti-proliferative, and anti-angiogenic effects as well as direct anti-MM activity. Previous studies have shown that IMiDs exert their anti-myeloma effect by binding to Cereblon (CRBN) a substrate receptor for cullin 4 ring E3 ubiquitin ligase complex.[45-48] Binding of IMiDs to CRBN induces ubiquitination and proteasomal degradation of the transcription factors Ikaros and Aiolos. This induces downregulation of interferon regulatory factor 4 (IRF-4) and cellular myelocytomatosis oncogene (*c-MYC*) which leads to growth inhibition and apoptosis of MM cells.[49] Thalidomide was introduced as treatment for MM in the late 1990s and lenalidomide was introduced in 2004. [50-52]

Pomalidomide has direct antiproliferative, anti-apoptotic, and antiangiogenic effects as well as modulatory effects on bone resorption, the immune system and the bone-marrow microenvironment.[53-55]

Currently, more potent next generation E3 ligase modulators (CELMoDs) such as iberdomide are being investigated in clinical trials. These CELMoDs show higher affinity in binding to CRBN. [56] Lonial et al. performed a phase 1/2 trial in patients with relapsed/ refractory MM (RRMM). Patients were treated with iberdomide 0.3-1.6mg on days 1-21 of each 28-day cycle combined with dexamethasone 40mg once per week. Iberdomide was well tolerated and showed clinical activity in heavily pretreated patients.[57] Currently, the EMN 26 is an ongoing phase 1/2 trial treating patients with iberdomide (CELMoD) maintenance.

1.4.2 Proteasome inhibitors

Bortezomib was introduced in clinical trials in 1999. It is a reversible inhibitor of the 26S proteasome complex. This proteasome complex plays a central role in destruction of cellular proteins and disrupts cell cycle regulation.[58] Nowadays it is standard of care in the treatment of patients with NDMM and RRRMM. In 2003 it was approved in patients with MM by the Food and Drug Administration (FDA) and in 2005 by the European Medicines Agency (EMA) based on three clinical trials.[59-61] In the APEX trial patients were randomized between treatment with bortezomib or high dose dexamethasone. The results showed a significant survival benefit in patients treated with bortezomib versus high dose dexamethasone, 80% versus 67% at 1 year respectively.[61] At present, bortezomib containing regimens are standard of care in treatment of NDMM and RRMM. Cavo et al. demonstrated an improvement in survival by adding bortezomib to thalidomide and dexamethasone (VTd) as induction and consolidation therapy (PFS at 3 years was 60% for VTd vs 48% for thalidomide and dexamethasone (Td).[62, 63]

Novel PI's have emerged: carfilzomib, oprozomib, marizomib and ixazomib. Carfilzomib is an epoxyketone proteasome inhibitor that binds selectively and irreversibly to the constitutive proteasome and immunoproteasome.[64] Carfilzomib is approved by the FDA

and the EMA as a single-agent for the treatment of patients with RRMM at a dose of 27 mg/m2 in combination with lenalidomide and dexamethasone (KTd) based on the data from the ASPIRE trial showing a superior PFS of median 26.3 months versus 17.4 months when patients were treated with lenalidomide/dexamethasone (Rd).[65] Carfilzomib is also approved at a dose of 56 mg/m2 in combination with dexamethasone (Kd), based on data from the ENDEAVOR trial showing a superior PFS over bortezomib/dexamethasone (Vd) of median 18.7 months versus 9.4 months (P<0.0001).[66]

Ixazomib is a reversible boronic ester oral prodrug PI. Preclinical studies have shown activity in myeloma cells resistent to bortezomib. In combination of ixazomib with Rd good responses were observed also in unfavourable CA. [67, 68]

1.4.3 Monoclonal antibodies

Monoclonal antibodies, i.e. daratumumab, isatuximab and elotuzumab have set the stage for a new treatment approach in MM.

Daratumumab is a monoclonal antibody targeting CD38 on the surface of plasmacells. CD38 is highly expressed on myeloma (plasma) cells and therefor an attractive target. Daratumumab is an anti-CD38 monoclonal antibody. It induces cell killing by multiple mechanisms: complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis through activation of complement proteins, natural killer cells, and macrophages, respectively.[69, 70] Currently, daratumumab combined with VTd or bortezomib/lenalidomide/dexamethasone (VRd) is approved for first line treatment in patients with transplant eligible and transplant ineligible NDMM. Isatuximab is a monoclonal antibody with the same target as daratumumab, CD38.[71] It is currently approved from second line treatment in patients with RRMM. The next chapters will outline the available treatment combinations with isatuximab.

Elotuzumab is a monoclonal antibody targeting signaling lymphocytic activation molecule F7 (SLAMF7). This is a cell surface glycoprotein highly expressed on MM cells and normal plasma cells.

1.4.4 New treatment modalities

Despite these major improvements in treatment modalities and thereby prognosis in patients with MM, the need for new treatment targets remains as survival is still limited. Currently, trials with treatment with BiTEs and CAR-T cell therapy are ongoing in patients with RRMM with promising results.

CAR-T cell therapy works by mechanisms distinct from those of other MM therapies. CAR-T cells are genetic modified T-cells expressing a CAR specific for a tumor antigen. It consist of an antigen-recognition domain and is connected by hinge and transmembrane domains to a co-stimulatory domain of the T-cell.[72] An important target of CAR-T cell therapy in patients with MM is B Cell Maturation Antigen (BCMA). BCMA is important for the differentation and maturation of B-cells. BCMA is expressed on plasmacells and myeloma cells and promotes expansion and suvival of myeloma cells. Moreover, BCMA suppresses the immunoenvironment of myeloma cells.[73, 74]

BiTEs such as talquetamab, AMG 420 and AMG 701 are currently under investigation in clinical trials. At present, teclistamab (BiTE) was approved by the European Medicines Agency (EMA), however not yet reimbursed in the Netherlands.

BiTEs have affinity for two different epitopes. They bind to both the CD3 T-cell receptor and a tumor-associated antigen such as BCMA or another antigen present on the myeloma cells, eventually leading to killing of the myeloma cell.[75] Teclistamab, AMG 420 and AMG 701 target BCMA. Talquetamab targets G protein-coupled receptor family C group 5-member D (GPRC5D). These agents show promising results in heavily pretreated patients.

1.4.5 Treatment in newly diagnosed multiple myeloma

1.4.5.1 Transplant eligible newly diagnosed multiple myeloma

Treatment in transplant eligible (TE) NDMM consists of induction, HDM and ASCT, consolidation and eventually maintenance therapy.

Induction

Until recently, the standard of care for patients with transplant eligible (TE) NDMM consisted of induction with four cycles VTd, bortezomib/cyclophosphamide/dexamethasone (VCd) or VRd followed by HDM and ASCT.[76-79] VTd is preferred over VCd, inducing higher overall response rates (ORR) than VCd (92.3% vs 83.4%; P = .01).[78] However treatment with VTd has a higher rate of peripheral neuropathy, therefor the need for improvement in therapy with less toxicity remains.

Several trials have investigated different treatment strategies in NDMM. In the Carthadex trial (included in this thesis) patients were treated with the combination of carfilzomib, thalidomide and dexamethasone (KTd). Median progression-free survival (PFS) was 58 months (95%CI: 45-67 months). Moreover, grade 3 polyneuropathy occurred in only one patient. In 2020 daratumumab combined with VTd (daraVTd) was approved by FDA and the EMA in the treatment of patients with TE NDMM. [80] Based on results of the phase III Cassiopeia study in which patients were randomized between treatment with daraVTd versus VTd alone, PFS at 18 months was 93% (95% CI 90–95) for daraVTd versus 85% (95% CI 81–88) for VTd ([Hazard ratio(HR)] 0·47, 95% CI 0·33–0·67, p<0·0001). [81] In 2022 this treatment was reimbursed in the Netherlands and is currently standard treatment in TE NDMM. Several other trials also showed an impressive improvement in response, PFS and overall survival (OS) in patients with NDMM by adding daratumumab to standard treatment. [80, 81] In the randomized phase II Griffin trial, patients were treated with daratumumab and VRD (daraVRd) versus VRd alone demonstrating a PFS at 24 months of 95.8% (95% CI,

89.2-98.4) for daraVRd versus 89.8% (95% CI, 77.1-95.7) for VRd. At ASH 2022, PFS data at a median follow up of 49.6 months were shown. Median PFS was not reached in both arms with a HR of 0.45 (0.21-0.95) in favour of daraVRd. In the phase 2 FORTE trial, patients were randomized between treatment with carfilzomib/lenalidomide/dexamethasonse (KRd) or carfilzomib/cyclophosphamide/dexamethasonse (KCd) followed by HDM and ASCT or treatment with 12 cycles of KRd. Hereafter patients were randomized between maintenance with carfilzomib and lenalidomide versus lenalidomide alone. The 4-year PFS from the first randomization was 69% with KRd and ASCT (95% CI 62–77; median not reached), 56% with KRd12 (median 55·3 months [95% CI 44–NR]), and 51% with KCd and ASCT (median 53 months [95% CI 36-NR]).[82] Table 3 shows survival data and response data from patients with TE NDMM, included in large clinical trials In the Perseus trial, the EMN 24 and the EMN 18 patients with TE NDMM are included using various combinations of induction and consolidation treatment combined with anti-CD38 therapy.

Table 3: Trials in transplant-eligible NDMM

	HOVON 95/EMN02[29]	**Cassiopeia [81]**	**Carthadex[83]**	**Griffin[80]**
Treatment	ASCT versus MPV, with or without VRD consolidation therapy, and lenalidomide maintenance	D-VTD versus VTD before and after ASCT	KTd before and after ASCT	D-VRD versus VRD before and after ASCT followed bij maintenance with D-len versus len
Number of patients	1197	1085	111	207
Results				
Progression free survival	56.7 months vs 41.9 months (p=0.0001)	93% versus 87% at 18 months	58 months	95,8% versus 89.8% at 24 months
Overall response rate	95% vs 95%	92.6% vs 89.9%	93%	99% versus 91.8%
CR/sCR rate	44% vs 42%	39% versus 26%	18%	51.5% versus 42.3%
EMA approved	yes	yes	no	no
Reimbursed	yes	yes	no	no

Intensification

In TE NDMM, HDM and ASCT is still the standard of care. In the HOVON 95/EMN02 trial, patients were randomized between treatment with continuous therapy versus HDM and ASCT, demonstrating an improvement in PFS, 56.7 months (95% CI 49.3–64.5) for ASCT vs 41.9 months (95% CI 37.5–46.9) for VMP (hazard ratio [HR] 0·73, 0·62–0·85; p=0·0001). [29]

Consolidation

Currently, consolidation treatment after HDM and ASCT is recommended based on several phase 3 trials. Consolidation treatment generates improvement of response and PFS as was shown in the EMN02/HOVON 95 trial, the Carthadex trial, the Cassiopeia trial and the DETERMINATION trial.[29, 81, 83, 84] Since daraVTd is approved for NDMM, consolidation with 2 cycles of daraVTd is the standard of care in the Netherlands.

Maintenance

Several trials have investigated the effect of maintenance therapy on outcome. In the HOVON 65/GMMG-HD 4 trial, patients were randomized between induction therapy with vincristine, doxorubicin, and dexamethasone (VAD) or bortezomib, doxorubicin, and dexamethasone (PAD) followed by HDM and ASCT. Maintenance consisted of thalidomide 50 mg (VAD) once per day or bortezomib 1.3 mg/m(2) (PAD) once every 2 weeks for 2 years showing an improvement in PFS in patients treated with bortezomib during induction and maintenance therapy with a median PFS of 35 months versus 28 months for patients treated with VAD and thalidomide maintenance (HR, 0.75; 95% CI, 0.62 to 0.90; P = .002).[38]

Currently, treatment with lenalidomide maintenance, until progression or unacceptable toxicity, is the standard of care. Several trials investigated the effect of maintenance therapy with lenalidomide on prognosis and showed an improvement in PFS for lenalidomide *versus* no maintenance.[85-87] Mc Carthy et al. performed a meta-analysis including three large randomized controlled trials (RCT's)[88]; (Cancer and Leukemia Group B 100104 (CALB)[86], Gruppo Italiano Malattie Ematologiche dell'Adulto RV-MM-PI-209 (GIMEMA)[87], and Intergroupe Francophone du Myélome 2005-02).[85] This pooled analysis showed a major improvement in PFS with lenalidomide maintenance of 52.8 months for the lenalidomide group and 23.5 months for the placebo or observation group (hazard ratio, 0.48; 95% CI, 0.41 to 0.55). The Myeloma XI also showed an improvement in PFS with lenalidomide maintenance, 39 months (95% CI 36-42) with lenalidomide and 20 months (18-22) with observation (hazard ratio [HR] 0·46 [95% CI 0·41-0·53]; p<0·0001).[89] In the EMN02/H95 improvement of PFS after consolidation was demonstrated. At a median follow-up of 73.4 months, median PFS from start of maintenance was 57.5 months in the consolidation arm and 42.3 months without consolidation (HR 5 0.83; 95% CI, 0.70 to 0.99; P 5 .04).[90]

In the future, maintenance duration may be based on minimal residual disease (MRD) status. For example, in the Master trial patients with NDMM were treated with daratumumab combined with KRd (daraKRd), using minimal residual disease (MRD) as guidance in treatment discontinuation. Patients were treated with 4 induction cycles of daraKRd followed by HDM and ASCT and up to two phases of consolidation with four cycles each. MRD assessment was performed at completion of induction, 60-80 days after ASCT and after the second cycle of daraKRd in each phase of consolidation. In patients with two consecutive assessments of MRD negativity, treatment was discontinued. If patients did not reach MRD negativity after the second phase of consolidation, lenalidomide maintenance was indicated. PFS was superior in patients who reached MRD negativity of 10^{-6} (2-year PFS of 91%) compared with patients with MRD between 10^{-5} and 10^{-6} (2-year PFS of 81%, P=0.005 versus MRD of 10^{-6}) and patients who remain MRD-positive (2- year PFS of 83%, P=0.20 versus MRD of 10^{-6}).[91]

In the Cassiopeia trial patients were randomized between maintenance with daratumumab versus no maintenance. Daratumumab was given every 8 weeks during 2 years. At a median follow-up of 35·4 months (IQR 30.2-39.9), median PFS was not reached (95% CI not evaluable [NE] with daratumumab versus 46.7 months (95% CI 40.0-NE) with observation only (HR 0.53, 95% CI 0.42-0.68, p<0·0001).[92] Longer follow-up and other ongoing studies will evaluate the additional value of maintenance treatment with daratumumab. In the PERSEUS trial, patients with NDMM were randomized between 4 induction cycles of daraVRd or VRd alone followed by HDM and ASCT and 2 consolidation cycles and hereafter maintenance with daratumumab-lenalidomide or lenalidomide alone. Patients in the daratumumab group who achieved sustainable MRD negativity discontinued daratumumab after 24 months with continuation of lenalidomide (NCT03710603).[93] This is an ongoing trial.

Currently trials are ongoing using other combinations such as isatuximab combined with KRd (EMN24/HOVON 503) in patients with TE NDMM(NCT04483739). Moreover trials are upcoming using CAR-T cells in TE NDMM (EMN 28/Emagine)(NCT05257083) We have to await the results of these trials.

1.4.5.2 Treatment in transplant ineligible newly diagnosed multiple myeloma

In transplant-ineligible NDMM (NTE NDMM) standard first-line treatment is with daratumumab/bortezomib/melphalan/prednisone (daraVMP), daratumumab/lenalidomide/dexamethasone (DRd), VMP or Rd. Table 4 shows survival data and response data from patients with NTE NDMM, included in large clinical trials. The FIRST trial has set the stage for Rd as first line treatment in NTE NDMM. Patients were randomized between treatment with Rd versus MPT. At a median follow-up of 67 months, PFS was significantly longer with Rd continuous vs MPT (hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.59-0.79; *P* < .00001). The preferred treatment options in NTE NDMM nowadays are daraVMP and DRd based on the results of two large phase III trials. In the Alcyone trial patients were randomized between treatment with VMP with or without daratumumab. They showed a median PFS at 40 months of 36·4 months (95% CI 32·1–45·9) for daraVMP versus 19·3 months (18·0–20·4) for VMP (HR 0·42 (95% CI 0·34–0·51; p<0·0001).[94] In the MAIA trial patients were randomized between treatment with DRd or Rd. Median PFS was not reached for DRd and was 31.9 months (95% CI, 28.9 to not reached) for Rd (HR 0.56 (95% CI, 0.43 to 0.73; P<0.001).[95] Given these results DRd may be the best treatment option, however DRd and daraVMP were never directly compared.

1.4.5.3 Treatment of high-risk multiple myeloma

In MM survival has improved during the last decade due to introduction of novel treatment options. However, in a subgroup of patients with high risk features survival remains poor with a median OS of 3 years, despite innovative treatment.[96, 97] The HOVON 95/EMN02 prospectively compared single versus double ASCT. PFS and OS were significantly improved with the greatest reduction in the risk of progression or death

in patients with high-risk features.[29] Median PFS for patients with high risk cytogenetics was 46.0 months (38.7–not estimable) with double ASCT versus 26.7 months (19.9–49.6) with single ASCT (HR 0.59, 0.34–1.03; p=0.062). In the CONCEPT trial patients with high risk MM were treated with isaximab combined with KRd (isaKRd). Study treatment consisted of six cycles isaKRd induction, four cycles isaKRd consolidation, and isaKR maintenance. Transplant-eligibe patients received HDM and ASCT after induction. The two-year PFS rate was 75.5% and CR/sCR rate was 46%, which is impressive in this patient population.[98] Longer follow-up is needed to evaluate the impact on survival.

In the Myeloma UK *nine* OPTIMUM trial (MUK*nine*) patients with high- risk MM (TE NDMM and NTE NDMM) were treated with the combination of daraVRd with addition of cyclophosphamide. They showed an ORR of 83% at day 100 post ASCT with a CR rate of 47% and MRD negativity in 41% of patients.[99] Further results with respect to survival are awaited. Furthermore, the IFM is investigating the combination of daraKRd for induction and consolidation with double ASCT in high risk MM. This is an ongoing trial (NCT03606577).

At present, according to Dutch guidelines, patients with high-risk NDMM receive a double ASCT due to the improvement in survival shown in the HOVON95/EMN02. Induction, consolidation and maintenance is similar as in patients with standard risk MM.

Table 4: Trials in transplant-ineligible NDMM

	ALCYONE[94]	MAIA[95]	TOURMALINE-MM2[67]	FIRST[122]	HOVON 87[123]
Study groups	Dara VMP vs VMP	DRd vs Rd	Ixa-Rd vs Placebo-Rd	Rd vs MPT	MPT-T vs MPR-R
Number of patients	706	737	705	1623	318
Results					
Progression free survival	36.4 months vs 19.3 months	NR vs 34.4 months	35.3 months vs 21.8 months	25.5 months vs 21.8 months	20 months vs 23 months
Overall response rate	90.9% vs 73.9%	92.9% vs 81.6%	82.1% vs 79.7%	75% vs 62%	81% vs 84 %
CR/sCR rate	46% vs 25%	51% vs 30%	25.6% vs 14.1%	15% vs 9%	10% vs 13%
EMA approved	Yes	Yes	No	Yes	Yes
Reimbursed	Yes	Yes	No	Yes	Yes

1.5 RELAPSED/REFRACTORY MULTIPLE MYELOMA

Despite the advances in new treatment modalities and hereby improvement of PFS and OS, eventually almost all patients with MM develop progression of disease due to drug resistance. Table 2 shows the IMWG criteria for progressive disease and relapse of MM. [44] Relapse of MM is based on the recurrence of disease after initial response. Refractory MM is defined by progression of disease after initial response within 60 days of last treatment or the absence of response.

In patients with RRMM, solely a biochemical relapse in M-protein alone is not an indication to start new treatment. Symptomatic relapse is an indication for treatment of patients with RRMM, and is defined by the appearance or reappearance of CRAB criteria, and/or a rapid biochemical progression defined by doubling of M-protein in two months in 2 consecutive measurements or an absolute increase of M-protein of ≥ 10g/l or an increase of urinary M-protein of ≥ 500mg per 24 hours or an increase of the involved FLC with ≥ 200mg/l (plus an abnormal FLC ratio) or an increase of ≥ 25% in 2 consecutive measurements.

1.5.1 Biology of resistant disease

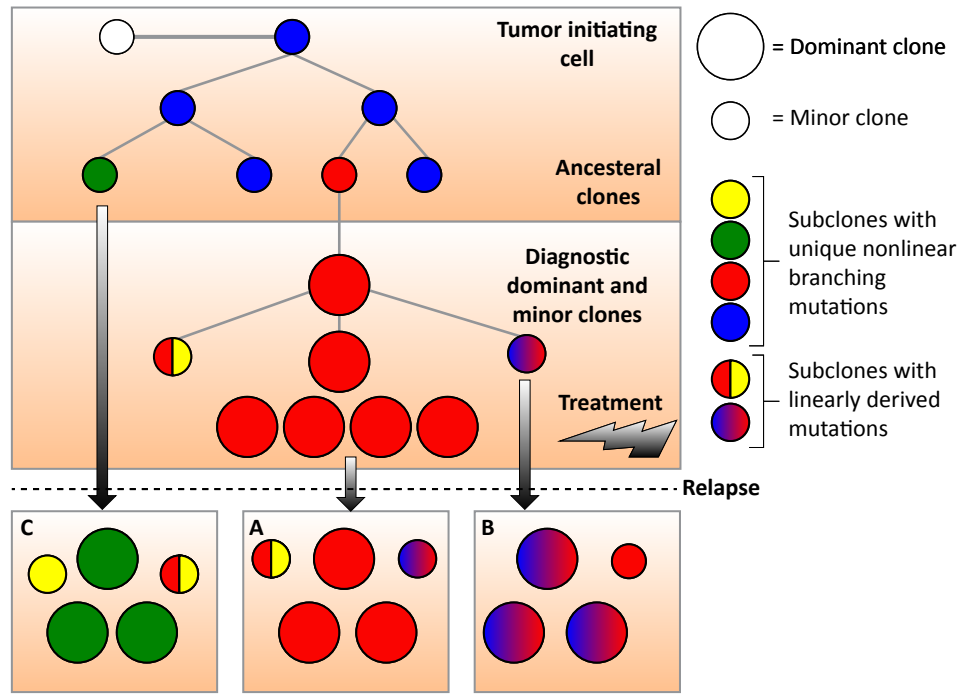
The cells of the microenvironment also contribute to therapy resistance in MM. In general, drug resistance can be divided in two categories: de novo and acquired. The microenvironment contributes to de novo drug resistance by secretion of cytokines and growth factors such as interleukin (IL)-6 and insulin-like growth factor-1 (IGF-1). [100, 101] Acquired drug resistance is mediated by sequential genetic changes, also called clonal evolution. MM is a heterogeneous disease with a wide variety of clonal abnormalities. Clonal evolution can be divided into branching, linear, and neutral clonal evolutions. (Figure 1). The definition of branching clonal evolution is the existence of different clones next to each other. Each clone develops individually and has no influence on the growth of the other co-existing clones. In linear clonal evolution, the clone harbors new mutations next to the mutations found in the original clone.[100, 102]

Neutral clonal evolution is defined by evolutionarily neutral mutations. Meaning, they do not affect growth and expansion of clones. [100]

These genetic changes could have therapeutic implications. Combination therapies could address multiple clones and may result in a deeper response. While, by using single treatment in patients with multiple genetically different clones, this may induce selecting more aggressive clones to become progressive. Drug sensitivity is determined by the type of clonal evolution as well as the maturation state of each clone. [102] This could implicate that treatment should be adapted to the specific type of clones. However more research is needed to be able to develop patient tailored treatment in the end.

Several markers in the bone marrow microenvironment in MM influence response to therapy and the development of resistance. For example, IMiDs exert their effect by binding to CRBN. This is a substrate receptor for cullin 4 ring E3 ubiquitin ligase complex. [45-47, 103] Binding of IMiDs to CRBN induces ubiquitination and proteasomal degradation of the transcription factors Ikaros and Aiolos. This induces downregulation of interferon regulatory factor 4 (IRF4) and *c-Myc* which leads to growth inhibition and apoptosis of MM cells.[49] (Figure 2).

Figure 1: clonal evolution in multiple myeloma[124]



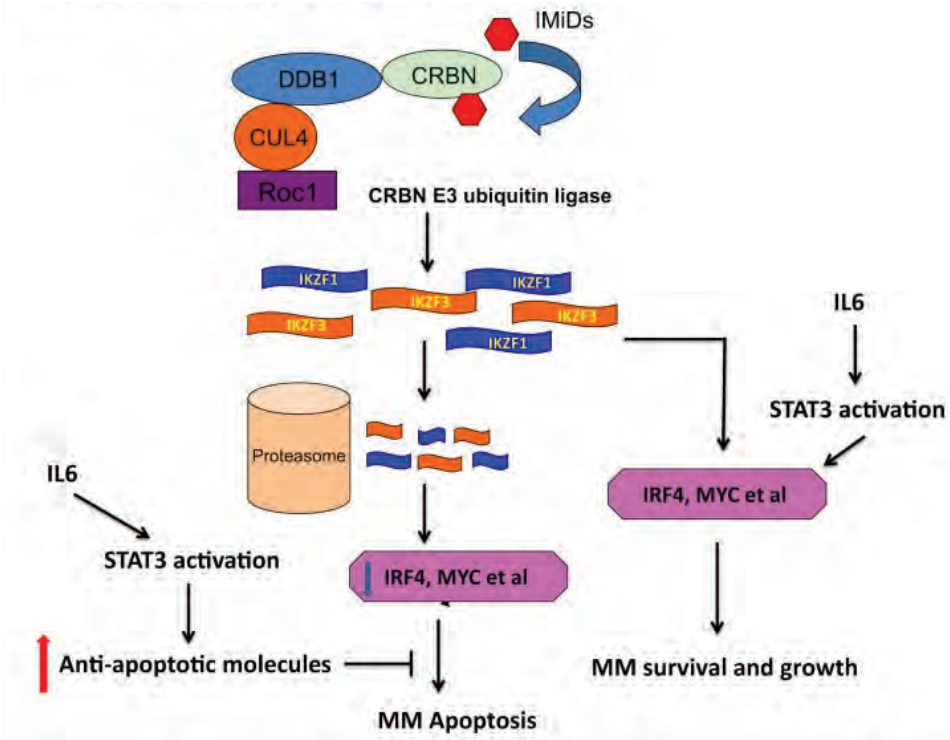
Schema illustrating the evolutional clonal architecture in multiple myeloma (MM) at diagnosis and relapse. Noted at diagnosis the clonal diversity with coexistence of dominant and minor subclones that have evolved from a common ancestral tumor-initiating cell or stem cell. The clonal disease at relapse may follow 1 of 3 evolutionary patterns with clones identical to the diagnostic sample and no newly acquired genomic alterations (A), or evolve from the diagnostic clone with linearly derived mutations (B), or, and as seen more commonly in cytogenetically high-risk disease, evolve from an ancestral minor clone(s) with newly acquired genomic mutations or structural rearrangements. (Source: Bahlis et al. Blood 2012;120:927-928)

1.5.2 Treatment of relapsed/refractory multiple myeloma

Treatment options for patients with RRMM are extensive due to the fast development of new treatment modalities in the last two decades. In the approach of selecting the next line of treatment in patients with RRMM the following aspects should be taken into consideration: prior response to last treatment, previous tolerability such as polyneuropathy and myelosuppression, current comorbidity, high risk cytogenetics and rapidly progressive MM i.e. extra medullary disease, plasma cell leukemia. Moreover the patients choice is an important factor to take into consideration.[104]

An important factor in choosing the optimal next line of treatment is response to previous therapy and of course availability of the selected treatment strategy in different countries. Salvage ASCT may be an option in patients with a PFS of 36 months after the first ASCT when treated with lenalidomide maintenance and with a PFS of 24 months in patients without lenalidomide maintenance. However it should be noted that with the availability of new treatment modalities, prognosis has improved without use of a second ASCT.

Figure 2: Mechanism of action of IMiDs [48]



Adapted from Zhu et al.

Second line treatment with a Rd backbone is preferred in patients who are not lenalidomide refractory. Triple therapy improves survival when compared to double therapy. Rd may be combined with daratumumab, carfilzomib or ixazomib. DRd provides an impressive PFS for patients with RRMM receiving 1-3 prior lines of therapy.[65, 68, 105] In the POLLUX trial patients were randomized between DRd versus Rd. DRd prolonged survival compared to Rd (median 44.5 vs 17.5 months; HR, 0.44; 95% CI, 0.35–0.55; *P* < 0.0001).[105] The ASPIRE trial evaluated safety and efficacy of KRd, versus Rd alone in patients with RRMM. PFS was significantly better with carfilzomib versus control group, 26.3 vs 17.6 months, respectively. [65] DRd and KRd are EMA approved and reimbursed in the Netherlands.

In lenalidomide refractory patients who are still sensitive to PI's, a combination with a PI is preferred. The following options are approved in the Netherlands: Bortezomib combined with daratumumab (DVd), carfilzomib/dexamethasone (Kd) and recently pomalidomide/bortezomib/dexamethasone (PVd). In the CASTOR trial, patients were treated with DVd versus Vd. Median PFS was prolonged with DVd versus Vd (16.7 vs. 7.1 months; hazard ratio [HR], 0.31; 95% CI, 0.25-0.40; P < .0001).[106] Moreover significant OS benefit was observed in DVd compared to Vd (49.6 months (95% CI 42.2 to 62.3) versus 38.5 months (95% CI 31.2 to 46.2)) respectively.[107]

Daratumumab combined with Kd and isatuximab combined with Kd have currently been improved by EMA and are reimbursed in the Netherlands. In the CANDOR trial patients were randomized between treatment with daraKd and Kd. The median progression-free survival was 28·6 months (95% CI 22·7-not estimable [NE]) in the carfilzomib, daratumumab, dexamethasone (KdD) group and 15·2 months (11·1-19·9) in the KD group (hazard ratio 0·59 [95% CI 0·45-0·78], log-rank p<0·0001).[108, 109] In the IKEMA trial patients were randomized between IsaKd and Kd showing a significant improvement in PFS with an HR of 0.53 (99% CI 0.32-0.89, p=0.0007).[110] The ENDEAVOR trial comparing carfilzomib with bortezomib in patients with RRMM showed that PFS was 18.7 months with carfilzomib versus 9.4 months with bortezomib (P< 0.0001).[111] Therefore in lenalidomide refractory patients still sensitive to treatment with anti CD38 therapy, treatment with DKd or IsaKd is preferred as second line treatment according to ESMO guidelines and Dutch guidelines.

Recently the combination of daratumumab/pomalidomide/dexamethasone (DPd) was EMA approved from 2nd line treatment, based on data from the Apollo trial, but not yet reimbursed in the Netherlands. Patients were randomized between treatment with DPd versus Pd, showing an improvement of PFS in the DPd arm; median PFS 12.4 months (95% CI 8.3-19.3) vs 6.9 months (95% CI 5.5-9.3); HR 0.63 [95% CI 0.47-0.85], two-sided p=0.0018). [112] And most recently the combination of PVd was EMA approved and reimbursed in the Netherlands based on the OPTIMISMM trial. They showed an improvement of PFS in patients treated with PVd versus Vd (median 11.20 months [95% CI 9.66–13.73] *vs* 7.10 months [5.88–8.48]; hazard ratio 0.61, 95% CI 0.49–0.77; p<0.0001).[113]

After second line of treatment the optimal treatment strategy becomes even more difficult. Most patients will be refractory to IMiDs, PI's and sometimes to anti-CD38 therapy and are therefore triple refractory, which implies dismal prognosis.[114] Currently, there is no consensus regarding the optimal treatment strategy after second line of treatment. In the Netherlands treatment with pomalidomide combined with dexamethasone (Pd) is approved. Often, cyclophosphamide is added based on the trial performed by Baz et al.[115] Another EMA approved option (reimbursed in the Netherlands) is combining Pd with elotuzumab (EPd). The ELOQUENT trial showed an improvement of PFS of 10.3 months for EPd versus 4.7 months for Pd. [116] The ELOQUENT trial showed an improvement of PFS of 10.3 months for EPd versus 4.7 months for Pd. The hazard ratio for disease progression or death was 0.54 (95% CI, 0.34 to 0.86; P=0.008). Recently the combination of isatuximab combined with Pd (IsaPd) was EMA approved and reimbursed in the Netherlands for 3d line of treatment based on data from the ICARIA trial. An improvement of PFS was shown for patients treated with isaPd with a median PFS of (11.5 months [95% CI 8.9–13.9] *vs* 6.5 months [4.5–8.3]; HR 0.596, 95% CI 0.44–0.81; p=0.001).[117] However at present, most patients receive anti-CD38 therapy in first or second line of treatment and no data are available of retreatment with anti-CD38 therapy.

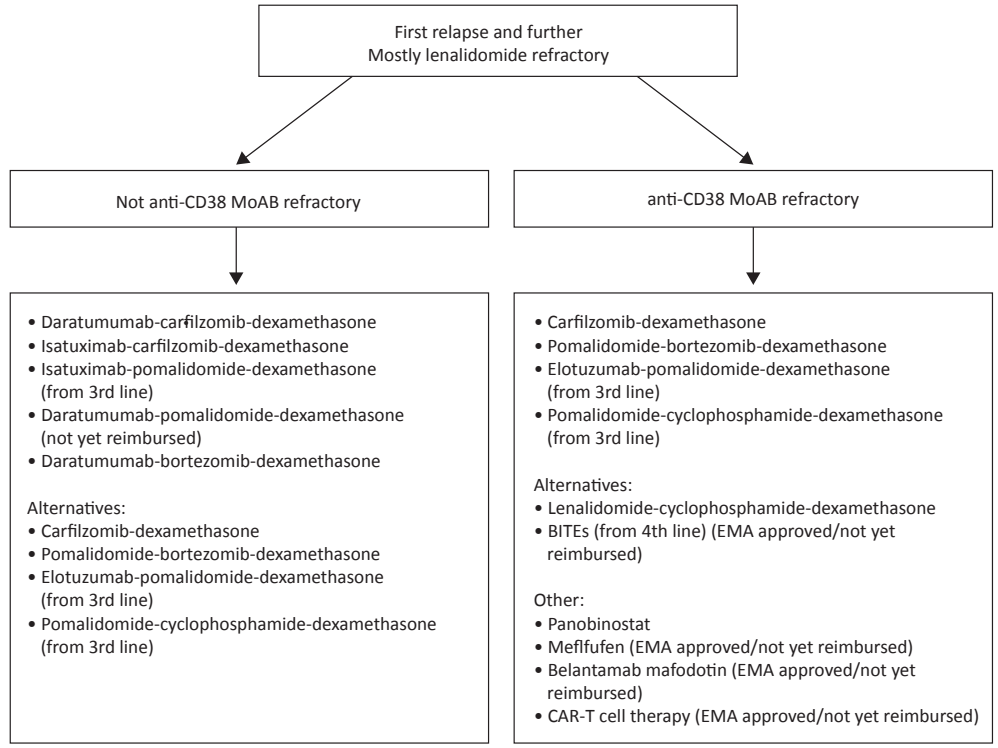
Table 5. Trials in RRMM

	POLLUX [105]	CASTOR [106]	IKEMA [110]	CANDOR [108]	APOLLO [112]	ASPIRE [65]	ENDEAVOUR [111]	KARMMA-2 [118]	CARTITUDE-1 [39]	MajesTEC-1 [120]	Monumental-1 [121]
Study groups	DRd vs Rd	DVd vs Vd	IsaKd vs Kd	DaraKd vs Kd	DaraPd vs Pd	KRd vs Rd	Kd vs Vd	Ide-cel, phase 2	Cilta-cel fase 1b/2	Teclistamab phase 1	Talquetamab phase 1/2
Number of patients	569	498	302	466	304	792	929	128	97	165	288
Median prior lines of therapy, n (range)	1	2	2	2	2	2	2	6	6	5	5
Results											
Progression free survival	83.2% vs 60.1% at 12 months	16.7 vs 7.1 months	NR vs 19.2 months at 21 months	NR vs 15.8 months at 16.9 months	12.4 vs 6.9 months at 16.9 months	26.3 vs 17.6 months	18.7 vs 9.4 months	12.1 months	NR at 12 months	11.3 months	7.5 months
Overall response rate	92.9% vs 76.4%	85% vs 63%	87% vs 83%	84% vs 75%	69% vs 46%	87.1% vs 66.7%	77% vs 63%	81%	97%	63%	74%
CR/sCR rate	43.1% vs 19.2%	30% vs 10%	40% vs 28%	29% vs 10%	25% vs 4%	31.8% vs 9.3%	13% vs 6%	33%	67%	39.4%	33.6%
EMA approved	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Reimbursed	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	No

The newest treatment modalities are CAR-T cells and BITEs as previously described in paragraph 1.4.4. In the phase 2 KARMMA -2 trial, highly pretreated patients were treated with anti-BCMA CAR-T cell therapy. Median PFS was 8.8 months (95% CI; 5.6-11.6) and median OS was 19.4 months (95% CI; 18.2-not reached).[118] In the KARMMA-3 trial CAR-T cell therapy was compared to standard of care. At a median follow-up of 18.6 months, the median PFS was 13.3 months in the CAR-T cell group, as compared with 4.4 months in the standard of care group (HR 0.49; 95% CI, 0.38 to 0.65; P<0.001). In the CARTITUDE-1, a phase 1 trial, evaluting anti-BCMA CAR-T cell treatment, median PFS and OS at 12 months were not reached in highly pretreated patients and was 77% and 89% respectively.[39] The CARTITUDE-2 is a phase 2 trial with CAR-T cell therapy in RRMM demonstrating a PFS at 6 months of 90% (95% CI 65.6–97.4).[119] Currently CAR-T cell therapy is investigated as second line treatment (CARTITUDE 4) and as first-line treatment (Cartitude 5 and 6). The CAR-T's Ciltacel and Idecel have been EMA approved for fourth line of treatment, however are not yet reimbursed in the Netherlands.

BITEs emerges as another promising treatment modality in the treatment of patients with MM. Teclistamab targets both CD3 and BCMA. In the MajesTEC-1 trial patients with haevily pretreated MM were included and treated with teclistamab demonstrating a median PFS of 11.3 months (95% CI, 8.8 to 17.1).[120] In the Monumental-1 patients with highly pretreated RRMM were treated with talquetamab, targeting both CD3 and GPRC5D. Median PFS was 7.5 months (95% CI, 5.7-9.2 [38% censored]). [121]Table 5 shows survival data and response data from patients with RRMM, included in large clinical trials. Figure 3 shows treatment options in patients with RRMM.

Figure 3: treatment options in RRMM



1.6 AIMS AND OUTLINE OF THE THESIS

Despite major improvements in the treatment of MM, it remains an incurable disease. Median survival is approximately 8 years. OS and PFS have improved with the introduction of IMiDs and PIs. These agents are currently standard of care in patients with MM. The studies described in this thesis were performed to evaluate improvement in outcome in patients with MM using different treatment strategies and doses. Moreover, we evaluated treatment with next generation IMiDs in real world setting. In addition, we investigated the effect of different IMiDs on downstream targets in the cereblon pathway.

Another objective in this thesis is the development of a clinical benefit scale in order to achieve availability of new treatment more quickly and to be able to detect the true value of new treatment modalities.

In chapter 2-4 three prospective clinical trials are presented. Chapter 2 describes the results of a multi-center phase 2 trial, the Carthadex trial. In this trial newly diagnosed patients were treated with the combination of carfilzomib, thalidomide and dexamethasone(KTd) during induction and consolidation. Patients were treated with 4 induction cycles followed by HDM and ASCT and consolidation with another four cycles of KTd. Different dose levels of carfilzomib were evaluated, because there is no consensus as to the optimum dose level of carfilzomib, implicating the need for dose-finding trials. Chapter 3 describes the results of an additional cohort treated with eight induction cycles of KTd in the Carthadex trial to evaluate the effect of more intensified induction therapy. Chapter 4 describes the effect of consolidation therapy in the EMN02/HOVON 95 trial. Patients were randomized between 2 cycles of bortezomib, lenalidomide and dexamethasone (VRD) versus no consolidation after induction and intensification therapy. At that time point few trials addressed the effect of consolidation in NDMM. Currently consolidation treatment is standard of care due to the advantage in survival.

Chapter 5 and 6 focus specifically on treatment with IMIDs and the role of CRBN in IMID activity. Chapter 5 presents data from a prospective study in relapsed/refractory patients treated with pomalidomide in the real world clinical setting. Pomalidomide has shown an impact on PFS and OS in patients with RRMM in large clinical trials. However, in randomized controlled trials (RCTs) patient selection is based on stringent inclusion criteria which precludes to capture the heterogeneity of the general patient population. Therefor it remains important to validate results of RCTs in real world practice. In Chapter 6 the role of cereblon, the primary target of IMIDs, and its downstream target molecules is investigated. Bone marrow biopsies from patients treated within the HOVON 87 trial were stained for markers involved in the CRBN pathway. We investigated the prognostic value of the levels of these markers in patients treated with the IMiDs lenalidomide and thalidomide in a prospective clinical trial.

Chapter 7 and 8 include data from the collaborative EHA and European Society for Medical Oncology (ESMO) working group. In these chapters data from the ESMO-Magnitude Clinical Benefit Scale are presented. The goal of this scale is to evaluate the clinical benefit of new treatment modalities. Nowadays it becomes increasingly important to evaluate the clinical benefit and cost effectiveness of new treatment modalities.

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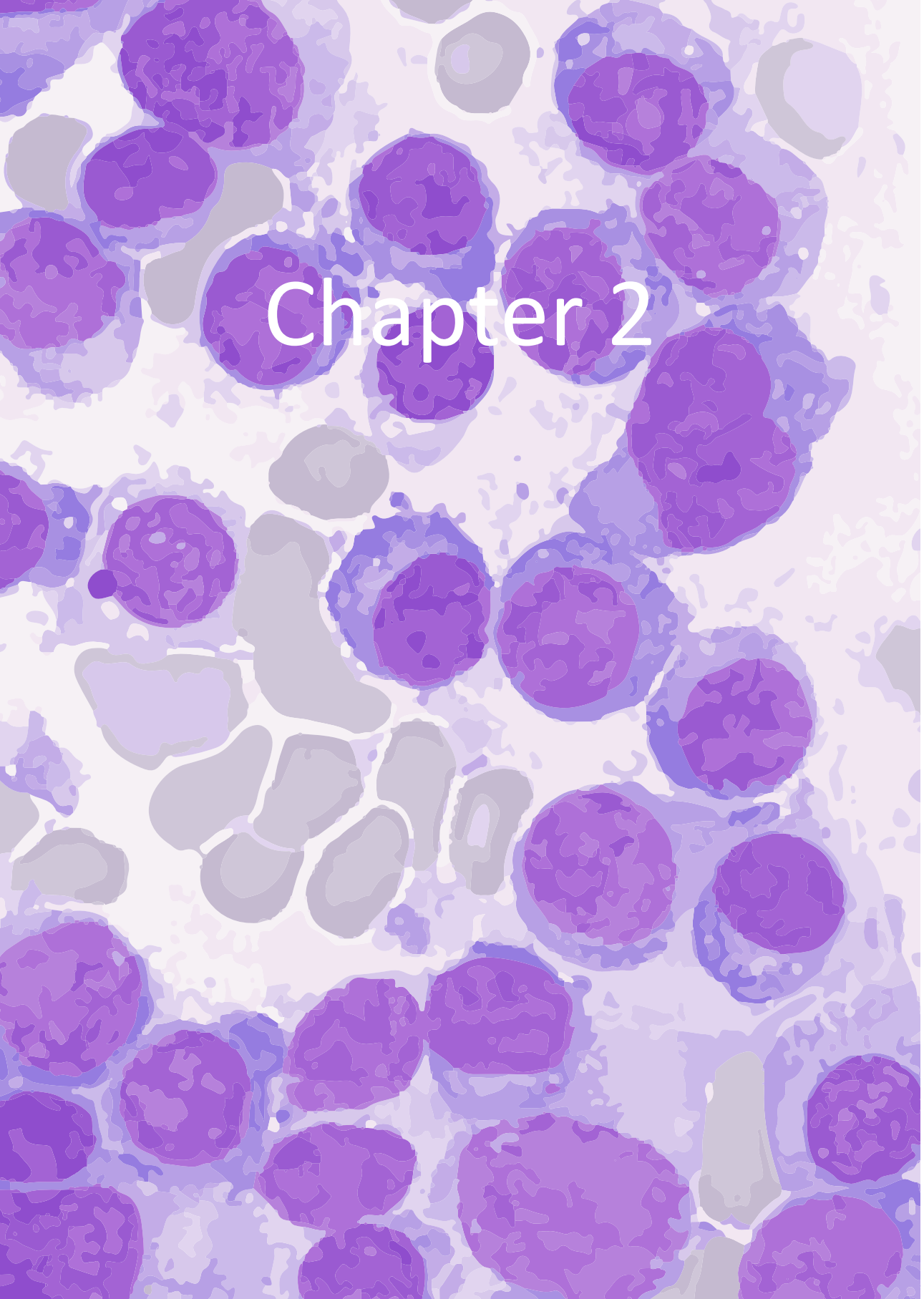
PART II

Prospective clinical trials



Phase 2 study of carfilzomib, thalidomide, and low-dose dexamethasone as induction and consolidation in newly diagnosed, transplant eligible patients with multiple myeloma; the carthadex trial

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Haematologica. 2019 Nov;104(11):2265-2273.

ABSTRACT

This is a phase 2 dose escalation trial of carfilzomib in combination with thalidomide and dexamethasone for induction and consolidation in transplant-eligible patients with newly diagnosed multiple myeloma (NDMM). The results of 4 dose levels are reported. Induction therapy consisted of 4 cycles of carfilzomib 20/27 mg/m^2 (n=50), 20/36 mg/m^2 (n=20), 20/45 mg/m^2 (n=21) and 20/56 mg/m^2 (n=20) on days 1, 2, 8, 9, 15, 16 of a 28-day cycle; thalidomide 200 mg on day 1 through 28 and dexamethasone 40 mg weekly. Induction therapy was followed by high dose melphalan and autologous stem cell transplantation and consolidation therapy with 4 cycles of carfilzomib, thalidomide and dexamethasone in the same schedule except a lower dose of thalidomide (50 mg).

Very good partial response rate or better and complete response rate or better after induction therapy were 65% and 18% respectively, increasing to 86% and 63% respectively after consolidation therapy. In all cohorts combined, after a median follow-up of 58.7 months, median progression-free survival was 58 months (95% CI 45-67 months). Median overall survival was 83 months (95% CI 83 months-not reached). Grade 3/4 adverse events consisted mainly of infections, respiratory disorders, skin and vascular disorders in 11%, 8%, 9%, and 9% respectively. Grade 3 polyneuropathy was only reported in one patient. Cardiac events were limited, grade 3/4 in 5% of patients. Carfilzomib, thalidomide and dexamethasone as induction and consolidation treatment after high dose melphalan and autologous stem cell transplantation is highly efficacious and safe in transplant-eligible patients with newly diagnosed multiple myeloma. This study was registered at http://www.trialregister.nl as #NTR2422.

INTRODUCTION

Survival rates in patients with multiple myeloma (MM) have significantly improved during the last decades. However, eventually the majority of patients progress and the need for new therapeutic approaches remains. In transplant-eligible patients with newly diagnosed multiple myeloma (NDMM), depth of response before and after high-dose melphalan/autologous stem cell transplantation (HDM/ASCT) is associated with improvement in progression-free survival (PFS) and overall survival (OS).(1-5) Therefore, it is important to select the appropriate induction and consolidation therapy in order to achieve a maximum response after ASCT and to maintain or even increase this response during consolidation therapy and thereafter.

Standard induction treatment consists of triple therapy including a proteasome inhibitor, and/or an immunomodulatory drug and dexamethasone. The combination of bortezomib, thalidomide and dexamethasone (VTD) has been extensively investigated in transplant-eligible patients with NDMM.(6-8) However, treatment with bortezomib is associated with higher rates of polyneuropathy (PN) and consequently discontinuation of treatment.(7, 8) It is important to use a regimen that is highly effective and safe in patients with NDMM. This could improve treatment adherence and subsequently outcome after induction and consolidation therapy.

Carfilzomib is a selective proteasome inhibitor with irreversible binding to the constitutive proteasome and immunoproteasome. It is approved in the United States and in Europe as a single-agent for the treatment of patients with relapsed and/or refractory MM (RRMM). Carfilzomib is approved at a dose of 27 mg/m^2 in combination with lenalidomide and dexamethasone in RRMM based on the data from the ASPIRE trial showing a superior PFS of median 26.3 months vs 17.4 months when patients were treated with lenalidomide/dexamethasone.(9) Carfilzomib is also approved at a dose of 56 mg/m^2 in combination with dexamethasone, based on data from the ENDEAVOR trial showing a superior PFS over bortezomib/dexamethasone of median 18.7 months vs 9.4 months ($p<0.0001$).(10) Previous trials showed that the incidence of PN with carfilzomib is lower compared to bortezomib.(9-11)

Carfilzomib has not yet been approved for treatment in NDMM in Europe. Recent trials in patients with NDMM, using different treatment regimens, showed high response rates.(12-15) A phase 1/2 trial of patients with NDMM treated with carfilzomib at a maximum dose of 36 mg/m^2 combined with lenalidomide and low-dose dexamethasone showed a very good partial response (VGPR) rate of 81%. PFS at 24 months was 92%.(12)

We have previously initiated a Phase 2 dose-escalation trial of carfilzomib combined with thalidomide and dexamethasone. The combination of a proteasome inhibitor and an immunomodulating agent has a proven synergystic effect.(6) Moreover, thalidomide is an effective and affordable drug available in many countries.

In NDMM no consensus exists about the optimum dose level of Carfilzomib, implicating the need for dose finding trials. Goal of this trial was to investigate the efficacy of this combination at various dose levels of carfilzomib in NDMM. Results of the first three cohorts of this Carthadex trial have been published in 2015.(11) Overall response rate (ORR) after induction therapy was 90% with a VGPR rate of 68%. PFS at 36 months was 72%. The combination of carfilzomib, thalidomide and dexamethasone (KTd) was well tolerated.(11). Four different dose levels were included in this trial based on the hypothesis that a higher dose level induces a higher response rate.(12, 16) We report herein the results of our dose escalation cohorts with long follow-up. This is the first study using KTd for both induction and consolidation therapy and comparing different dose levels.

METHODS

Patients

Transplant-eligible patients with NDMM, aged 18 to 65 years, were eligible for enrollment. Patients were required to have a World Health Organization (WHO) performance status of 0 to 3 (WHO 3 was allowed only when caused by MM and not by co-morbid conditions).

Patients were ineligible if they had grade 3/4 polyneuropathy (PN) or grade 2 painful PN, severe cardiac dysfunction (New York Heart Association class II to IV), known intolerance of thalidomide, systemic amyloid light-chain amyloidosis, non-secretory MM, Waldenström macroglobulinemia or IgM MM, creatinine clearance < 15 mL/min, absolute neutrophil count < 1.0 x 10^9/L, platelets < 75 x 10^9/L, hemoglobin < 4.9 mmol/L, active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma.

This independent investigator-initiated multi-institutional study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the European Clinical Trial Directive as implemented in Dutch law. The protocol was approved by institutional review boards and ethics committees. All patients gave informed consent.

Study design and treatment

This single-arm, open-label, phase 2 trial was conducted at 8 hematology centers. Patients were treated with 4 cycles KTd of a 28-day cycle for induction therapy. Carfilzomib was administered in a 30 minutes infusion. The dose in the first dosing cohort was 20 mg/m^2 on days 1 and 2 and was escalated to a dose of 27 mg/m^2 on days 8, 9, 15 and 16 of cycle 1 and on days 1, 2, 8, 9, 15 and 16 of cycles 2 to 4. Thalidomide 200 mg was given orally on days 1 through 28 and dexamethasone 40 mg was given orally on days 1, 8, 15 and 22. Induction therapy was followed by stem cell harvest after Cyclophosphamide priming (2 to 4 mg/m^2 IV) and daily 10 µg/kg granulocyte colony-stimulating factor. Hereafter patients received high-dose Melphalan (HDM, 200mg/m^2) and ASCT followed by consolidation treatment with 4 cycles of KTd in the same schedule and dose as induction treatment except that the dose of thalidomide was 50 mg instead of 200 mg. The dose of carfilzomib was escalated to 20/36 mg/m^2, 20/45 mg/m^2 and 20/56 mg/m^2 in cohort 2, 3 and 4 respectively. During the study protocol patients were required to maintain adequate hydration. In addition, patients were treated prophylactically with antibiotics (ciprofloxacin or another fluoroquinolone) and with antiviral medication (acyclovir or a similar anti varicella agent). All patients received antithrombotic prophylaxis with aspirin in case of low thrombotic risk or with low-molecular-weight heparin in patients with pre-existing thrombotic risk factors.(17)

The primary endpoint of the study was response after induction therapy and overall response, specifically complete response (CR) and VGPR. Secondary endpoints were efficacy

and safety, maximum tolerated dose (MTD), dose limiting toxicities (DLT), PFS and overall survival (OS). PFS was defined as time from registration to progression or death, whichever came first. OS was calculated from registration to death from any cause; patients still alive at last contact were censored.

This study was registered at http://www.trialregister.nl as #NTR2422.

Assessments

Treatment responses and disease progression were assessed by study investigators and were classified according to International Myeloma Working Group (IMWG) Uniform Response Criteria, with categories for CR, VGPR, and partial response (PR).(18) Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria of Adverse Events version 4.0.(19) Bone marrow analysis was performed at diagnosis to quantify myeloma cell involvement. Molecular, cytogenetic and fluorescence in situ hybridization studies were performed on these samples. CD138+ purified MM cells were used to determine the presence of the following cytogenetic abnormalities: t(4;14)(p16;q32), t(14;16)(q32;q32), del(13q), del(17p), 1p/q abnormalities, numerical abnormalities of chromosome 9 or 11, and complex cytogenetic abnormalities.(11)

Statistical analysis

This study was designed to investigate whether induction treatment with KTd warrants further investigation in future trials. The intention-to-treat principle was used for all analyses, restricted to eligible patients. A CR + VGPR rate lower than 25% after induction treatment, was considered too low to warrant further investigation in future trials, however if the CR + VGPR rate was higher than 45% therapeutic activity was considered sufficiently high to support further investigation. To reject the null hypothesis in favor of the alternative hypothesis with power 1 - β = 0.80 (2-sided significance level α = 0.05), a minimum of 41 patients should be included. A 95% confidence interval (CI) was constructed around the CR + VGPR rate after induction treatment and the null hypothesis was rejected if the lower boundary was larger than 25%.

Predefined subgroup analyses were performed to investigate the effect of risk status, using cytogenetic/fluorescence in situ hybridization criteria, ISS stage and R-ISS stage, on response and survival. In this trial patients were considered to be high-risk if they had t(4;14) and/or del(17p) and/or add(1q) and/or ISS stage III.

Continuous and categorical data were summarized with descriptive statistics. Survival end points were estimated using the Kaplan-Meier method, and 95% CI were constructed. The log- rank was used to evaluate differences in PFS and OS between subgroups. Statistical analysis was performed using Stata v15.1 software (StataCorp, College Station, TX).

RESULTS

Patients and treatment

One hundred and eleven patients were enrolled between September 16, 2010 and December 30, 2013. The analysis was based on data available as of February 27, 2018 with a median follow-up of 58.7 months (range 25.1-88.0 months). Four different dose levels were investigated (27mg/m^2 n=50, 36 mg/m^2 n=20, 45 mg/m^2 n=21 and 56 mg/m^2 n=20). Baseline demographics and disease characteristics are shown in table 1. Median age was 58 years with a range of 29 to 66 years and the male/female distribution 61/39%. Nine percent of patients had an R-ISS stage 3 and in 9% of patients R-ISS stage was unknown mainly due to missing cytogenetics. A total of 39% of patients were classified as high-risk based on cytogenetics and ISS stage, 41% of patients were classified as standard risk. In 20% of patients risk status was unknown, mainly due to missing cytogenetics. Seven patients had a history of grade 1/2 PN and two patients a grade 3 PN at diagnosis, whereas in 9 patients baseline assessment of PN was missing at enrollment. A total of 5% of patients had renal insufficiency with a creatinine ≥ 177 µmol/L at diagnosis.

All 111 patients started induction therapy with KTd (figure 1). Six patients discontinued treatment because of the following adverse events (AEs): grade 3 rash (carfilzomib 27 mg/m^2), grade 2 fever with sepsis (carfilzomib 27 mg/m^2), grade 1 hyponatremia (carfilzomib 27 mg/m^2), grade 2 exanthema (carfilzomib 27 mg/m^2), grade 3 congestive heart failure (carfilzomib 27 mg/m^2), grade 3 pneumonitis (carfilzomib 36 mg/m^2), grade 3 drug reaction with eosinophilia and systemic symptoms (Dress syndrome) (carfilzomib 56 mg/m^2). One patient appeared not eligible for further treatment and two patients discontinued treatment due to progressive disease. 102/111 patients (92%) continued treatment with high dose cyclophosphamide and stem cell collection. Stem cell collection was successful in 100 of 102 patients with a median CD34+ yield of 5.5 x 10^6. A total of 98 patients (88%) continued treatment with a single HDM (200 mg/m^2) and ASCT. Four patients were not eligible for HDM, one because of insufficient CD34+ yield and three because of progression of disease after stem cell collection. After treatment with HDM and ASCT 94 patients (85%) initiated consolidation therapy. Four patients were not eligible for consolidation treatment because of progression of disease (n=1), a delayed hematologic recovery after ASCT (n=1), non-related disease (n=1) and uncontrolled pain after ASCT (n=1). Nine patients discontinued consolidation treatment because of progressive disease (n=2), thrombotic thrombocytopenic purpura (TTP) (n=1), a TTP like syndrome (n=1), overall worsening of condition (n=1), grade 3 fatigue (n=1), refusal of further treatment (n=2) and persisting PNP (n=1). A total of 83 patients (75%) completed all 4 consolidation cycles.

Table 1: Baseline characteristics

Characteristic	20/27 mg/m2	20/36 mg/m²	20/45 mg/m²	20/56 mg/m²	All patients
Patients, n	50	20	21	20	111
Male, n (%)	34 (68)	11 (55)	16 (76)	7 (35)	68 (61)
Age, median (range), years	58 (29-66)	58 (47-64)	56 (33-65)	58 (37-65)	58 (29-66)
ISS stage, n (%)					
1	18 (36)	5 (25)	14 (67)	9 (45)	46 (41)
2	20 (40)	7 (35)	4 (19)	7 (35)	38 (34)
3	12 (24)	8 (40)	2 (10)	4 (20)	26 (23)
Unknown	0 (0)	0 (0)	1 (5)	0 (0)	1 (1)
R-ISS stage, n (%)					
1	7 (14)	3 (15)	10 (48)	6 (30)	26 (23)
2	37 (74)	10 (50)	7 (33)	11 (55)	65 (59)
3	2 (4)	5 (25)	0 (0)	3 (15)	10 (9)
Unknown	4 (8)	2 (10)	4 (19)	0 (0)	10 (9)
WHO performance status, n (%)					
0	24 (48)	7 (35)	11 (52)	12 (60)	54 (49)
1	20 (40)	10 (50)	7 (33)	8 (40)	45 (41)
2	2 (4)	1 (5)	1 (5)	0 (0)	4 (4)
3	0 (0)	0 (0)	2 (10)	0 (0)	2 (2)
Unknown	4 (8)	2 (10)	0 (0)	0 (0)	6 (5)
M-protein isotype, n (%)					
IgA	11 (22)	5 (25)	4 (19)	4 (20)	24 (22)
IgG	30 (60)	8 (40)	10 (48)	11 (55)	59 (53)
IgD	1 (2)	1 (5)	1 (5)	0 (0)	3 (3)
Light-chain disease	7 (14)	4 (20)	6 (29)	5 (25)	22 (20)
Unknown	1 (2)	2 (10)	0 (0)	0 (0)	3 (3)
Genetic abnormalities, n (%)*					
add 1q					
Yes	5 (10)	4 (20)	2 (10)	7 (35)	18 (16)
No	35 (70)	12 (60)	15 (71)	10 (50)	72 (65)
Unknown	10 (20)	4 (20)	4 (19)	3 (15)	21 (19)
t(4;14)(p16;32)					
Yes	2 (4)	2 (10)	0 (0)	3 (15)	7 (6)
No	39 (78)	14 (70)	19 (90)	13 (65)	85 (77)
Unknown	9 (18)	4 (20)	2 (10)	4 (20)	19 (17)
del(17p13)					
Yes	3 (6)	2 (10)	1 (5)	1 (5)	7 (6)
No	38 (76)	14 (70)	18 (86)	16 (80)	86 (77)
Unknown	9 (18)	4 (20)	2 (10)	3 (15)	18 (16)
t(11;14)(q13;q32)					
Yes	5 (10)	1 (5)	2 (10)	1 (5)	9 (8)
No	36 (72)	15 (75)	17 (81)	15 (75)	83 (75)
Unknown	9 (18)	4 (20)	2 (10)	4 (20)	19 (17)
t(14;16)(q32;q23)					
Yes	3 (6)	1 (5)	0 (0)	0 (0)	4 (4)
No	38 (76)	15 (75)	19 (90)	16 (80)	88 (79)
Unknown	9 (18)	4 (20)	2 (10)	4 (20)	19 (17)
Risk status, n (%)†					
High	19 (38)	10 (50)	4 (19)	10 (50)	43 (39)
Standard	21 (42)	6 (30)	12 (57)	7 (35)	46 (41)
Unknown	10 (20)	4 (20)	5 (24)	3 (15)	22 (20)
Grade 1/2 PNP, n (%)‡	3 (6)	2 (10)	0 (0)	2 (10)	7 (7)

PNP, polyneuropathy. *A total of 93 patients were evaluable. The table shows the presence of the genetic abnormality in all four dose levels together and in each dose level separately. †High-risk: t(4;14) and/or 17p- and/or add1q cytogenetic abnormalities and/or ISS stage 3 disease. Standard risk: the remaining patients with available cytogenetics and ISS stage. ‡Not recorded in 9 patients.

Efficacy

Table 2 shows response to induction, HDM/ASCT and consolidation therapy. Response according to risk group and R-ISS is shown in table 3. Overall response after induction therapy in all 111 patients was 93% with a CR rate of 18%. The ≥ VGPR rate after induction therapy was 65% (95% CI 55% to 74%) leading to rejection of the null hypothesis, as the 95% CI is above 25%. The ≥ VGPR rate increased to 77% after HDM/ASCT and to 86% after consolidation therapy. ORR increased to 94% after consolidation therapy. CR rate after induction therapy between the four different dose levels was comparable and increased after consolidation therapy. In the three highest dose levels CR rate after consolidation therapy was higher in comparison to the lowest dose level (75%, 67% and 65% vs. 56%, respectively, however this was not statistically significant (test for trend, p=0.39; chi-square test 27 mg/m² vs 36-56 mg/m², p=0.16)). Response after consolidation treatment between standard risk patients and high-risk patients (defined by ISS stage and cytogenetics) was

similar with CR rates of 67% vs 58%. Response after consolidation therapy according to R-ISS stage (I,II and III) was comparable with CR rates of 73%, 57% and 60% respectively.

Median PFS in all 111 patients was 58 months (95% CI 45-67 months). Dose level was not associated with PFS. Median PFS in high-risk patients was worse compared to standard risk patients (42 vs 60 months, p=0.006), while a higher R-ISS stage was also associated with a worse PFS (p=0.04) (figure 2).

Median OS was 83 months and 5-year OS was 76% (95% CI 66% to 83%) as shown in figure 3. Dose level and risk status were not associated with OS.

Table 2: Response after induction, after HDM and after consolidation therapy.

Dosing level carfilzomib	20/27 mg/m²	20/36 mg/m²	20/45 mg/m²	20/56 mg/m²	All patients
Patients, n	50	20	21	20	111
Response after induction, n (%)					
sCR	4 (8)	1 (5)	0 (0)	1 (5)	6 (5)
≥ CR	8 (16)	5 (25)	3 (14)	4 (20)	20 (18)
≥ VGPR	27 (54)	16 (80)	13 (62)	16 (80)	72 (65)
≥ PR	45 (90)	20 (100)	20 (95)	18 (90)	103 (93)
Response after HDM, n (%)					
sCR	5 (10)	2 (10)	3 (14)	1 (5)	11 (10)
≥ CR	12 (24)	7 (35)	9 (43)	6 (30)	34 (31)
≥ VGPR	32 (64)	17 (85)	19 (90)	18 (90)	86 (77)
≥ PR	46 (92)	20 (100)	20 (95)	18 (90)	104 (94)
Response after consolidation, n (%)					
sCR	17 (34)	4 (20)	8 (38)	4 (20)	33 (30)
≥ CR	28 (56)	15 (75)	14 (67)	13 (65)	70 (63)
≥ VGPR	40 (80)	18 (90)	20 (95)	18 (90)	96 (86)
≥ PR	46 (92)	20 (100)	20 (95)	18 (90)	104 (94)

sCR, stringent complete remission. CR, complete remission. VGPR, very good partial response. PR, partial response

Table 3: Response after consolidation therapy according to risk status and R-ISS

	Standard risk*	High-risk*	R-ISS 1	R-ISS 2	R-ISS 3	Total
Patients, n	46	43	26	65	10	111
sCR, n (%)	16 (35)	9 (21)	10 (38)	19 (29)	0 (0)	33 (30)
≥ CR, n (%)	31 (67)	25 (58)	19 (73)	37 (57)	6 (60)	70 (63)
≥ VGPR, n (%)	40 (87)	36 (84)	24 (92)	54 (83)	9 (90)	96 (86)
≥ PR, n (%)	44 (96)	38 (88)	26 (100)	58 (91)	10 (100)	104 (94)

*High-risk: t(4;14) and/or 17p- and/or add1q cytogenetic abnormalities and/or ISS stage 3 disease. Standard risk: the remaining patients with available cytogenetics and ISS stage. ISS: International Staging System; R-ISS: Revised International Staging System; sCR: stringent complete remission; CR: complete remission; VGPR: very good partial; response; PR: partial response

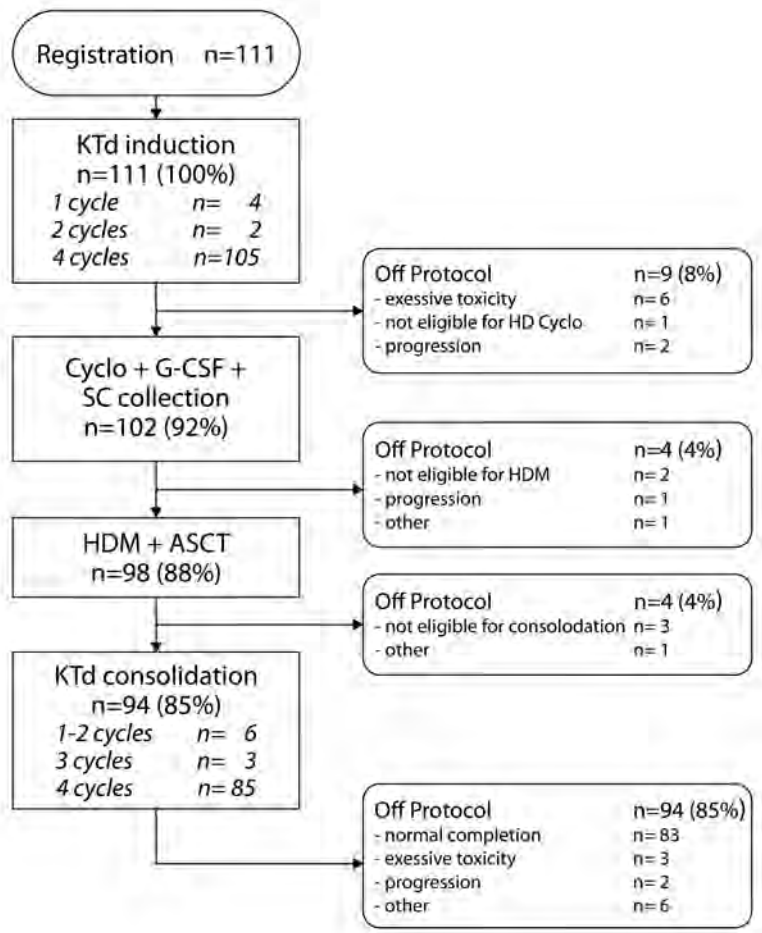

Figure 1: Cyclo, cyclophosphamide; G-CSF, granulocyte colony-stimulating factor; HD, high dose; SC, stem cell; KTd, carfilzomib, thalidomide and dexamethasone; n, number; HDM + ASCT; high-dose melphalan + autologous stem cell transplantation.

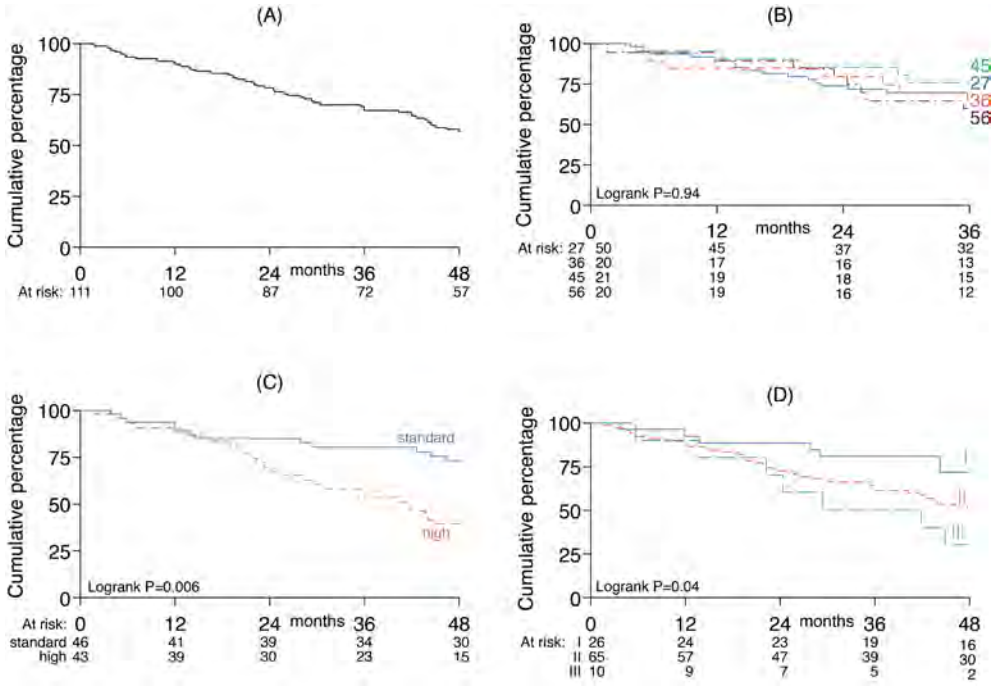

Figure 2. Kaplan-Meier curve of progression-free survival (PFS). (A) PFS in all 111 patients. (B) PFS per dose level. (C) PFS according to risk status. (D) PFS according to R-ISS.

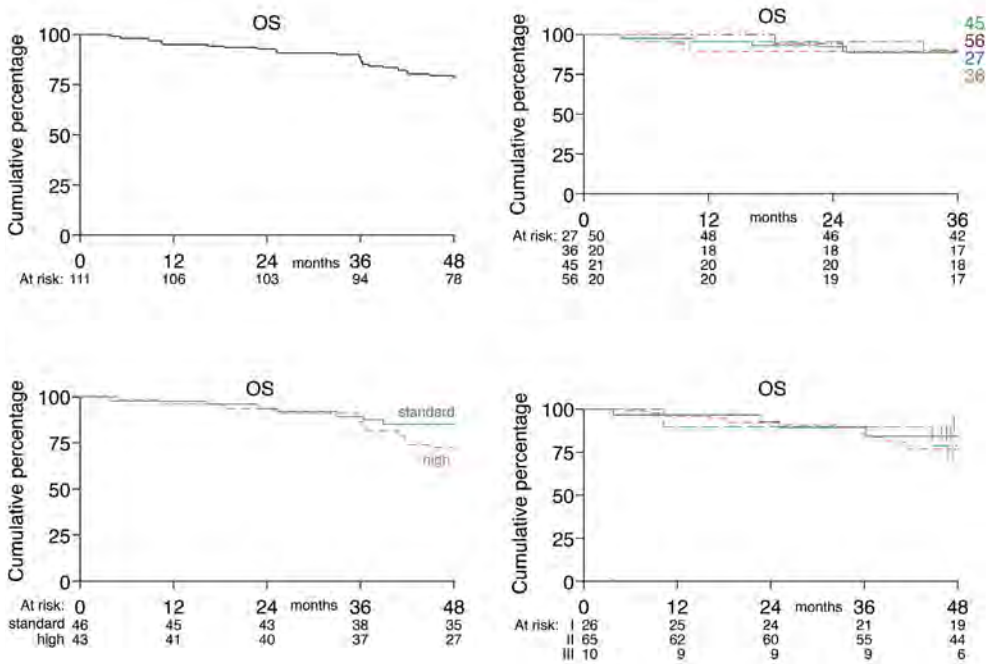

Figure 3. Kaplan-Meier curve overall survival (OS). (A) OS in all 111 patients. (B) OS per dose level. (C) OS according to risk status. (D) OS according to R-ISS.

Safety

Any grade hematological toxicity occurred in 15% of patients. Grade 3/4 hematological toxicity occurred in 10% of patients. In dose level 27 mg/m^2, 36 mg/m^2, 45 mg/m^2 and 56mg/m^2 grade 3/4 hematological toxicity occurred in 12%, 10%, 10% and 10% respectively. Main grade 3/4 non-hematological toxicity consisted of infections, respiratory disorders, skin and vascular disorders in 11%, 8%, 9%, and 9% respectively. There was a gradual increase in grade 3/4 infections from lower to higher doses of carfilzomib; 0%, 5%, 10% and 15% respectively, and consisted mainly of pneumonia (supplementary table 1).

Table 4 summarizes cardiac AEs. Any grade cardiac AEs were reported in 12% of patients after induction therapy (14% in carfilzomib 27mg/m^2, 15% in carfilzomib 36 mg/m^2, 19% in carfilzomib 45 mg/m^2 and 5% in carfilzomib 56mg/m^2.) These cardiac events consisted mainly of grade 1/2 toxicity (11 out of 15 events). Five (5%) grade 3 cardiac AEs were reported, three in dose level 27 mg/m^2, one in dose level 45 mg/ m^2 and one in dose level 56 mg/m^2.

Any grade cardiac AEs increased to 18% after consolidation therapy with no reports of grade 4 AEs in all four dose levels, (18% in carfilzomib 27mg/m^2, 15% in carfilzomib 36 mg/m^2, 19% in carfilzomib 45 mg/m^2 and 15% in carfilzomib 56mg/m^2.) These cardiac events consisted mainly of grade 1/2 toxicity (14 out of 19 events). Five (5%) grade 3 cardiac AEs were reported.

Nine patients (8%) developed hypertension during treatment (carfilzomib 27 mg/m^2 n=3, carfilzomib 36 mg/m^2 n=3, carfilzomib 45 mg/m^2 n=2, carfilzomib 56 mg/m^2 n=1), four (4%) of them had grade 3 toxicity. Five (5%) patients needed antihypertensive treatment. Seven patients (6%) had preexisting PN grade 1/2 and two patients (2%) had preexisting grade 3 PN. During induction and consolidation therapy 52 patients (47%) developed PN. Grade ≥ 2 PN events occurred in 23 patients (20%) independent from carfilzomib dose and was clinically manageable (carfilzomib 27 mg/m^2 n=11, carfilzomib 36 mg/m^2 n=3, carfilzomib 45 mg/m^2 n=6, carfilzomib 56 mg/m^2 n=3). Only one patient (1%) reported grade 3 PN (carfilzomib 27mg/m^2).

At least one Serious AE (SAE) was reported in 43% of patients. In cohort 1 an SAE was reported in 21 (42%) patients, in cohort 2 in 8 (40%) patients, in cohort 3 in 7 (33%) patients and in cohort 4 in 12 (60%) patients.

As shown earlier 9 patients (8%) discontinued treatment protocol due to excessive toxicity, six patients during induction therapy and three patients during consolidation therapy. In cohort 1, four (8%) patients went off protocol due to AEs, one (5%) patient in cohort 2 and four (20%) patients in cohort 4. Table 5 shows an analysis of treatment adherence to protocol. During consolidation treatment normal completion rate for carfilzomib and dexamethasone was similar to induction treatment whereas this was higher for thalidomide, probably due to the lower dose of thalidomide during consolidation treatment. A higher percentage of patients prematurely discontinued treatment at the highest dose level of carfilzomib (5

patients (25%)). One patient (5%) had infectious complications, one patient (5%) developed thrombotic microangiopathy, one patient (5%) developed thrombotic thrombocytopenic purpura, one patient (5%) had hematological complications and one patient (5%) requested to discontinue treatment (supplementary table 2).

Table 4. Cardiac adverse events during induction and consolidation between dose levels.

	20/27 mg/m², n=50		20/36 mg/m², n=20		20/45 mg/m², n=21		20/56 mg/m², n=20	
Cardiac toxicity, n (%)	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Acute coronary syndrome	0 (0)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Atrial flutter	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Atrial fibrillation	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Angina pectoris	3 (6)	0 (0)	1 (5)	0 (0)	2 (10)	1 (5)	1 (5)	0 (0)
Congestive heart failure	1 (2)	2 (4)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Dyspnea	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Palpitations	1 (2)	0 (0)	1 (5)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)
Pericardial fluid	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)
Total of cardiac evens	7 (14)	3 (6)	4 (20)	0 (0)	3 (14)	1 (5)	1 (5)	1 (5)

Table 5. Adherence to treatment protocol during induction and consolidation

	Induction (N=111)	Consolidation (N=94)
Carfilzomib		
Normal completion	68 (61)	61 (55)
Dose delay, reduction and/or interruption	37 (33)	24 (22)
Premature stop	6 (5)	9 (10)
Thalidomide		
Normal completion	54 (49)	63 (67)
Dose delay, reduction and/or interruption	42 (38)	8 (9)
Premature stop	15 (14) (a)	23 (24) (b)
Dexamethasone		
Normal completion	85 (77)	66 (70)
Dose delay, reduction and/or interruption	20 (18)	18 (19)
Premature stop	6 (5)	10 (11)

(a) Including 9 patients who received no thalidomide during induction cycle 4. (b) Including 14 patients who received no thalidomide during consolidation cycle 4

DISCUSSION

Results of the first 3 dose levels of this phase 2 trial have been published before.(11) In this paper we discuss the results of 4 dose levels of carfilzomib. As reported above, treatment with KTd for induction and consolidation in transplant eligible patients with NDMM is safe, tolerable and effective. We included the additional cohort with the highest dose level of 56 mg/m², based on the hypothesis that a higher dose level induces a higher response rate. (12, 16) Response after induction was high with 65% of patients reaching at least VGPR, increasing to 86% after consolidation therapy. CR rate after consolidation was high with 63%. Response (i.e. >CR) after consolidation in the higher three dose levels (20/36, 20/45, 20/56) was better than in the lowest dose level (20/27) however, the small sample size and the non-randomized design of the study preclude firm conclusions about superiority of the highest dose levels. In the ARROW trial, 478 patients with RRMM were randomized between treatment with carfilzomib twice a week 27 mg/m² or once weekly 70 mg/m². PFS was higher with once weekly 70 mg/m² than with twice weekly 27 mg/m² (11.2 months vs 7.6 months).(20) These data and our data (based on response) suggest that a dose of at least 36 mg/m² twice weekly (which equals 70 mg/m² once weekly), would be the preferred dose.

An important remaining question relates to the efficacy of this regimen in high-risk patients. In this trial with limited numbers, the negative impact of high-risk cytogenetics was not abrogated by carfilzomib.(21) At the same time, overall risk status, based on cytogenetics and ISS stage, was not significantly associated with response. However, high-risk patients and patients with a higher R-ISS score had a significantly worse PFS. Median PFS and OS for all patients were 58 months and 83 months, respectively. These data show that treatment with KTd is effective as frontline treatment of transplant eligible patients with NDMM. Also, this regimen had no effect on stem cell mobilization and collection, with the exception of 2 patients in whom stem cell collection failed. Several phase 2 trials have investigated treatment with carfilzomib in NDMM using different regimens.(12-15) In the CYKLONE trial cyclophosphamide was added to the KTd regimen. They showed a comparable ORR of 91% and a PFS at 24 months of 76%. In this study MTD was 20/36 mg/m².(13) In comparison, in the Carthadex trial dose levels of 45 mg/m² and 56 mg/m² were well tolerated without additional toxicity compared to dose levels 27 mg/m² and 36 mg/m². The number of patients going off treatment due to excessive toxicity was low, 9 out of 111 patients (8%). Our data show that efficacy and safety are comparable at dose levels 36 mg/m² and upward. Main grade 3/4 non-hematological toxicity consisted of infections, respiratory disorders, skin and vascular disorders. The rate of cardiac AEs was low in this trial. Five patients (5%) experienced grade 3 cardiac AE, including congestive heart failure, dyspnea and chest pain. This is comparable to other trials investigating carfilzomib in NDMM. (12-14) The rate of grade 3/4 cardiac toxicity is slightly higher in RRMM, most likely because

patients are older and due to previous treatment.(9, 10) However, the limited number of patients preclude firm conclusions about safety regarding cardiac events between the different dose levels. Jakubowiak et al. performed a phase 1/2 trial of carfilzomib combined with lenalidomide and dexamethasone (CRd). In this trial patients not proceeding to ASCT continued treatment with CRd beyond 8 cycles with a median of 12 cycles. PFS at 24 months was 92%.(12) However, thalidomide remains a valuable and available treatment option in many countries, due to availability and due to low costs, and offers a great alternative to treatment with lenalidomide.

Recently several trials have been performed in patients with NDMM, using alternative schedules for induction and consolidation. The Intergroupe Francophone du Myélome (IFM) performed a phase 2 trial of lenalidomide combined with bortezomib and dexamethasone (RVD) for induction and consolidation. PFS at 3 years was 77% and CR rate was 58%. Most common toxicities were grade 1/2 PN in 55%.(22) In the EMN02 trial VCD for induction was followed by VRD for consolidation treatment. CR rate was 55% and PFS not reached at 60 months.(23) Although it should be taken into account that this is a cross comparison between trials, the Carthadex trial efficacy data are similar with median PFS of 58 months and CR rate of 63% and acceptable toxicity. Moreover, the combination of carfilzomib, thalidomide and dexamethasone is an affordable treatment regimen. These data suggest that KTd is an effective and safe induction and consolidation regimen in newly diagnosed MM.

In conclusion, the combination of carfilzomib, thalidomide and low-dose dexamethasone appears highly efficacious and safe in transplant-eligible patients with NDMM across all dose levels with manageable toxicities. Consolidation therapy after ASCT results in a major improvement in response. In addition, we observed that higher dose levels of carfilzomib (36 to 56 mg/m^2) result in better response rates after consolidation therapy. Current studies in newly diagnosed multiple myeloma patients are performed using 36 mg/m^2 twice weekly. 36 mg/m^2 twice weekly (or 70 mg/m^2 once weekly) will be the preferred dose to be used in practice, which we would recommend based on our carthadex response data. Results of cohort 5 in which patients were treated with 8 instead of 4 induction cycles will follow in the near future.

Further randomized, prospective studies are needed to confirm these data and determine the position of carfilzomib in the treatment of patients with NDMM.

Acknowledgements

This trial was supported by funding from Onyx Pharmaceuticals, Inc., an Amgen subsidiary.

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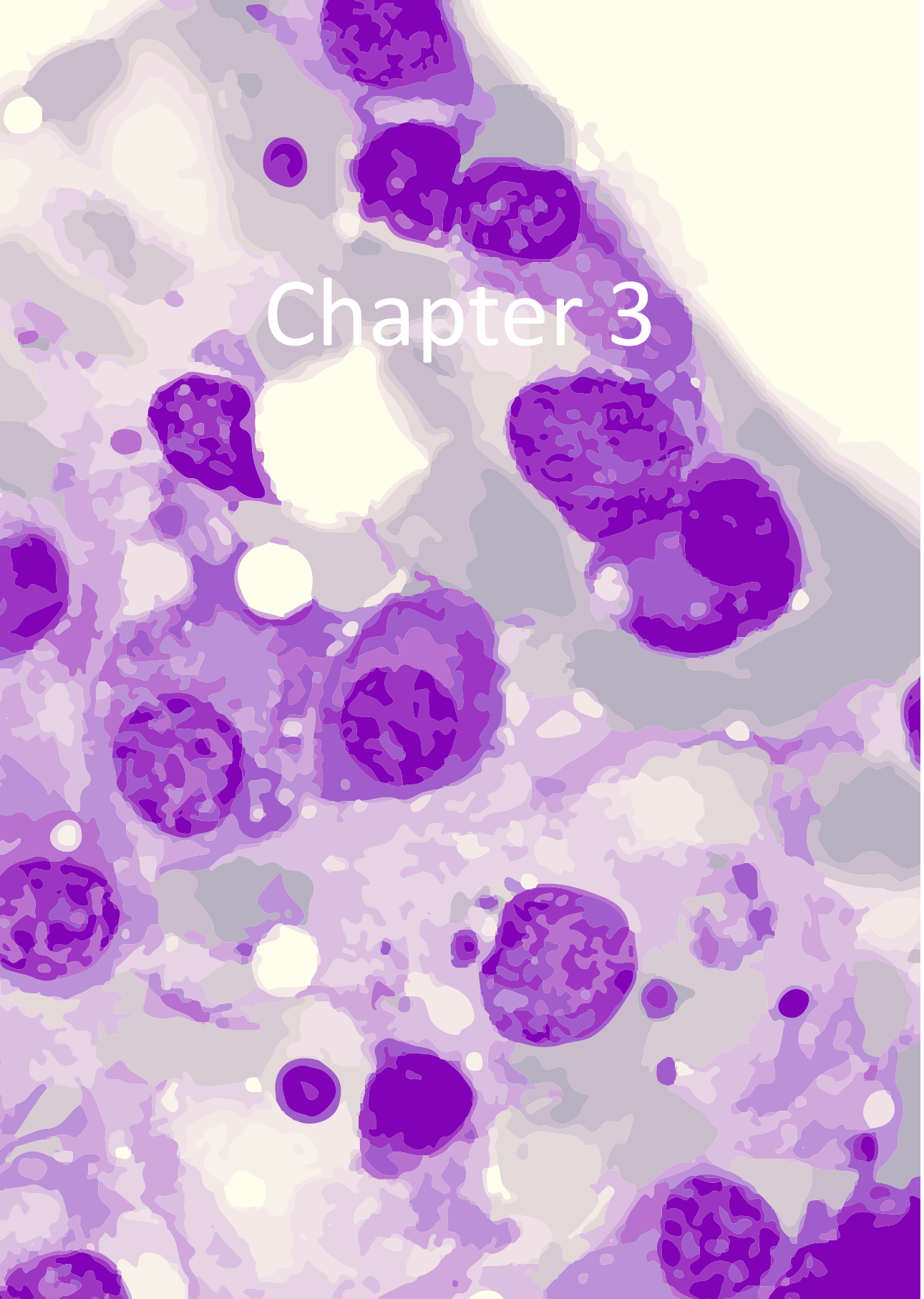
SUPPLEMANTARY TABLES

	Induction therapy (N=111)		Induction and consolidation therapy (N=111)		
Toxicity, n (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**SAE**
Hematologic	7 (6)	5 (5)	17 (15)	11 (10)	3 (3)
Anemia	5 (5)	4 (4)	9 (8)	4 (4)	0 (0)
(Febrile) Neutropenia	1 (1)	1 (1)	2 (2)	2 (2)	0 (0)
Thrombopenia	0 (0)	0 (0)	5 (5)	5 (5)	2 (2)
Leukopenia	1 (1)	0 (0)	3 (3)	0 (0)	0 (0)
Other	1 (1)	1 (1)	2 (2)	1 (1)	1 (1)
Non-hematologic	110 (99)	42 (38)	110 (99)	51 (46)	57 (51)
General disorders and administration site conditions	67 (60)	2 (2)	77 (69)	3 (3)	10 (9)
Gastrointestinal disorders	59 (53)	3 (3)	64 (58)	3 (3)	6 (5)
Respiratory, thoracic, and mediastinal disorders	37 (33)	7 (6)	51 (46)	9 (8)	4 (4)
PNP	43 (39)	0 (0)	50 (45)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders	43 (39)	9 (8)	45 (41)	10 (9)	2 (2)
Musculature, skeletal, and connective tissue disorders	34 (31)	5 (5)	48 (43)	7 (6)	1 (1)
Vascular disorders	34 (31)	9 (8)	35 (32)	10 (9)	7 (6)
Cardiac disorders	15 (14)	4 (4)	19 (17)	5 (5)	6 (5)
Infections and infestations	26 (23)	2 (2)	47 (42)	6 (5)	12 (11)
Metabolism and nutrition disorders	19 (17)	10 (9)	21 (19)	10 (9)	5 (5)
Investigations	12 (11)	5 (5)	13 (12)	6 (5)	0 (0)
Eye disorders	13 (12)	1 (1)	18 (16)	1 (1)	0 (0)
Psychiatric disorders	8 (7)	0 (0)	12 (11)	0 (0)	0 (0)
Renal and urinary disorders	9 (8)	3 (3)	12 (11)	3 (3)	2 (2)
Endocrine disorders	2 (2)	1 (1)	2 (2)	1 (1)	0 (0)
Surgical and medical procedures	1 (1)	1 (1)	2 (2)	1 (1)	1 (1)
Immune system disorders	3 (3)	2 (2)	4 (4)	2 (2)	1 (1)

Table S1. Treatment-emergent adverse events during induction and consolidation therapy, excluding cyclophosphamide and HDM.

	Induction				Consolidation			
	20/27 mg/m²	**20/36 mg/m²**	**20/45 mg/m²**	**20/56 mg/m²**	**20/27 mg/m²**	**20/36 mg/m²**	**20/45 mg/m²**	**20/56 mg/m²**
Patients (n)	**50**	**20**	**21**	**20**	**41**	**15**	**19**	**19**
Carfilzomib								
Normal completion	29 (58)	13 (65)	12 (57)	15 (75)	29 (71)	8 (53)	14 (74)	10 (53)
Dose delay, reduction and/or interuption	17 (34)	6 (30)	9 (43)	4 (20)	11 (27)	6 (40)	3 (16)	4 (21)
Premature stop	4 (8)	1 (5)	-	1 (5)	1 (2)	1 (7)	2(11)	5 (26)
Thalidomide								
Normal completion	29 (58)	15 (75)	5 (24)	7 (35)	32 (78)	12 (80)	12 (63)	7 (37)
Dose delay, reduction and/or interuption	15 (30)	4 (20)	14 (67)	10 (50)	3 (7)	-	2 (11)	3 (16)
Premature stop	6 (12)	1 (5)	2 (10)	3 (15)	6(15)	3 (20)	5 (26)	9 (47)
Dexamethasone								
Normal completion	38 (76)	18 (90)	15 (71)	14 (70)	31 (76)	11 (73)	13 (68)	11 (58)
Dose delay, reduction and/or interuption	8 (16)	1 (5)	6 (29)	5 (25)	8 (20)	3 (20)	4 (21)	3 (16)
Premature stop	4 (8)	1(5)	-	1 (5)	2 (5)	1 (7)	2 (11)	5 (26)

Table S2. Adherence to treatment protocol during induction and consolidation between dose levels.



Chapter 3

Carfilzomib combined with thalidomide and low-dose dexamethasone for remission induction and consolidation in newly diagnosed transplant eligible patients with multiple myeloma: eight versus four induction cycles; the carthadex trial.

Ruth Wester, Sonja Zweegman, Bronno van der Holt, Marie José Kersten, Edo Vellenga, Marinus van Marwijk-Kooy, Emelie Asselbergs, Okke de Weerdt, Monique C. Minnema, Sarah Lonergan, Antonio Palumbo, Annemiek Broijl, Pieter Sonneveld

Hemasphere 2020 Aug 12;4(4):e370.

Survival in patients with multiple myeloma (MM) has significantly improved during the last decades due to introduction of novel therapies. In transplant-eligible patients with newly diagnosed multiple myeloma (NDMM) the depth of response following induction therapy is associated with a better progression free survival (PFS) and overall survival (OS).(1, 2) However, it is currently unknown whether further improvement in response by increasing the number of induction cycles will translate in a better long-term outcome. Standard induction therapy consists of four to a maximum of six(3) cycles of treatment including a proteasome inhibitor, an immunomodulatory drug and dexamethasone. The paradigm that improvement in response that in general is observed with increasing number of induction cycles will lead to a better outcome might be false. To the best of our knowledge data from randomized clinical trials are lacking. Therefore, we here describe the outcome of a cohort study in which cohorts were treated with either 4 or 8 induction cycles of KTd.

Widely accepted regimens are combinations of bortezomib, thalidomide and dexamethasone (VTd) or bortezomib, lenalidomide and dexamethasone (VRd). Unfortunately, the combination of bortezomib and these Imids is associated with the occurrence of polyneuropathy (PNP), which may require dose reductions or early discontinuation of treatment.(4) Carfilzomib is a selective proteasome inhibitor that has irreversible binding to the 20S proteasome resulting in accumulation of the proteasome substrates. Previous trials showed that the incidence of PNP in patients treated with carfilzomib is lower than with bortezomib, which makes Carfilzomib a good alternative for use in NDMM.(5, 6)

In this single-arm, open-label, phase 2 dose escalation trial of the European Myeloma Network the combination of carfilzomib with thalidomide and dexamethasone (KTd) for induction and consolidation therapy was investigated in transplant eligible patients with NDMM. The results of 4 dose levels of Carfilzomib (27, 36, 45, 56 mg/m^2) have recently been published(6). Overall response rate (ORR) after induction therapy was 93% with a complete remission (CR) rate of 18%. ORR increased to 94% after consolidation therapy with a CR rate of 63%. Median PFS was 58 months and median OS was 83 months.(6) There were no significant differences in outcome between the dose levels of Carfilzomib.

We here present the results of intensified induction with 8 cycles of KTd, and compared these data to the data we obtained from treatment with 4 cycles of KTd whereby carfilzomib was dosed twice weekly at 56 mg/m^2.

This is an open-label, phase 2 trial in which 20 patients dosed with 4 KTd induction cycles in the previous dose-escalation trial were compared with a new cohort of patients treated with 8 induction cycles.(6) Transplant eligible patients aged between 18 and 65 years with NDMM were included. Patients were treated with 4 or 8 cycles of KTd for induction, respectively. The dose of carfilzomib was 20 mg/m^2 i.v. on days 1,2 followed by 56 mg/m^2 on days 8,9,15,16 of cycle 1 and on days 1,2, 8,9,15,16 of cycles 2-4 or 2-8. Thalidomide dose was 200 mg orally on days 1 through 28 and dexamethasone dose was 40 mg orally on days 1,8,15 and 22 of a 28-day cycle. Induction therapy was followed by stem cell

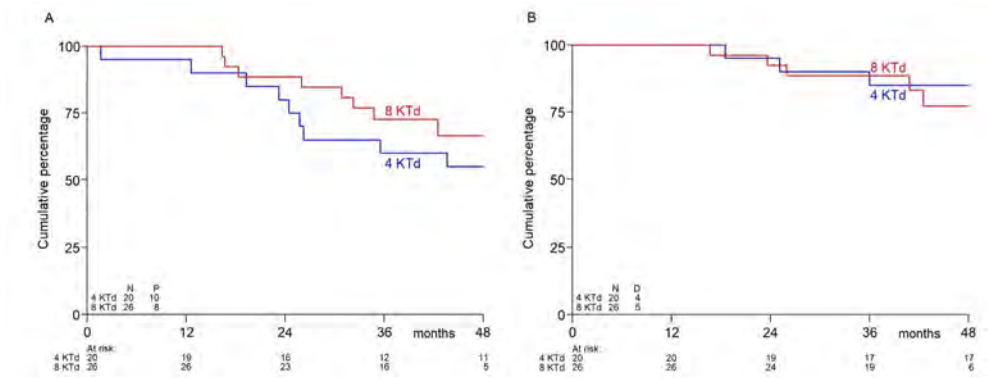
harvest after cyclophosphamide priming (2 mg/m^2) and daily 10 µg/kg granulocyte colony-stimulating factor. Hereafter, patients received HDM (200 mg/m^2) and ASCT followed by 4 consolidation cycles with KTd in the same schedule as during induction therapy except a lower dose of Thalidomide (50 mg). The primary endpoint was response after induction therapy, specifically CR and very good partial response (VGPR). Secondary endpoints were efficacy and safety, PFS and OS.

For this prospective analysis 46 eligible patients were analyzed, 26 patients were treated with 8 cycles of KTd induction therapy versus 20 patients treated with 4 cycles of KTd at carfilzomib 56 mg/m^2. Median age was 57 years [range 37-66 years]. ISS stages I/II/III/unknown were 43%/35%/20%/2%, respectively. A total of 50% of patients were classified as high risk based on cytogenetics and ISS stage; 33% of patients were classified as standard risk. In 17% of patients, risk status was unknown, mainly due to missing cytogenetics. Patients were considered to be high-risk if they had t(4;14) and/or del(17p) and/or add(1q) and/or ISS stage III.

Median follow-up was 51.4 months [range 33.3-74.1 months]. Response with 8 KTd and with 4 KTd after induction was ≥ CR in 27% vs 20%, ≥ VGPR in 92% vs 80% and ≥ PR in 96% vs 90%. Response with 8 KTd vs 4 KTd after HDM was CR in 35% vs 30%. After consolidation treatment CR rate increased to 58% vs 65%, respectively.

In patients treated with 8 KTd induction, PFS and OS at 48 months were 67% and 77% respectively, as compared with 55% and 85% after 4 KTd (Figure 1).

Figure 1: A: Progression free survival, B: Overall survival



Induction treatment with 8 KTd resulted in a higher incidence of premature discontinuation of carfilzomib (12%) and dexamethasone (12%) than with 4 KTd (5% and 5%, respectively) (Table 1). Reason for premature discontinuation were PNP (n=3), anemia and fatigue (n=1), skin toxicity (n=1), progression of disease (n=1). With 4 and 8 KTD median relative dose intensity of carfilzomib was 98% [IQR 92-100]. Seven patients (27%) completed 8 induction cycles without any reduction in dose level.

Table 1: Adherence to treatment protocol during induction and consolidation between dose levels.

	Induction 4 induction cycles at 56 mg/m^2	8 induction cycles at 56 mg/m^2	Consolidation 4 induction cycles at 56 mg/m^2	8 induction cycles at 56 mg/m^2
Patients, n	20	26	19	22
Carfilzomib				
Normal completion	15 (75)	10 (38)	10 (53)	10 (45)
Dose delay, reduction and/or interruption	4 (20)	13 (50)	4 (21)	6 (27)
Premature stop	1 (5)	3 (12)	5 (26)	6 (27)
Thalidomide				
Normal completion	7 (35)	7 (27)	7 (37)	9 (41)
Dose delay, reduction and/or interruption	10 (50)	16 (62)	3 (16)	3 (14)
Premature stop	3 (15)	3 (12)	9 (47)	10 (45)
Dexamethasone				
Normal completion	14 (70)	13 (50)	11 (58)	10 (45)
Dose delay, reduction and/or interruption	5 (25)	10 (38)	3 (16)	5 (23)
Premature stop	1 (5)	3 (12)	5 (26)	7 (32)

Grade 3 and 4 toxicity rates were higher with 8 KTd with respect to anemia, respiratory complications, polyneuropathy and cardiac disorders. Cardiac events grade 3 and 4 in patients treated with 8 KTd occurred in 4 patients (15%, heart failure (2 patients) and hypertension (2 patients)). With 4 KTd heart failure grade 3 was reported in one patient (5%).

In conclusion, in this prospective, multicenter, non-randomized phase 2 trial, 8 cycles of KTd resulted in slightly higher percentages of CR and VGPR as compared to 4 KTd, with almost all patients achieving at least a PR. However, more cardiac events and premature discontinuation of treatment were observed. Moreover, response percentages after HDM/ASCT as well as after consolidation were comparable between the two groups and more importantly, also PFS and OS were not different. A limitation of our study is that we used cohorts of patients instead of a randomization. Moreover, we choose a regimen that is less feasible with only 38% of patients being treated as planned. As a consequence, the improvement in response was limited. Therefore, we cannot define whether increasing response with additional cycles of therapy will translate in a better (progression free) survival or indicates more refractory disease with inferior outcome.

Our data do not support lengthening induction therapy with KTd, as the increase in response is limited and does not translate in an improvement in PFS and OS. Moreover, feasibility was modest with only 38% of patients receiving full dose in time. Therefore we conclude that in transplant-eligible NDMM 4 induction cycles should remain the standard.

Acknowledgments

This trial was supported by funding from Onyx Pharmaceuticals, Inc., an Amgen subsidiary.

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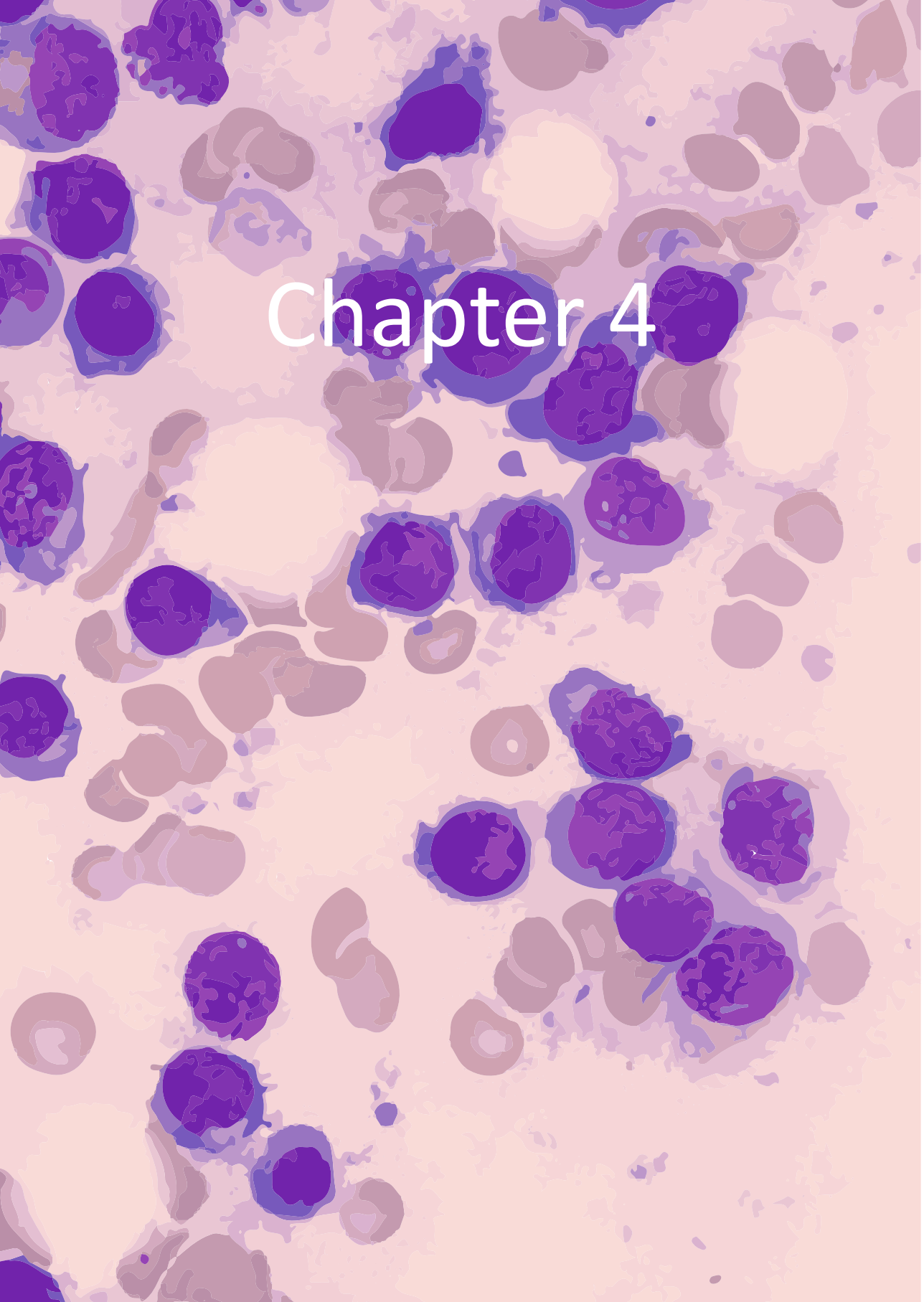

Chapter 4

Consolidation and maintenance in newly diagnosed multiple myeloma

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JCO 2021 Nov 10;39(32):3613-3622.

ABSTRACT:

PURPOSE

To address the role of consolidation treatment for newly diagnosed, transplant eligible patients with multiple myeloma in a controlled clinical trial.

PATIENTS AND METHODS

The EMN02/HOVON95 trial compared consolidation treatment with two cycles of bortezomib, lenalidomide, and dexamethasone (VRD) or no consolidation after induction and intensification therapy, followed by continuous lenalidomide maintenance. Primary study end point was progression-free survival (PFS).

RESULTS

Eight hundred seventy-eight eligible patients were randomly assigned to receive VRD consolidation (451 patients) or no consolidation (427 patients). At a median follow-up of 74.8 months, median PFS with adjustment for pretreatment was prolonged in patients randomly assigned to VRD consolidation (59.3 v 42.9 months, hazard ratio [HR] 5 0.81; 95% CI, 0.68 to 0.96; P = .016). The PFS benefit was observed across most predefined subgroups, including revised International Staging System (ISS) stage, cytogenetics, and prior treatment. Revised ISS3 stage (HR, 2.00; 95% CI, 1.41 to 2.86) and ampl1q (HR, 1.67; 95% CI, 1.37 to 2.04) were significant adverse prognostic factors. The median duration of maintenance was 33 months (interquartile range 13-86 months). Response ≥complete response (CR) after consolidation versus no consolidation before start of maintenance was 34% versus 18%, respectively (P < .001). Response ≥ CR on protocol including maintenance was 59% with consolidation and 46% without (P < .001). Minimal residual disease analysis by flow cytometry in a subgroup of 226 patients with CR or stringent complete response or very good partial response before start of maintenance demonstrated a 74% minimal residual disease–negativity rate in VRD treated patients. Toxicity from VRD was acceptable and manageable.

CONCLUSION

Consolidation treatment with VRD followed by lenalidomide maintenance improves PFS and depth of response in newly diagnosed patients with multiple myeloma as compared to maintenance alone.

BACKGROUND AND MOTIVATION

The role of consolidation treatment for newly diagnosed, transplant-eligible patients with multiple myeloma (TE-NDMM) needs prospective evaluation.

INTRODUCTION

The treatment outcome of patients with multiple myeloma (MM) significantly improved by the introduction of proteasome inhibitors and immunomodulatory agents, resulting in higher response rates, as well as longer progression-free survival (PFS) and overall survival (OS). High-dose melphalan followed by autologous stem-cell transplantation (HDM/ASCT) remains a backbone.[1] Maintenance with lenalidomide is now a standard treatment.[2] We reported the results of the EMN02/HO95 trial, which demonstrates the superiority for PFS of HDM/ASCT over chemotherapy.[3] Few trials prospectively addressed the effect of consolidation treatment in NDMM.[4] Superior complete response (CR) or near complete response rates and PFS were demonstrated with bortezomib, thalidomide, and dexamethasone (VTD) versus thalidomide-dexamethasone as consolidation after double ASCT for NDMM.[5] The BMT CTN0702 (STaMINA) trial compared a second ASCT with consolidation plus maintenance or maintenance alone.[6] At a follow-up of 38 months, no difference was observed. A later analysis demonstrated a PFS advantage of double ASCT in high-risk disease.[7] One retrospective analysis demonstrated an advantage for VTD consolidation.[8] Recent prospective trials usually included standard consolidation.[9-11] In the EMN02/HO95 trial, patients were randomly assigned to consolidation treatment with two cycles of bortezomib, lenalidomide, and dexamethasone (VRD) versus no consolidation, followed by lenalidomide maintenance until progressive disease or toxicity.

PATIENTS AND METHODS

Study Design

This randomized, open-label, phase III study was performed by the European Myeloma Network (EMN).[3] Previously untreated patients age 18-65 years with symptomatic MM stage 1-3 according to the International Staging System (ISS), measurable disease defined by the presence of serum M-protein > 10 g/L or urine M-protein > 200 mg/24 hours or abnormal free light-chain ratio with involved free light-chain > 100 mg/L or proven plasmacytoma by biopsy, and a WHO performance status grade 0-2 or 3 when because of myeloma were included (Appendix Table A1, online only). Exclusion criteria were listed in the recent publication of Part 1 and in the Protocol (online only). All patients provided written informed consent. The study was approved by independent ethics committees or the institutional review board of participating sites and performed according to the International Conference on Harmonization Guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki. The Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON) sponsored and designed this study.

Treatment and Procedures

After registration patients received induction with 3-4 cycles of vincristine, cyclophosphamide, and dexamethasone and mobilization of stem cells was performed.[3] Next, patients were randomly assigned (R1) to receive four cycles of bortezomib, melphalan, and prednisone (VMP) or HDM/ASCT once or twice as described.[3] Within 2months after ASCT or last VMP, a second random assignment (R2) assigned eligible patients to two 28-day cycles of VRD consolidation VRD (bortezomib [1.3 mg/m2 either intravenous or subcutaneously once daily on days 1, 4, 8, and 11] combined with lenalidomide [25 mg orally once daily, days 1-21] and dexamethasone [20 mg orally once daily, on days 1, 2, 4, 5, 8, 9, 11, and 12]) or no consolidation. No masking or stratification was done. Patients started lenalidomidemaintenance (10 mg orally once daily on days 1-21 of a 28-day cycle) 1-2 months after ASCT or consolidation until disease progression (PD) or toxicity.

Outcomes

The primary end point PFS was defined as time from R2 to disease progression or death. Secondary end points were partial response or higher defined by the International Uniform Response Criteria for Multiple Myeloma[12] (Appendix Table A3, online only), OS from R2 until death from any cause, and toxicity. Predefined high-risk prognostic subgroups for PFS included cytogenetic abnormalities defined by fluorescent in situ hybridization: deletion (17p) in ≥ 20% of enriched plasma cells; t(4;14) in ≥ 10% of enriched plasma cells; t(14;16) in ≥ 10% of enriched plasma cells; and amplification 1q. Standard clinical variables such as hemoglobin content, serum creatinine, and serum lactate dehydrogenase were included.[13] Disease assessment was performed before and after consolidation and every 2 months until progression according to standard criteria (Appendix Table A3). Minimal residual disease (MRD) assessment was performed by multicolor flow cytometry in bone marrow with a detection of 10^{-4} to 10^{-5} in central laboratories of the EMN Network using a standard protocol.[14,15] Here, we report the final analysis, which was performed in November 2020 at a median follow-up of 74.8 months from R2.

Statistical Analysis

The sample size was estimated based on the primary end point PFS from R2. Assuming a median PFS of 25 months without consolidation and 32 months with consolidation, we estimated that with uniform accrual for 30 months and additional follow-up of 24 months after the last patient was randomly assigned, 848 patients were required to be randomly assigned 1:1 and 514 events of PD or death would be needed to provide 80% power to detect a 22% reduced risk of PD or death (hazard ratio [HR] 0.78) in the consolidation group compared with no consolidation, using Cox regression analysis, with an overall two-sided significance level of 0.05. Two prespecified interim analyses were performed in 2016 and 2018 after 33% and 66% of events had occurred; therefore, the *P* value for the primary end point at the final analysis was set at .045. These interim analyses showed PFS was longer with consolidation than without consolidation. An independent data monitoring committee reviewed the results of interim analyses. Efficacy was analyzed in the intention-to-treat population, which includes all eligible patients in R2 who also were in R1. PFS and OS were estimated by Kaplan-Meier method from the date of R2. Cox regression analysis including only the R2 arm and the stratification factor R1 group (VMP v HDM) was used for the primary comparison of PFS between treatment groups and to estimate HRs and 95% CIs. The consistency of effects of consolidation versus no consolidation within predefined subgroups was evaluated using interaction-p terms between each of the covariates included in the Cox model. Forest plots were generated to illustrate PFS from R2 within subgroups.

As a post hoc analysis, we also performed a multivariable Cox regression analysis with R2 arm together with the variables that were statistically significant in the multivariable analysis for PFS in the VMP versus HDM random assignment.[3] To include all patients in this analysis, the method of multiple imputation by chained equations was used to cope with possible missing data on these covariates. Responses were compared between treatments using the chi-squared test. Safety was assessed in all patients who received at least one dose of study drugs. Toxicities were tabulated as adverse events (CTCAE version 4) and second primary malignancies (SPMs). Cumulative incidence curves of SPMs were generated by treatment group. MRD was evaluated in patients with at least one evaluable MRD sample. The prognostic impact of MRD on PFS from R2 was assessed by comparing PFS from R2 in MRD-negative versus MRD-positive patients. Patients with the last sample during or after intensification with VMP or HDM/ASCT but before start of VRD or start of maintenance, whichever first, were considered MRD-negative if the last sample was MRD-negative. All other patients, including those without an evaluable MRD sample, were considered as MRD-positive at R2. Similarly, the prognostic impact of MRD on PFS from start of maintenance was assessed. In that analysis, patients were considered MRD-negative if the last sample during or after intensification, VRD consolidation, or within 4 months after start maintenance was MRD-negative. All analyses were performed using Stata (version 15.1). Data were monitored by an external contract organization and verified for accuracy by a supporting research team at the EMN data center. This trial is registered with the EU Clinical Trials Register (EudraCT 2009-017903-28) and ClinicalTrials.gov identifier: NCT01208766.

Role of Funding Sources

Funding for this study was provided by the Dutch National Cancer Society and by Janssen and Celgene. The study was performed as an independent, investigator-sponsored study. All patients provided written informed consent and the study was approved by the independent ethics committee or institutional review board of each participating hospital. Funders had no role in study design, data collection, data analysis, data interpretation, or manuscript writing. The corresponding author had full access to the data and carried the final responsibility for the submission of the manuscript.

RESULTS

Consolidation

From February 2011 to April 2014, a total of 1,503 patientsage ≤65 years with MM were enrolled in 172 EMN centers, of whom 1,500 were eligible. 1,197 patients were randomly assigned (stratified by ISS stage) to VMP (495 patients) or HDM (one or two ASCT; 702 patients). The results were recently published and an update on OS was presented.[3,16]

For the second random assignment, 878 patients were eligible and 24 patients were ineligible (Appendix Table A1). Patients were randomly assigned to consolidation (arm B, 451 patients) or no consolidation (arm A, 427 patients; Appendix Fig A1, online only). Median follow-up from R2 of 630 patients still alive was 74.8 months (interquartile range [IQR] 64.4-82.3 months). Response status at R2 was equal in both arms, ie, ≥ CR (18%, 22%), ≥ very good partial response (67%, 67%), and ≥ PR (91%, 93%) according to uniform criteria (ST3). At the time of analysis, 519 events for PFS after R2 had been reported. The median PFS from R2 was 59.3 (95% CI, 49.8 to 66.9) versus 42.9 (95% CI, 39.3 to 50.5) months, respectively (HR 0.81 in favor of consolidation, 95% CI, 0.68 to 0.96; P5.016; Fig 1). Five-year PFS from R2 was 50% (95% CI, 45 to 54) with consolidation and 41% (95% CI, 37 to 46) without consolidation. The primary comparison of PFS from R2 between treatment groups also included the R1 group (VMP v HDM), and showed that prior treatment with HDM/ASCT (HR, 0.77; 95% CI, 0.64 to 0.92; P=.003) was statistically significant.

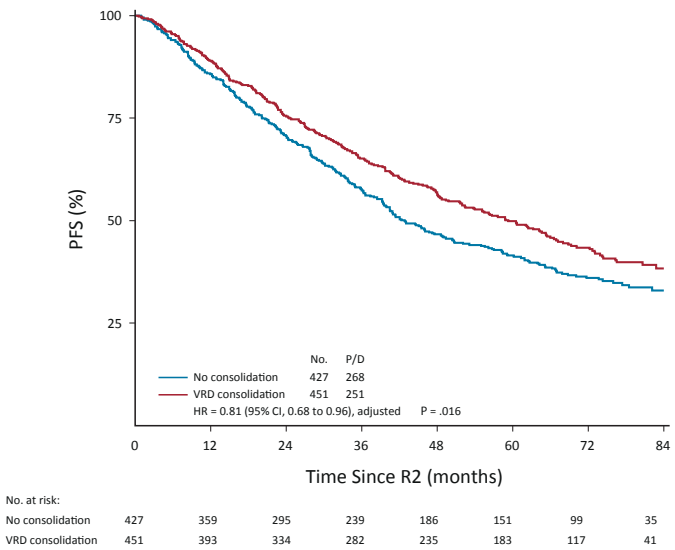

Figure 1. PFS from R2 with consolidation plus maintenance versus maintenance alone. HR, hazard ratio; P/D, progression PFS, progression-free survival; VRD, bortezomib, lenalidomide, and dexamethasone.

There was no significant interaction between the first random assignment (R1) and the arms of the R2 random assignment, indicating that the benefit of consolidation is not different between VMP and HDM (Fig 2).

Consolidation reduced the risk of progression or death in most predefined subgroups, including revised ISS stage I-III, standard-risk cytogenetics, and prior treatment arms (Fig 3). However, the interaction term for del(17p) was significant (P = .04), indicating that VRD consolidation was beneficial in patients without del(17p), HR=0.77 (95% CI,0.64 to 0.94), but not in del(17p), HR=1.50 (95% CI, 0.84 to 2.67).

Univariate Cox regression analysis of all patients randomly assigned in R2 showed that revised ISS stage 3 (HR, 2.00; 95% CI, 1.41 to 2.86), B2M > 5.5, ISS stage 3, t(4;14), revised ISS 2 versus 1, high-risk cytogenetics (HR, 1.49; 95% CI, 1.20 to 1.85), and addition of chromosome 1q by fluorescent in situ hybridization (HR, 1.67; 95% CI, 1.37 to 2.04) at diagnosis were adverse prognostic factors for PFS from R2.

The multiple imputation by chained equation method was used to cope with missing data in the multivariable analysis because platelet count was missing in 2%, revised ISS in 15%, and cytogenetics in 20% of patients. The post hoc multivariable Cox regression analysis with R2 arm together with the variables that were statistically significant in the multivariable analysis for PFS in the R1 (VMP v HDM) random assignment revealed that all covariates were statistically significant, except for standard-risk cytogenetics (P=.08). The significant covariates as displayed in Table 1 also show that the HRs for VRD consolidation (R2; 0.81 v 0.81) and HDM (R1; 0.79 v 0.77) are almost identical to those in the primary analysis of PFS2.[16] Before R2, response ≥ CR was 22% (95% CI, 18 to 26) versus 18% (95% CI, 15 to 22) of patients. Response ≥ CR before start of maintenance was 34% (95% CI, 29 to 38) versus 18% (95% CI, 15 to 22) after consolidation or no consolidation, respectively (P < .001). Response ≥ CR on protocol was 59% (95% CI, 54 to 63) with consolidation and 46% (95% CI, 41 to 51) without (P < .001; Table 2).

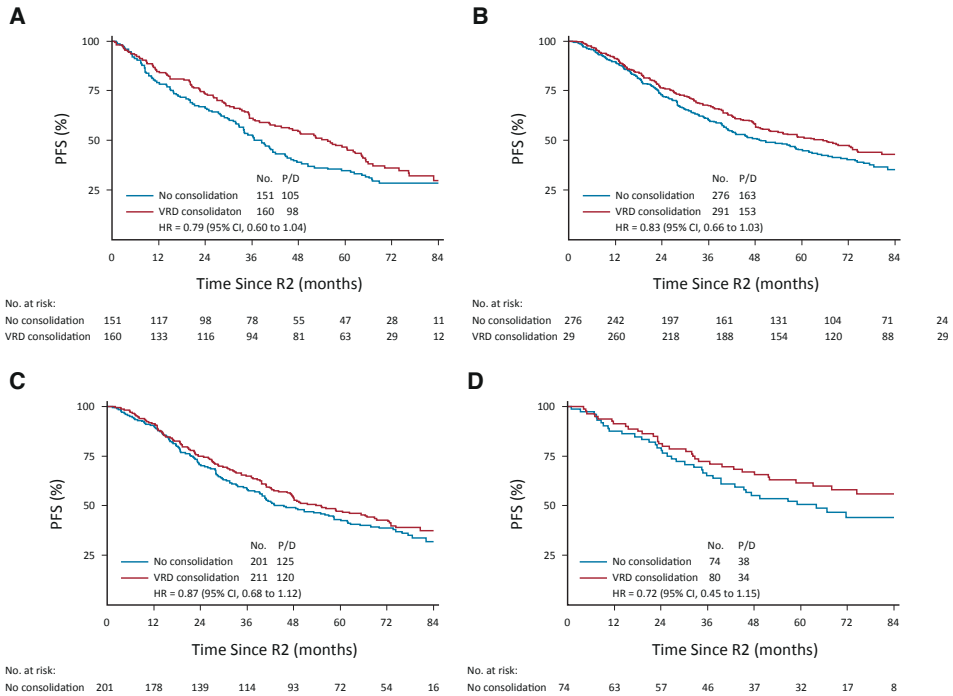

Figure 2. Effect of consolidation treatment on PFS from R2 in patients who were randomly assigned in (A) R1 according to VMP, (B) single or double ASCT, (C) single ASCT, or (D) double ASCT. ASCT, autologous stem-cell transplantation; HR, hazard ratio; P/D, progression or death; PFS, progression-free survival; VMP, bortezomib, melphalan, and prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.

Table 1. Multivariate Analysis for Progression-Free Survival

Covariates	HR	95% CI	P
R2: VRD consolidation v none	0.81	0.68 to 0.96	.015
R1: HDM v VMP	0.79	0.66 to 0.94	.009
≥ VGPR at the time of R2 random assignment	0.70	0.59 to 0.84	< .001
R-ISS I v II[a]	0.77	0.63 to 0.95	.015
R-ISS I v III[a]	0.52	0.37 to 0.73	< .001
Platelet count ≥ 150 3 109/L[a]	0.60	0.47 to 0.77	< .001

Abbreviations: HDM, high-dose melphalan; HR, hazard ratio; ISS, International Staging System; R-ISS, revised International Staging System; VGPR, very good partial response; VMP, bortezomib, melphalan, and prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.[a]R-ISS and platelet count measured at entry in the trial.

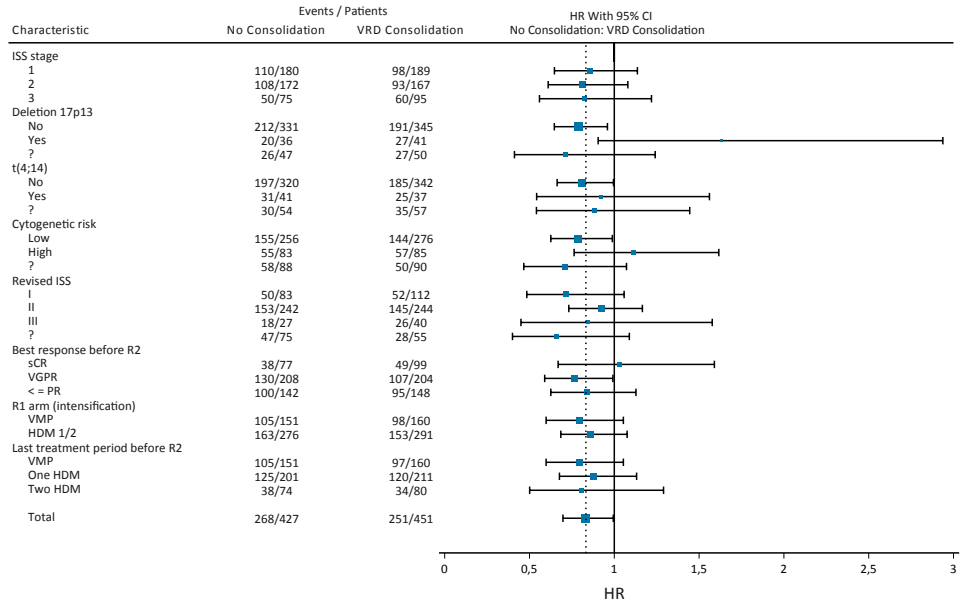

Figure 3. Forest plot for PFS from R2 of predefined subgroups. HDM, high-dose melphalan; HR, hazard ratio; ISS, International Staging System; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response; VMP, bortezomib, melphalan, and prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.

Table 2. Response Status

Time	Response % of Patients	Consolidation No	Consolidation Yes	P
Before R2	≥ CR	18	22	.15
	≥ VGPR	67	67	.94
	ORR	91	93	.38
Before maintenance	≥ CR	18	34	< .001
	≥ VGPR	67	78	< .001
Best on protocol	≥ CR	46	59	< .001
	≥ VGPR	87	89	.26

Abbreviations: CR, complete response; ORR, overall response rate; VGPR, very good partial response.

Maintenance

Maintenance with lenalidomide 10 mg was initiated in 847 patients, 428 (95%) with and 419 (98%) without consolidation. The median duration of maintenance was not different at 35.7 months (IQR 13-78 months) and 31.8 months (IQR 14-88 months), respectively (P = .24; Appendix Fig A2, online only). At 5 years after random assignment, 35% (consolidation) and 30% (no consolidation) of patients were still receiving maintenance treatment. Maintenance was discontinued in 288 of 428 (67%) versus 302 of 419 (72%) patients, of whom 186 of 288 (65%) versus 189 of 302 (63%) because of progressive disease after consolidation or no consolidation, respectively.

At a median follow-up of 73.4 months, median PFS from start of maintenance was 57.5 months in the consolidation arm and 42.3 months without consolidation (HR 5 0.83; 95% CI, 0.70 to 0.99; P = .04).

At 4 years after R2, OS was 81%-82% in both arms, whereas at 6 years, OS was 76% (95% CI, 71 to 79) with consolidation and 69% (95% CI, 64 to 73) without consolidation, indicating that longer follow-up is required to evaluate OS (Appendix Fig A3, online only).

Toxicity

Ninety-six percent of patients randomly assigned to consolidation completed two cycles of VRD. Toxicity was acceptable and manageable with 28% CTCAE grade 3 or 4, mainly neutropenia (13%), thrombocytopenia (12%), and infections (5%; Appendix Table A2, online only). The cumulative incidence of SPM excluding superficial skin cancer at 6 years was 5% and 6%, respectively.

MRD

Minimal residual disease studies were initiated only when a standard assessment protocol became available. MRD was performed by 8-color flow cytometry on bone marrow aspirates of patients in CR or stringent complete response or very good partial response at R2 and at the start of maintenance. Of 878 randomly assigned patients in the consolidation ITT analysis, 103 patients had an MRD sample after the last treatment before R2. Thirty-five of 49 (71%) patients without consolidation were MRD-negative, versus 44 of 54 (81%) with consolidation. Similarly, 226 patients had at least one MRD sample before or within 4 months after start maintenance, which were considered as MRD sample at the start of maintenance. Sixty-two of 89 (70%) of evaluable patients without consolidation were MRD-negative, versus 101 of 137 (74%) with consolidation. Figure 4 shows the Kaplan-Meier curves of PFS from R2 random assignment according to R2 arm and MRD status at R2 and PFS from start maintenance according to R2 arm and MRD status at start maintenance.

Both figures indicate that PFS is improved in MRD-negative patients. Median PFS from start of maintenance in patients randomly assigned to no consolidation was 85.3 months in MRD-negative patients and 39.3 months in MRD-positive patients (HR = 0.49; 95% CI, 0.32 to 0.73; P <.001), and in patients randomly assigned to consolidation, it was median 70.1 months in MRD-negative patients and 50.6 months in MRD-positive patients (HR=0.65; 95% CI, 0.47 to 0.89; P = .008). The detailed analysis of MRD for the EMN02/HO95 trial including R1 is described elsewhere.[14]

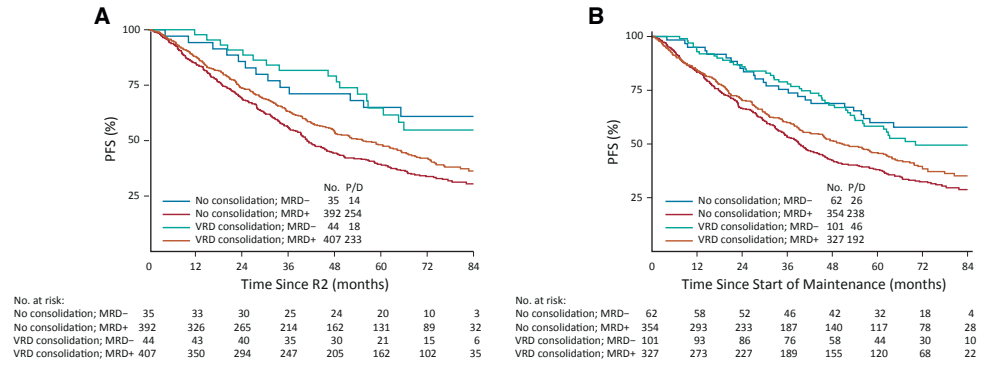

FIG 4. (A) PFS from R2 by R2-arm and MRD status and (B) PFS from start of maintenance by R2-arm and MRD status before start maintenance. MRD, minimal residual disease; P/D, progression or death; PFS, progression-free survival; VRD, bortezomib, lenalidomide, and dexamethasone.

DISCUSSION

This randomized trial evaluated the efficacy of consolidation after intensification with VMP or HDM/ASCT in TENDMM. Standard treatment for TE-NDMM consists of 3-6 cycles of induction therapy followed by melphalan 200 mg/m2 and ASCT.[17] Lenalidomide maintenance is now used for continuous or fixed duration (1-2 years). Consolidation therapy is given to improve the response after ASCT and to prevent early relapse.[18] However, there are few published randomized consolidation studies.

The use of consolidation therapy with VTD compared with thalidomide-dexamethasone was associated with a significant upgrade of overall response and CR rate, resulting in enhanced PFS.[5,19] The phase III PETHEMA/GEM2012 study demonstrated that consolidation with VRD in all patients after ASCT improves CR and MRD-negativity.[20] Other trials used VRD as consolidation.[10,21] In the STaMINA trial, four cycles of VRD consolidation did not improve PFS when compared with a second HDM/ASCT or no consolidation.[6] Double HDM/ASCT was superior in the high-risk group at the longer follow-up.[7] Possible explanations for the different outcome of consolidation are the heterogeneous induction regimens and 5%-32% noncompliance rate in STaMINA, whereas in EMN02, all patients were lenalidomide-naïve and randomly assigned after prior ASCT or VMP just before consolidation. Together, these trials may be informative for OS after additional follow-up. Several trials in TE-NDMM used standard consolidation.[1,22] It was part of the Cassiopeia trial comparing daratumumab-VTD versus VTD and in the Griffin trial using daratumumablenalidomide, bortezomib, and dexamethasone versus lenalidomide, bortezomib, and dexamethasone.[9,11] It is unknown to what extent consolidation has contributed to the outcome of these trials. A superior PFS after consolidation was only demonstrated in the current EMN02/HO95 trial. The impact on OS requires still longer follow-up. This uncertainty illustrates the need for exploratory predictive end points such as MRD assessment after induction, after transplant, and during subsequent treatment.[12,23-25] We observed a deepening of response after consolidation including ≥CR rate from 22% to 34% and sCR from 6% to 12%, resulting in a ≥ CR rate on protocol of 59% compared with 46% without consolidation. The MRD negativity rate did not significantly differ between patients with or without consolidation. The imbalance in MRD-negativity at R2 prevents any formal conclusion about MRD response achieved with consolidation before start of maintenance. The relevance of this finding pertains to the observation that MRD-negative patients had a significantly longer PFS. Overall, consolidation resulted in a consistent improvement of median PFS after R2 from 43 to 59 months.

These data indicate that consolidation improves PFS across subgroups, except in the small subgroup of high-risk (del17p) patients. The results also show that continuous maintenance with lenalidomide is feasible. Like in previous trials and in a meta-analysis, a significant PFS benefit was observed.[2,26-28] A higher probability of achieving CR or sCR after start of maintenance was observed, especially after consolidation. This benefit was also observed in recent trials in transplant-eligible patients where CD38 antibody therapy was followed by maintenance.[2,9,11,29] The Spanish group observed an upgrade of MRD-negativity by 17% during prolonged maintenance with lenalidomide and ixazomib.[24] Hence, the question remains: Which duration of maintenance is optimal.[30]

In the current trial, there is a trend that consolidation improves OS. However, while the OS curves separate after 5-6 years, median OS was not reached at 84 months in both arms. Consequently, longer follow-up is needed to evaluate the full-scale impact of consolidation followed by continuous maintenance. Future trials will evaluate to what extent consolidation treatment will improve treatment outcome when quadruplet induction therapy with a CD38 antibody may become standard.

In conclusion, consolidation treatment with VRD followed by continuous lenalidomide maintenance improves PFS and quality of response in NDMM as compared to maintenance alone. The rate of toxicity and SPMs is acceptable.

ACKNOWLEDGMENT

The authors thank the HOVON Data Center team and European Myeloma Network Data Center for their efforts. The authors also thank the members of the Data and Safety Monitoring Board J. Blad´ e, M. Delforge, and K. Wheatley.

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SUPPLEMENTALS

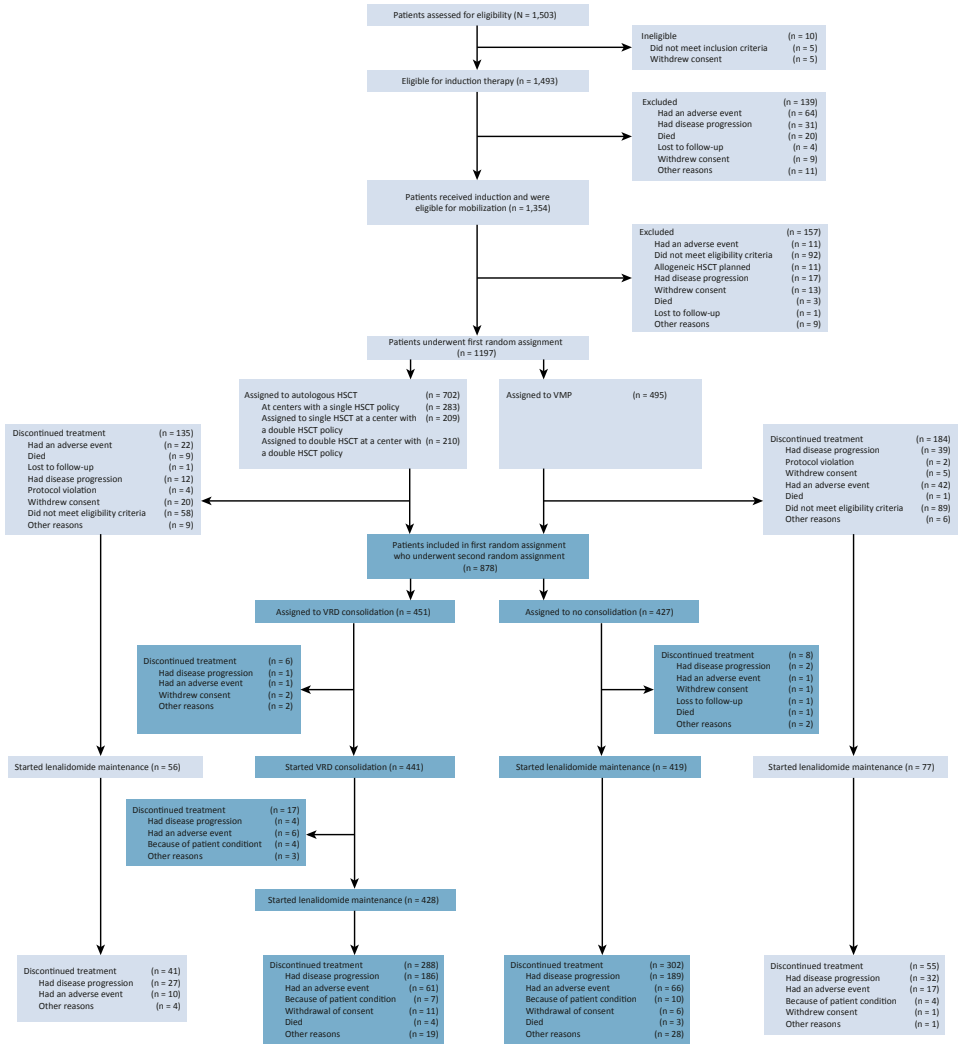
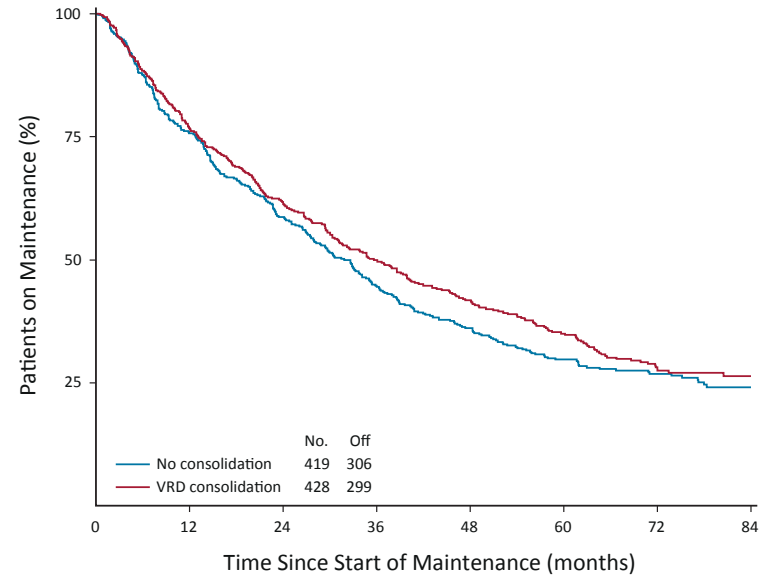


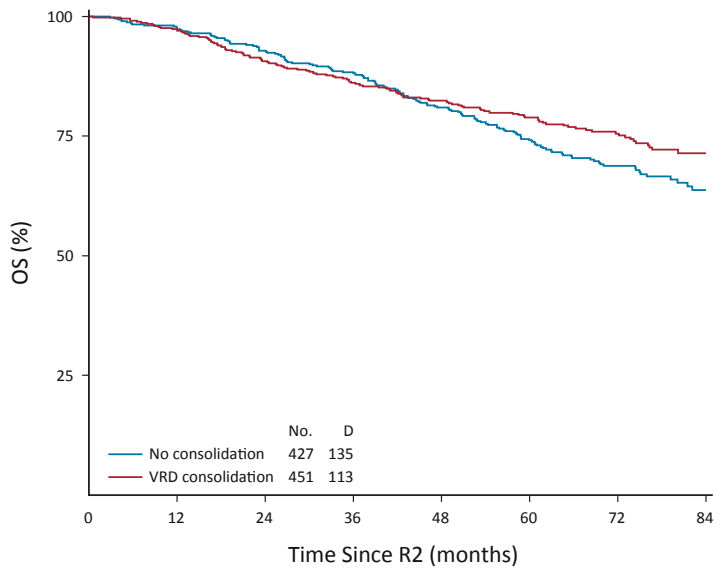
Figure A1. CONSORT diagram oftrial patients. The part related to the R2 random assignment has been marked with blue. HSCT, hematopoietic stem-cell transplantation; VMP, bortezomib/melphalan/prednisone; VRD, bortezomib, lenalidomide, and dexamethasone.



No. at risk:

No consolidation	419	313	241	181	145	111	76	28
VRD consolidation	428	325	259	204	163	131	79	29

Figure A2. Duration of Maintenance. VRD, bortezomib, lenalidomide, and dexamethasone.



No. at risk:

No consolidation	427	411	389	366	320	271	177	62
VRD consolidation	451	431	396	374	345	291	200	75

Figure A3. OS from R2. D, death; OS, overall survival; VRD, bortezomib, lenalidomide, and dexamethasone.

TABLE A1. Baseline Characteristics at Entry

Characteristic	No Consolidation	Consolidation
Patients, No.	427	451
Age, years, median (IQR)	58 (52-62)	57 (52-62)
Sex, No. (%)		
Male	242 (57)	260 (58)
Female	185 (43)	191 (42)
WHO PS 2 plus 3, No. (%)	56 (13)	62 (14)
ISS stage, No. (%)		
1	180 (42)	189 (42)
2	172 (40)	167 (37)
3	75 (18)	95 (21)
FISH available, No. (%)	379 (89)	402 (89)
del(17p), No. (%)	36/367 (10)	41/386 (11)
t(4;14), No. (%)	41/361 (11)	37/379 (10)
t(14;16), No. (%)	15/335 (4)	12/370 (3)
1qampl, No. (%)	130/329 (34)	120/356 (30)
Genetic risk available, No. (%)	339 (79)	361 (80)
Standard	256 (76)	276 (76)
High	83 (24)	85 (24)
Revised ISS, No. (%)		
I	83 (19)	112 (25)
II	242 (57)	244 (54)
III	27(6)40 (9)	
Unknown	75 (18)	55 (12)

Abbreviations: FISH, fluorescent in situ hybridization; IQR, interquartile range; ISS, International Staging System; PS, performance status.

TABLE A2. AEs of CTCAE Grade 3 and 4 During Bortezomib, Lenalidomide, and Dexamethasone

AE	Grade 3, No. (%)	Grade 4, No. (%)
Any	101 (23)	21 (5)
Neutropenia	47 (11)	10 (2)
Thrombocytopenia	43 (10)	9 (2)
General disorders	10 (2)	1 (< 1)
Infections and febrile neutropenia	17 (4)	2 (< 1)
Nervous system disorders	4 (1)	—
Anemia	6 (1)	—
GI and hepatic disorders	3 (1)	—
Metabolic 10	(2)	—
Skin and subcutaneous disorders	1 (< 1)	2 (< 1)
Respiratory, thoracic, and mediastinal disorders	4 (1)	1 (< 1)
Vascular	3 (1)	—
Cardiac	1(< 1)	—

Abbreviation: AE, adverse event.

TABLE A3. International Uniform Response Criteria Consensus Recommendations[11]

Response	Definition
sCR[a]	CR as defined below, plus Normal free light-chain ratio, and
	Absence of clonal plasma cells by immunohistochemistry, immunofluorescencea, or two-color to fourcolor flow cytometry
CR[b]	Negative immunofixation of serum and urine, and Disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow
VGPR[c]	Serum and urine M-component detectable by immunofixation but not on electrophoresis, or ≥ 90% reduction in serum M-protein plus urine M-protein < 100 mg/24 hours
PR	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 hours
	If the serum and urine M-protein are not measurable, a decrease of ≥ 50% in the difference between involved and uninvolved free light-chain levels is required in place of the M-protein criteria
	If serum and urine M-protein are not measureable and serum free light-chain assay is also not ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided measurable, baseline bone marrow plasma cell percentage was ≥ 30%
	In addition to the above criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD	Not meeting criteria for CR, VGPR, PR, or PD
PD	Increase of 25% from lowest response value in any one of the following:
	Serum M-component (absolute increase must be ≥ 0.5 g/dL)
	Urine M-component (absolute increase must be ≥ 200 mg/24 hours)
	Only in patients without measureable serum and urine M-protein levels: the difference between involved and uninvolved free light-chain levels (absolute increase must be > 10 mg/dL)
	Only in patients without measureable serum and urine M-protein levels and without measureable disease by free light-chain levels: bone marrow plasma cell percentage (absolute percentage must be > 10%)
	Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
	Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

NOTE. All response categories (sCR, CR, VGPR, PR, and PD) require two consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

Abbreviations: CR, complete response; IMWG, International Myeloma Working Group; PD, disease progression; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

[a] Presence or absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is a kappa/lambda ratio of > 4:1 or < 1:2.

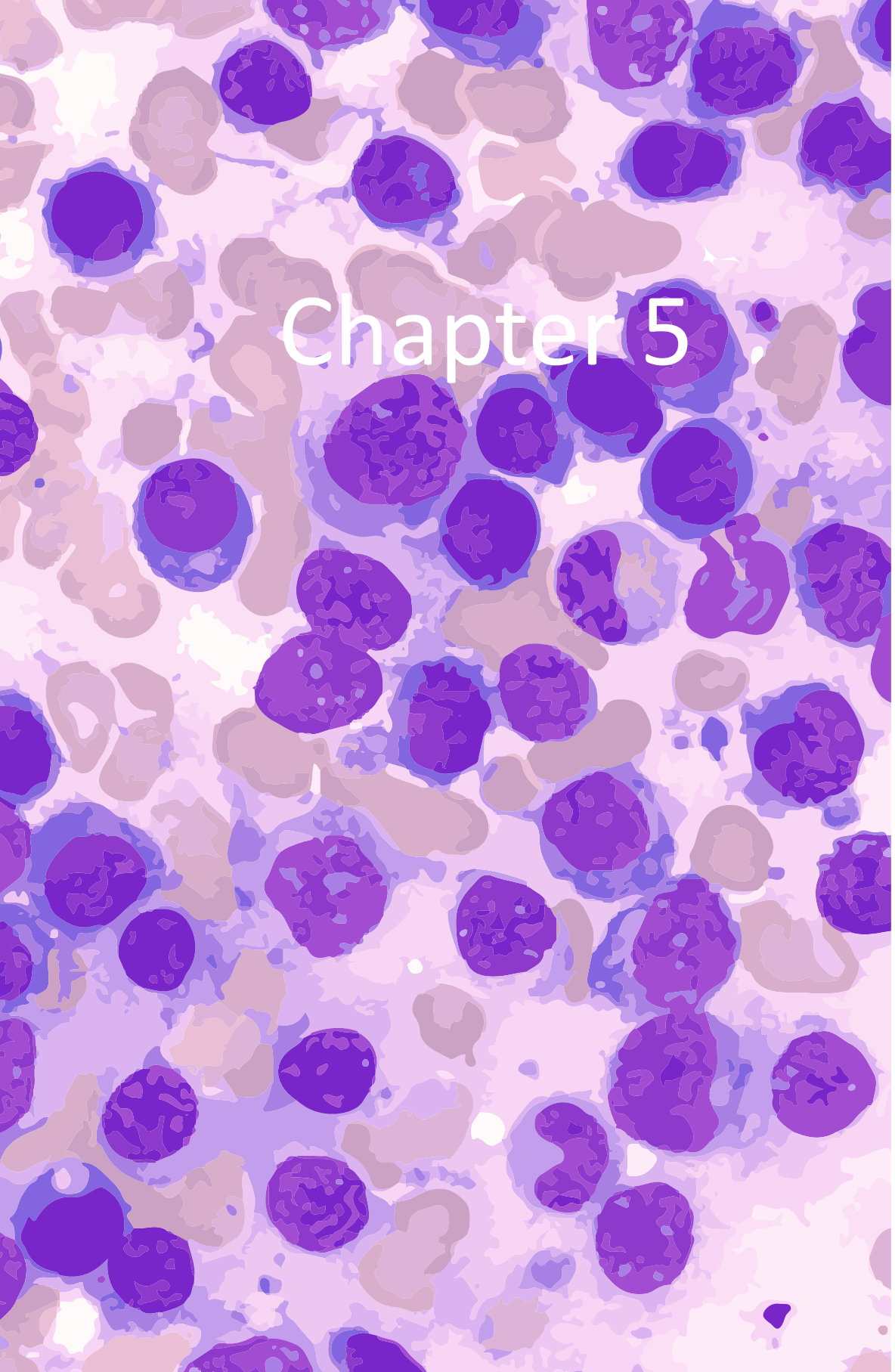
[b] Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum free light-chain levels:

CR in such subjects indicates a normal free light-chain ratio of 0.26-1.65 in addition to the CR criteria listed above. VGPR in such subjects requires a > 90% decrease in the difference between involved and uninvolved free light-chain levels.

[c] Clarifications to IMWG criteria for coding PD: bone marrow criteria for PD are to be used only in subjects without measurable disease by Mprotein and by free light-chain levels; 25% increase refers to M-protein, free light-chain, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia, and the lowest response value does not need to be a confirmed value.

PART III

Registry and correlative studies in treatment with IMIDs



Pomalidomide in patients with relapsed and/or refractory multiple myeloma: a prospective study within the nationwide Netherlands Cancer Registry

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Hemasphere 2022 Jan 27;6(2)e683.

Abstract

Patients with relapsed and/or refractory multiple myeloma (RRMM) generally have limited treatment options and a poor prognosis. Previous trials demonstrated that pomalidomide combined with low-dose dexamethasone (Pd) is effective in these patients with significant responses and improved progression-free survival (PFS). Pd has been approved in RRMM patients who received ≥2 prior lines of therapy. Here, we present the results of a population-based study of patients with RRMM treated with Pd in the Netherlands from time of pomalidomide approval.

Methods

Using the nationwide Netherlands Cancer Registry, data from all non-trial patients with RRMM treated with Pd were collected. Data was analyzed of respons, PFS, and overall survival (OS).

Results

A total of 237 patients were included in this analysis. Previous treatment consisted of a proteasome inhibitor (PI) in 227 patients (96%) and/or an immune-modulating agent (IMiD) in 235 patients (99%). One hundred and forty patients (59%) were refractory to an IMiD in their last line of therapy. Median time from diagnosis to treatment with Pd was 4.9 years (Interquartile range (IQR), 2.7-7.9), and median number of prior treatments was 4 (IQR, 3-5). Median PFS and OS for all patients were 3.6 months (95% confidence interval (CI), 3.1-3.8) and 7.7 months (95% CI, 5.7-9.7), respectively. For patients achieving ≥PR, median PFS and OS were 10.6 months (95% CI, 8.3-12.9) and 16.3 months (95% CI, 13.6-23.2), respectively.

Conclusions

This nationwide, population-based registry study confirms data shown in pivotal clinical trials on Pd. PFS in this analysis is comparable to PFS observed in those clinical trials.

INTRODUCTION

Treatment of patients with refractory and/or relapsed multiple myeloma (RRMM) has improved during the last two decades. However, patients refractory to proteasome inhibitors (PI) and immune-modulating agents (IMiDs) still have a poor prognosis.(1, 2) With the treatment of each relapse, progression-free survival (PFS) and overall survival (OS) decrease due to the emergence of drug resistance. Therefore, effective therapeutic strategies to treat RRMM are needed. At first relapse, combinations of carfilzomib/lenalidomide/dexamethasone, daratumumab/dexamethasone with either bortezomib or lenalidomide have proven to be effective and tolerable (3-5) and have become the standard of care in many countries. At second and third relapse, it is more challenging to achieve durable remissions. Pomalidomide is a third-generation IMiD with tumoricidal and anti-angiogenic activities through binding to cereblon, a protein in the E3 ubiquitin ligase complex. Compared to lenalidomide and thalidomide, pomalidomide has a higher potency towards binding to cereblon and thereby exerts higher antiproliferative activity against myeloma cells. (6) Moreover, pomalidomide has been observed to be effective in IMiD and PI refractory patients. (7-10)

Previous trials showed that pomalidomide combined with low-dose dexamethasone (Pd) in patients with RRMM induces improvement in response, PFS, and OS.

In the MM-002 trial, patients were treated with Pd versus pomalidomide alone. PFS was significantly longer in patients treated with Pd than with pomalidomide alone (4.2 vs 2.7 months, hazard ratio (HR) 0.68, [95% CI, 0.51-0.90], P = 0.003). (7) The MM-003 trial randomized patients between treatment with Pd versus high-dose dexamethasone alone. Median PFS was 4.0 months in patients treated with Pd versus 1.9 months in patients treated with dexamethasone alone (HR 0·48 [95% CI, 0·39-0·60]; P<0·0001).(8) This study subsequently led to the approval of Pd in patients with RRMM who received ≥2 prior lines of therapy, including IMiDs, PIs, and alkylating therapy. Moreover, a subanalysis showed that treatment with Pd in patients with renal impairment is well tolerated and leads to comparable efficacy.(11) In addition treatment with Pd improves and prolongs health-related quality of life.(12)

Pd is reimbursed in most European countries, and currently it is one of the most used agents in third and further lines of treatment. Kastritis et al. performed an analysis of treatment with Pd in the real world. In their cohort, PFS and OS were 5.0 months and 12.1 months, respectively, showing that treatment with Pd is an effective regimen in patients in the real world.(13) Pd remains an important treatment regimen in elderly and frail patients for whom more intensive treatment with triplets is not an option due to performance status and comorbidity.

From the moment of approval and reimbursement of pomalidomide in the Netherlands, we prospectively collected data of patients treated with Pd in a collaborative program

of the Haemato Oncology Foundation for Adults in the Netherlands (HOVON) and the nationwide Netherlands Cancer Registry (NCR) from the Netherlands Comprehensive Cancer Organisation (IKNL). Here, we present an analysis of nationwide, population-based data on the effectiveness of Pd in 237 patients with RRMM in the Netherlands treated between January 2015 and December 2018.

METHODS

Patients and study design

This study is a prospective analysis integrated in the reimbursement program for pomalidomide in the Netherlands. Data of patients with RRMM treated with Pd were collected to analyze this regimen's effectiveness in the real-world and evaluate cost-effectiveness.

The treating physician prospectively enrolled patients in the nationwide NCR via an online registration tool (ALEA). Furthermore, patients not registered by the treating physician were additionally ascertained via the Nationwide Registry of Hospital Discharges (i.e. inpatient and outpatient discharges) that hold data on all hospitals' medical claims in the Netherlands.(14)

Patients with RRMM treated with Pd according to the label were included; that is, patients with ≥2 previous treatments consisting of at least an IMiD and a PI. According to the cost-effectiveness requirements of the reimbursement program, treatment with Pd was discontinued after three courses if the patient showed no response.

Standard baseline characteristics were collected such as age, gender, ISS stage pre-treatment and cytogenetic data when available. Also, various details about the treatment with Pd were collected, i.e. the number of treatment cycles, best response and whether cyclophosphamide was added to Pd. In addition, data about previous treatments were collected, including response and time to progression.

According to the Central Committee on Research involving Human Subjects (CCMO), this type of observational study does not require approval from an ethics committee in the Netherlands. The Privacy Review Board of the NCR approved the use of anonymous data for this study.

Assessments

Symptomatic MM was defined according to the International Myeloma Working Group (IMWG) criteria.(15) Treatment responses and disease progression were classified according to IMWG Uniform Response Criteria by the treating physician, with categories for complete response (CR), very good partial response (VGPR), partial response (PR) and stable disease (SD). (15) Refractory disease was defined as progression of disease (PD) on treatment or within 60 days after treatment was discontinued according to IMWG criteria.

The primary outcome was PFS, defined as the time from Pd initiation until disease progression or death, whichever occurred first. Secondary outcomes included OS (time from pomalidomide initiation to death from any cause), overall response rate (ORR; at least PR), and time to response.

STATISTICAL ANALYSIS

Baseline characteristics at the start of Pd were presented using descriptive statistics. Fisher's exact test was applied to compare categorical variables between subgroups, whereas the Kruskal-Wallis test was used for continuous variables. We constructed survival distributions using the Kaplan-Meier method. The survival distributions were compared between subgroups using the log-rank test. Multivariable Cox regression was performed to investigate the association of gender, age, and the number of prior therapy with PFS and OS. Results from the Cox regression produce hazard ratios (HRs) with associated 95% confidence intervals (CIs). Proportional hazard assumptions were tested based on Schoenfeld residuals.

All *P* values are two-sided, and a significance level $\alpha = 0.05$ was used. All statistical analyses were performed using STATA Statistical Software Release 16.1 (College Station, TX, USA).

RESULTS

A total of 237 patients (56% males, median age, 67 years; interquartile range (IQR), 60-74 years; 35% >70 years), who started with Pd between January 2015 and December 2018, were included in this analysis. Baseline demographics and disease characteristics are shown in Table 1. FISH data were only known in a minority of patients; therefore, these data are not included in this analysis.

Most patients received pomalidomide combined with dexamethasone or prednisolone (179 patients dexamethasone and 40 patients prednisolone). Eighteen patients were treated with pomalidomide monotherapy.

The median time from diagnosis to treatment with Pd was 4.9 years (IQR, 2.7-7.9) and the median number of prior treatments was 4 (IQR, 3-5). The vast majority of patients was previously treated with bortezomib (n=227, 96%) and lenalidomide (n=235, 99%). One hundred twenty-three patients (52%) were previously treated with thalidomide. Hundred and twenty-six patients (53%) received an autologous stem cell transplantation and twenty-nine patients (12%) received an allogeneic stem cell transplantation previously. One hundred and forty (59%) patients were refractory to an IMiD in their last line of therapy, 118 patients (50%) were refractory to lenalidomide, and 22 patients (9%) were refractory to thalidomide.

The median number of treatment cycles with Pd in all patients was 3 (IQR, 2-7) at the time of database lock (June 12, 2019). Two hundred thirty patients (97%) had discontinued

Pd treatment due to progressive disease (n=118, 51%), unacceptable toxicity (n=27, 12%), refractory disease (n=26, 11%), and death of any cause (n=22, 10%). In 29 patients (13%), the reason for discontinuation of treatment was unknown. Eight patients (3%) stopped Pd treatment to receive a stem cell transplantation, comprising of two patients with an autologous stem cell transplantation, four with an allogeneic stem cell transplantation, and two patients received a donor lymphocyte infusion.

Table 1: Patient characteristics

Patient Characteristics	Patients (n = 237)	Cyclo (n = 72)	No cyclo (n = 165)
Age (y)	67 [35–88]	66 [38–83]	68 [35–88]
>70	82 (35)	20 (28)	62 (38)
Sex			
Male	133 (56)	42 (58)	91 (55)
Female	104 (44)	30 (42)	74 (45)
WHO performance status			
0	26 (11)	11 (15)	15 (9)
1	50 (21)	17 (24)	33(20)
2	22 (9)	9 (13)	13(8)
3	5 (2)	0 (0)	5 (3)
Unknown	134 (57)	35 (49)	99 (60)
ISS			
1	3 (1)	0 (0)	3 (2)
2	10 (4)	3 (40	7 (4)
3	20 (9)	7 (10)	13 (8)
Unknown	204 (86)	62 (86)	142 (86)
Hemoglobin (mmol/L), median [range]	6.7 [5.7–7.3]	6.7 [6.2–7.5]	6.6 [5.7–7.2]
Platelets (10^9/L), median [range]	126 [69–190]	115 [58–175]	126 [74–192]
Creatinin (µmol/L), median [range][a]	92 [73–119]	89 [73–110]	92 [73–128]
Calcium (mmol/L), median [range][b]	2.4 [2.3–2.5]	2.4 [2.3–3.5]	2.4 [2.3–2.5]
Albumin (g/L), median [range][c]	35 [31–40]	35 [31–40]	36 [31–40]
Time from diagnosis, median [range]	4.9 [1–18]	4 [1–18]	5 [1–18]
Number of prior treatment, median [range]	4 [2–10]	4 [2–9]	4 [2–10]
Previous treatment			
Lenalidomide	235 (99)	71 (99)	164 (99)
Thalidomide	123 (52)	38 (53)	85 (52)
Bortezomib	227 (96)	70 (97)	157 (95)
Carfilzomib	29 (12)	15 (21)	14 (8)
Ixazomib	6 (3)	4 (6)	2 (1)
Alkylating therapy	232 (98)	71 (99)	161 (98)

[a]Unknown in one patient; [b]Unknown in 12 patients; [c]Unknown in 23 patients.
Cyclo = cyclophosphamide; ISS = International Staging System; WHO = World Health Organization.

ORR was 38%, fifteen patients (6%) achieved ≥ VGPR, and 7 patients (3%) achieved CR (Table 2). The median time to response was 1.6 months (IQR 0.9-2.8).

ORR was not significantly different between age groups, 48 patients (37%) in patients ≤70 years, versus 33 patients (40%) in patients >70 years (*P*=0.68).

Table 2: Response

Response	All Patients (n = 237), n (%)	Cyclo (n = 72), n (%)	No Cyclo (n = 165), n (%)
CR	7(3)	2 (3)	5 (3)
VGPR	8(3)	0 (0)	8 (5)
PR	76 (32)	26 (36)	50 (30)
SD	66 (28)	22 (31)	44 (27)
PD	54(23)	18(25)	36 (22)
Unknown	26 (11)	4 (6)	22 (13)

CR = complete respons; Cyclo = cyclophosphamide; PD = progressive disease; PR = partial response; SD = stable disease; VGPR = very good partial response.

Median PFS and OS for all patients was 3.6 months (95% CI, 3.1-3.8) and 7.7 months (95% CI, 5.7-9.7), respectively; (Figure 1). In patients refractory to lenalidomide, median PFS was 3.5 months (95% CI 2.8-4.3) versus 3.6 months (95% CI 2.8-4.3) in patients not refractory to lenalidomide (HR 0.96 [95% CI, 0.73-1.26]; P=0.77). The corresponding median OS was 7.7 months (95% CI 5.4-10.5) versus 6.8 months (95% CI 5.2-9.7) respectively (HR 1.04 [95% CI, 0.78-1.38]; P=0.79). Patients >70 years had a median PFS of 3.7 months (95% CI, 3.4-5.9) *versus* 3.3 months (95% CI, 2.7-3.8) in patients ≤70 years (HR 0.89 [95% CI, 0.67-1.18]; P=0.41). The corresponding median OS was 10.3 months (95% CI, 4.7-11.6) *versus* 6.8 months (95% CI, 5.4-8.8), respectively (HR 1.00 [95% CI, 0.75-1.35]; P=0.98); (Figure 2). Median PFS in patients diagnosed ≥6 years ago and within 3 years before the initiation of treatment with Pd was 5.7 months (95% CI, 3.5-8.0) versus 2.1 months (95% CI, 1.8-3.3), respectively (HR 0.49 [95% CI 0.36-0.67]; P<0.001). Median PFS in patients diagnosed between 3-6 years was 3.6 months (95% CI, 3.0-4.4) (HR 0.78 [0.55-1.10]; P=0.15). The corresponding median OS (95% CI) was 14.0 months (95% CI, 7.7-18.0) and 4.0 months (95% CI, 2.6-5.8), respectively, between patients diagnosed ≥6 years and within 3 years before the initiation of treatment with Pd (HR 0.45 [95% CI 0.32-0.63]; P<0.001).

Table 3: multivariable analysis for PFS and OS.

	Progression-free survival						Overall survival					
	Univeriable			Multivariable			Univeriable			Multivariable		
Covariate	HR	95% CI	***P***	HR	95% CI	***P***	HR	95% CI	***P***	HR	95% CI	***P***
Gender												
Male	1			1			1					
Female	1.05	0.80-1.37	0.745	0.99	0.76-1.29	0.970	0.94	0.71-1.26	0.691	0.92	0.70-1.22	0.577
Age												
≤70 years	1			1			1					
> 70 years	0.89	0.67-1.18	0.408	0.85	0.65-1.13	0.266	1.00	0.75-1.35	0.979	0.99	0.74-1.32	0.921
Time from diagnosis to treatment												
<3 years	1			1			1					
3-6 years	0.78	0.55-1.10	0.151	0.81	0.58-1.12	0.198	0.71	0.50-1.01	0.058	0.73	0.52-1.03	0.076
≥6 years	0.49	0.36-0.67	<0.001	0.52	0.38-0.70	<0.001	0.45	0.32-0.63	<0.001	0.46	0.33-0.64	<0.001

Median OS in patients diagnosed between 3-6 years was 8.5 months (HR 0.71 [95% CI 0.50-1.01]; P=0.058). In a multivariable analysis including gender, age and time from diagnosis, only time from diagnosis was independently associated with survival (Table 3). Median PFS for patients treated with >3 prior lines and patients treated with ≤ 3 prior lines was identical (3.6 months (95% CI, 3.2-4.3) versus 3.3 months (95% CI 2.3-3.9), (adj HR 1.28 [95% CI, 0.90-1.28]; P=0.77)).

For patients achieving ≥PR, median PFS and OS were 10.6 months (95% CI, 8.3-12.9) and 16.3 months (95% CI, 13.6-23.2), respectively.

In 72 patients (30%), cyclophosphamide was added to treatment with Pd (PCd). Table 1 shows the characteristics of patients treated with and without the addition of cyclophosphamide. ORR in patients treated with PCd was comparable to patients treated without the addition of cyclophosphamide (Table 2), 28 patients (39%) versus 63 patients (38%), (*P*=1.00). Median PFS in patients treated with PCd compared to patients treated with Pd was 5.6 months (95% CI, 3.6-7.9) *versus* 3.6 months (95% CI, 3.1-3.8) (HR 0.74 [95% CI, 0.55-0.99]; P=0.046). The corresponding median OS was 8.8 months (95% CI, 6.4-13.2) *versus* 6.1 months (95% CI, 4.7-9.2) (HR 0.78 [95% CI, 0.57-1.07]; P=0.20)

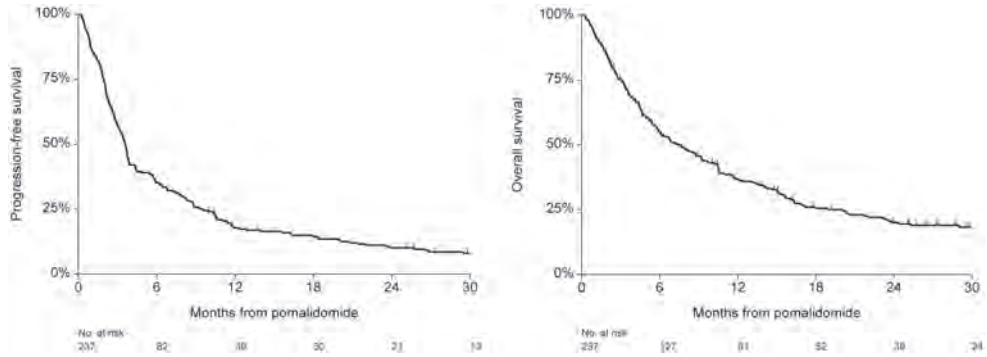

Figure 1. PFS and OS in all patients. OS = overall survival; PFS = progression-free survival.

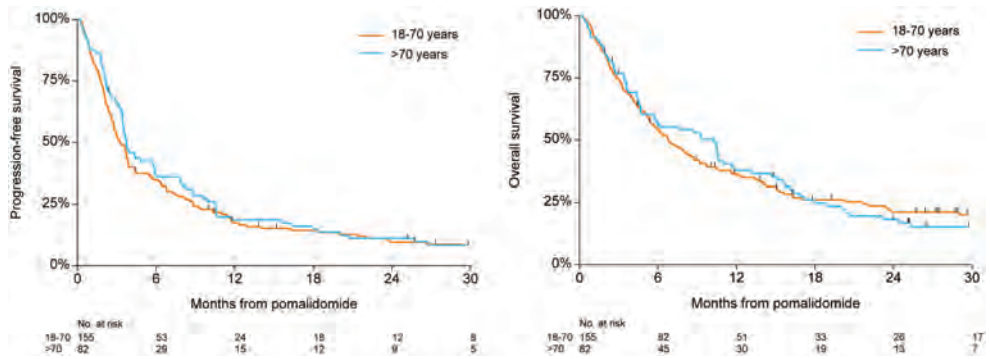

Figure 2. PFS and OS based on age. OS = overall survival; PFS = progression-free survival.

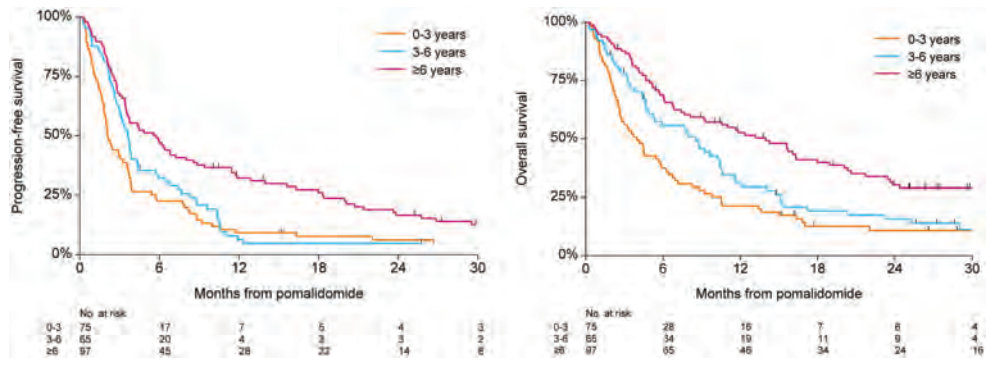

Figure 3. PFS and OS based on time from diagnosis. OS = overall survival; PFS = progression-free survival.

DISCUSSION

Previous trials have shown that Pd is an effective treatment regimen in patients with RRMM, including patients with lenalidomide refractory disease.(7-10, 13) This analysis presents real-world data from patients treated with Pd with or without cyclophosphamide in the Netherlands. ORR in our real-world data was 42% which is slightly higher than observed in the MM-002 (ORR=32.8%), MM-003 (31.4%) and the STRATUS trials (32.6%). (7-9). The observed median PFS of 3.6 months was comparable to these trials, while the median OS of 7.7 months was inferior compared to these trials. However, cross-comparison between trials should be interpreted with caution. (Table 4).

Table 4: ORR, PFS, OS between trials

	ORR (%)	PFS (mo)	OS (mo)
Real-world data	42	3.6	7.0
MM-002[7]	32.78	4.2	16.5
MM-003[8]	31.4	4.0	12.7
STRATUS[9]	32.6	4.6	11.9
Kastritis[13]	33	5	12.1

ORR = overall response rate; OS = overall survival; PFS = progression free survival.

As previously mentioned, most patients were refractory to an IMiD before the start of Pd. Therefore, the question arises if Pd is an effective treatment regimen in IMiD refractory patients. Siegel et al. showed that treatment with Pd is an effective regimen directly after failure on treatment with lenalidomide. (10) Kastritis et al. performed an analysis in patients from Greece who were treated with Pd in the real world to evaluate the impact of the last lenalidomide treatment. In their cohort, PFS and OS were 5.0 months and 12.1 months, respectively, including patients who received lenalidomide just before treatment with Pd. However, PFS and OS improved to 10.3 months and 27.1 months, respectively, in patients with an IMiD-free interval of ≥18 months. Nonetheless, these data confirm that Pd is an effective treatment in patients previously treated with an IMiD. Our data are similar to these results with no difference in PFS between IMiD refractory patients versus IMiD non-refractory patients.

In our cohort, we attempted to identify subpopulations who would benefit most from treatment with Pd. We looked at age and duration of the disease. Cytogenetic evaluation was available in only a small subset of patients and therefore not included in the analysis. Time from diagnosis was significantly associated with PFS and OS, in favor of patients diagnosed ≥ 6 years before initiation of Pd compared to patients treated within 3 years from diagnosis. (Figure 3). Probably, these latter patients had a more aggressive MM with short responses to different treatment modalities. This analysis suggests that patients with a longer interval from diagnosis are more likely to benefit from treatment with Pd.

Previous trials showed that the addition of a third agent improves response and survival. (16-21) The REPEAT trial showed that the addition of cyclophosphamide to lenalidomide and dexamethasone improves response and survival.(21) Baz et al. performed a phase 2 study randomizing patients with lenalidomide refractory disease to treatment with Pd or PCd, which showed a difference in PFS of 4.4 months versus 9.5 months.(16) Therefore, it is an attractive option to add cyclophosphamide to treatment with Pd to improve efficacy. In our real-world data, a subset of patients was treated with PCd. ORR was not different in patients treated with Pd or PCd. However, PFS and OS improved by adding cyclophosphamide to treatment with Pd, which we expected based on data from previous trials. It should be kept in mind that this analysis was not designed to retrieve information to answer this specific question. From our series, we could not extract data to explain why cyclophosphamide was added to Pd. Data concerning the extent and severity of other co-morbidities were not available in our database. Generally, the decision to add cyclophosphamide in individual patients usually is based on expectations regarding disease activity, tolerance and other patient-related factors.

Recently, several phase 3 trials showed an improvement in response and survival by adding a third treatment modality to Pd, other than cyclophosphamide. (18-20) In the ICARIA trial, isatuximab was added to treatment with Pd and showed an improvement in PFS of 6.5 months to 11.5 months compared to patients treated with Pd.(18) The OPTIMISMM trial showed a comparable improvement in response by adding bortezomib to Pd. PFS was improved from 7.1 months to 11.2 months.(19) In the APOLLO trial, daratumumab was added to Pd, which also improved PFS of 6.9 months to 12.4 months compared to treatment with Pd.(20) These data show that, concerning PFS, patients should preferably be treated with a third agent added to the backbone Pd. In pretreated patients refractory to a PI or anti-CD38 treatment, the addition of cyclophosphamide may be an attractive option. In conclusion, this nationwide, population-based study confirms data observed in key clinical trials. The lower OS probably reflects the heterogeneity of patients treated in the 'real-world' versus patients included in 'clinical trials'. Therefore, it is reasonable to assume that survival rates in these real-world patients present a more realistic view. (22) The addition of cyclophosphamide did improve PFS and OS, as shown in previous trials.

This analysis confirms the effectiveness of treatment with Pd or PCd in heavily pretreated patients considered not eligible for inclusion in clinical trials. Moreover, it is an affordable and available treatment modality in many countries.

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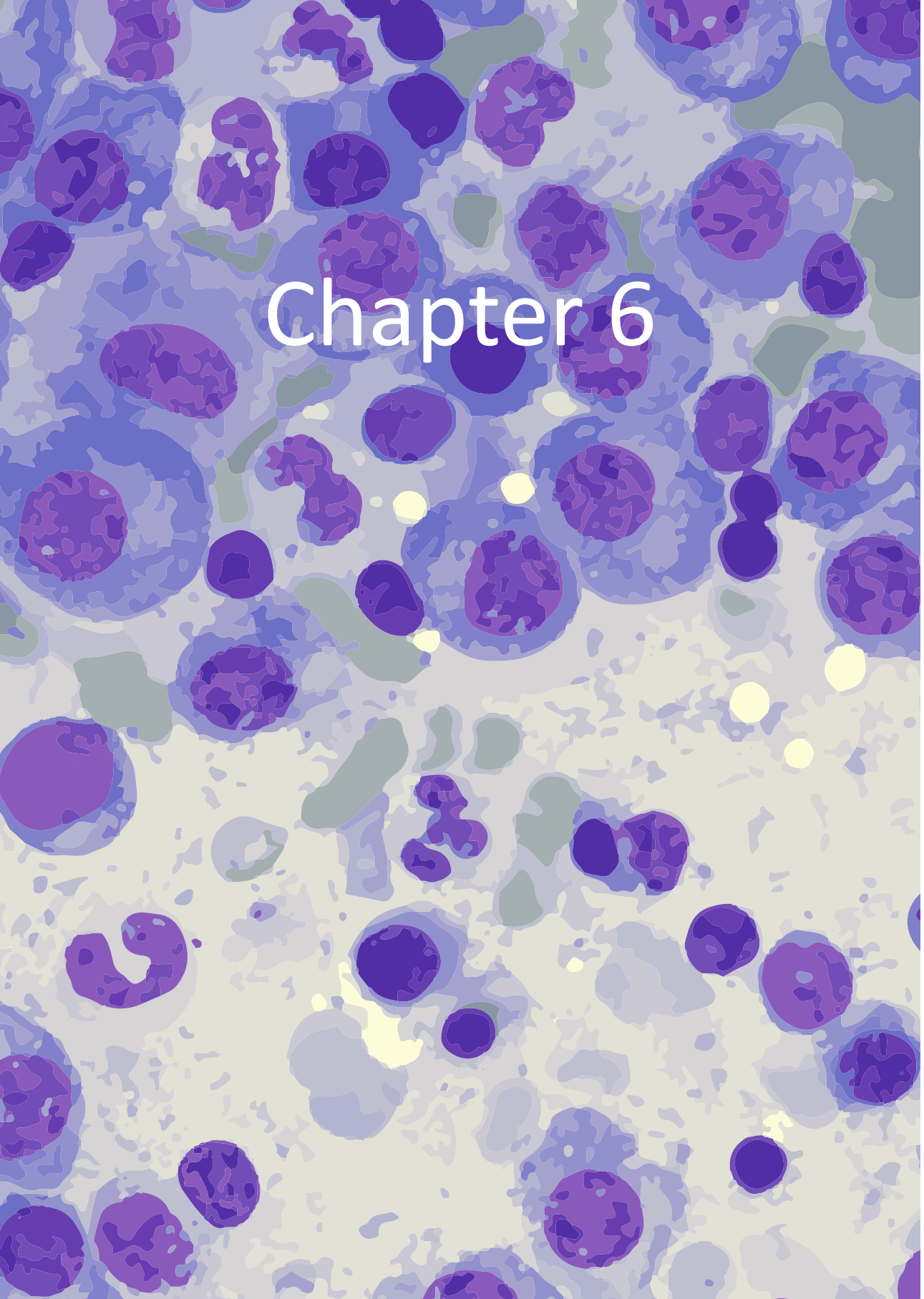

Chapter 6

High expression of nuclear Cereblon in bone marrow biopsies of elderly patients with multiple myeloma treated with IMIDs is associated with longer PFS and OS

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ABSTRACT

Patients with multiple myeloma (MM) demonstrate variable outcomes with treatment. With increasing treatment options, predictive factors for response and outcome are relevant for treatment choices. Immunomodulating agents (IMiDs) represent a cornerstone treatment of MM and act by binding Cereblon (CRBN), which in turn affects downstream targets. We hypothesized that proteins of the CRBN pathway predict outcome in patients treated with IMiDs. Bone marrow (BM) biopsies were obtained from 148 newly diagnosed, transplant non-eligible patients with MM. Per HOVON-87/NMSG-18 trial protocol, these patients were treated with thalidomide or lenalidomide combined with Melphalan and Prednisone followed by thalidomide or lenalidomide maintenance (i.e. MPT-T or MPR-R). Immunohistochemistry was performed for CRBN, Ikaros,Aiolos,interferon regulatory factor 4 (IRF4) and cellular myelocytomatosis oncogene (Myc).

Higher nuclear CRBN expression was associated with a longer progression-free survival (PFS) and overall survival (OS). For PFS a hazard ratio (HR) of 0.53 was found (95% confidence interval (CI) =0.37-0.77; p<0.001); for OS: HR = 0.59 (95% CI=0.38-0.90; p=0.02). The association between CRBN and OS varied with IRF4 levels. In patients with IRF4 levels above the median, a hazard ratio of HR 0.48 was found (95% CI=0.27-0.83; p=0.009); in contrast, in patients with IRF4 levels below the median, a hazard ratio of 1.05 was found (95% CI=0.59-1.84; p=0.88). In conclusion, higher expression of nuclear CRBN was associated with a superior PFS and OS upon MPT-T or MPR-R treatment. Levels of CRBN protein, possibly in combination with IRF4, represent a biomarker for predicting outcome in patients treated with IMiDs.

INTRODUCTION

Treatment options for multiple myeloma (MM) patients are rapidly increasing. Induction treatment consists routinely of 3 or 4 components, combining immunomodulating agents (IMiDs; e.g. lenalidomide) or proteasome inhibitors (e.g. bortezomib) with therapeutic monoclonal antibodies such as daratumumab. Preferred first line treatment for non-transplant eligible patients is either daratumumab/lenalidomide/dexamethasone (DRd) or daratumumab/bortezomib/melphalan/prednisone (DVMP). The median progression-free survival (PFS) for DRd is 62 months, which reflects the efficacy of this combination, while the median PFS is 35 months with DVMP.[1,2] Treatment with DRd is preferred due to improvement in PFS and less toxicity compared to DVMP. However, cross trial comparisons should be interpreted with caution. DRd contains the IMiD lenalidomide. IMiDs act on several levels, directly causing cell death of MM cells, and by a wide range of immunomodulatory effects.[3] Central to both is the binding of IMiDs to the E3 ubiquitin ligase complex component cereblon (CRBN). E3 ubiquitin ligase complexes act as regulators of protein homeostasis, using ubiquitination to mark specific proteins for proteasome mediated degradation. Binding of IMiDs to CRBN results in the proteins Ikaros (IKZF1) and Aiolos (IKZF3) being marked for degradation, which, in MM cells, causes cell death via consequential downregulation of IRF4 and Myc .[4-7] The mechanism of CRBN bound to IMiDs resulting in degradation of Ikaros and Aiolos also explains at least in part immunomodulatory effects, for example increased expression and secretion of cytokine IL-2 in T-cells.[8] In addition, CRBN dependent but ubiquitin independent mechanisms of IMiD action may be relevant, as well as CRBN independent mechanisms, for instance through ZAP70.[3,9]

Previous studies investigated whether CRBN is a potential biomarker of response and/or resistance in patients treated with IMiDs. These studies generally demonstrated that higher CRBN expression was associated with a better response to thalidomide, lenalidomide or pomalidomide. [6,10-12] Furthermore, in patients and cell line models with resistance to IMiDs, decreased levels of CRBN have been identified, as well as inactivating acquired single nucleotide variants [13,14] Copy number loss is an underlying cause for reduced CRBN levels.[14] However, particularly for newly diagnosed, non-transplant eligible patients the value of CRBN as a biomarker is less clear. Over the course of these studies the need for standardization of CRBN measurement became apparent, resulting in the development of a standardized immunohistochemical assay for assessing CRBN protein levels in CD138 positive cells.[15] Despite this, there is an apparent paucity of large patient series assessed for the clinical value of this method.

In the current study, we analyzed, using this standardized method, whether cellular levels of CRBN (nuclear and cytoplasmic) and of the downstream pathways Ikaros, Aiolos, IRF4 and Myc are associated with outcome of IMiD treatment in elderly, non-transplant eligible patients with NDMM. For this purpose we selected a cohort of patients who were

treated in a randomized trial with an IMiD-containing regimen, without a PI or anti-CD38 antibody, which could influence the outcome in these patients. This analysis was a planned correlative sub study of the collaborative, independent HOVON-87/NMSG-18 prospective, randomized clinical trial.[16] We hypothesized that increased levels of CRBN and/or altered levels of associated proteins in this pathway, would identify patients with improved outcome after IMiD treatment.

MATERIALS AND METHODS

Patients and study design

Patients included in the HOVON-87/NMSG-18 trial were selected for this analysis. This study was performed by the Dutch Hematology Oncology Group HOVON and the Nordic Myeloma Study Group. [16]

The trial is registered at the European Union Drug Regulating Authorities Clinical Trials (EudraCT) as 2004-000944-26 and at the International Standard Randomized Controlled Trial Number (ISRCTN) as 64455289.

In this trial, transplant ineligible patients (non-transplant eligible patients ≤65 years and all patients >65 years) with NDMM were randomized between treatment with nine 28-day induction cycles of Melphalan-Prednisone (MP) –Thalidomide (MPT) followed by thalidomide maintenance (MPT-T) or with nine 28-day induction cycles of MP-Lenalidomide (MPR) followed by lenalidomide maintenance (MPR-R). MPT induction consisted of 9 cycles of oral melphalan 0.18 mg/kg on days 1 to 4, prednisone 2mg/kg on days 1 to 4 and thalidomide 200 mg continuously until 4 weeks of the last cycle of MP. MPR induction consisted of 9 cycles of oral melphalan 0.18 mg/kg on days 1 to 4, prednisone 2mg/kg on days 1 to 4 and lenalidomide 10mg on days 1 to 21. Maintenance therapy was continued until progression of disease or intolerable side effects. [16] (Supplemental (Suppl.) Table 1) Patients in the MPT-T arm received maintenance with oral thalidomide 100mg daily, patients in the MPR-R arm received maintenance with oral lenalidomide 10 mg on days 1 to 21 in a 28-day cycle until progression, intolerance or death, whatever came first.

Bone marrow samples of patients, included in the HOVON-87/NMSG-18 trial, were obtained after informed consent before start of treatment . The selection of bone marrow samples for this analysis was made based on availability and quality of biopsies at diagnosis. (Suppl. figure 1). All patients gave written consent and the trial was conducted according to the European Clinical Trial Directive 2005 and the Declaration of Helsinki.

Immunohistochemical staining

Paraffin embedded bone marrow (BM) biopsies were stained with a fully automated dual color, bright-field immunohistochemical assay for CRBN, Ikaros, Aiolos, IRF4 and Myc. CD138 was used to identify MM plasma cells in the BM samples. For CRBN, both nuclear and cytoplasmic staining was evaluated. Sequential dual-color IHC assays were performed [17], with the addition of Dako Protein Block (Catalog No. X0909), before applying the CD138 primary antibody to reduce non-specific red background staining. Primary antibodies used were: CRBN, Celgene custom rabbit monoclonal, CRBN65, SD Lot #1, used at 1/2000; Aiolos, Celgene custom rabbit monoclonal, Clone 9B-9-7, used at 1/400; Ikaros, Celgene custom rabbit monoclonal, Clone 36-8-5, used at 1/12000; IRF4, mouse monoclonal, Dako, Catalog No. M7259, Clone MUM1P, used at 1/7500; Myc, rabbit monoclonal, Abcam, Catalog No. ab32072, Clone Y69, used at 1/200; CD138, mouse monoclonal, Dako, Catalog No. M7228,

Clone MI15, used at 1/2000. Mouse monoclonal IgG1 (BD Bioscience; Catalog No 550878) and rabbit monoclonal IgG (Abcam, Catalog No. Ab172730) were used as isotype controls at the matched concentrations as the respective primary antibodies. All slides were counterstained with hematoxylin (Figure 1).

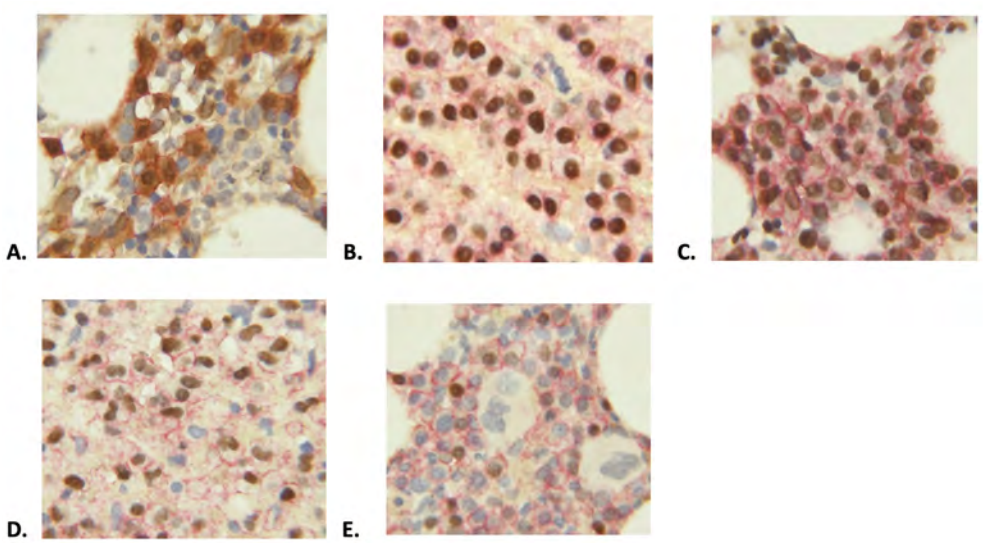


Figure 1. Immunohistochemical staining of CRBN, Aiolos, Ikaros, IRF4 and Myc. Magnification 63x. CD138 was used to identify MM plasma cells in the bone marrow samples. For CRBN, both nuclear and cytoplasmic staining was evaluated. The distribution and intensity of the immunostaining was assessed using the H-score. For definition of the H-score, see Materials and methods. A, CRBN; B, Aiolos; C, Ikaros; D, IRF4; E, Myc.

Pathology scores

Evaluation of dual color IHC slides was performed by a board-certified pathologist and a trained hematologist under the light microscope. The target markers CRBN (cytoplasmic and nuclear), Aiolos (nuclear), Ikaros (nuclear), IRF4 (nuclear), and Myc (nuclear) were evaluated in at least 100 CD138 (membrane) positive plasma cells in the bone marrow of each patient to generate an H-score. [18] H-scores range from 0 to 300 and take into account range and intensity of staining. Scores for intensity range from 0 to 3 for negative, mild, moderate and strong immunoreactivity, respectively. The final H-score is the sum of the products of percent of cells and intensity of staining, calculated by this validated formula: [H-score = (% at 1+) X 1 + (% at 2+) X 2 + (% at 3+) X 3]. Cytoplasmic and nuclear H-Scores of CRBN were scored separately.

Statistical analysis

Baseline characteristics are presented using descriptive statistics. For the Cox regression analysis H-scores were corrected by dividing these by a factor 100: hazard rates were considered per 100 points increase of the H-score. Fisher's exact test was applied to compare categorical variables between subgroups, whereas the Mann-Whitney test was used for continuous variables. Protein levels of the CRBN pathway were compared between patients with (stringent) complete response (sCR/CR) or very good partial response (VGPR) versus partial response (PR) or no change/progressive disease (NC/PD) using best response during protocol treatment. High-risk cytogenetic abnormalities (FISH) were defined as deletion of 17p (cut-off of 10%), and/or translocation t(4;14) and/or t(14;16); in a subset of cases deletion of 17p was evaluated using SNP array using a validated, diagnostic protocol. To evaluate the association of protein level and survival, univariable Cox regression analysis for progression free survival (PFS) and overall survival (OS) was performed, which resulted in hazard ratios (HRs) with associated 95% confidence intervals (CIs). To illustrate the association between protein level and survival, Kaplan-Meier curves with corresponding logrank p-value were generated based on median protein levels. Multivariable analysis was performed by Cox regression analysis including study arm (MPT-T vs MPR-R), nuclear CRBN, high-risk FISH abnormalities and R-ISS. In order to be able to include all patients in the multivariable analysis, the method of multiple imputation by chained equations was used to cope with missing data on these covariates. All *P* values are two-sided, and a significance level $\alpha = 0.05$ was used. Analysis were performed using SPSS 25 [19], Stata 16.1 [StataCorp. 2019. Stata: Release 16. Statistical Software. College Station, TX: StataCorp LLC] [20] and GraphPad Prism.

RESULTS

Bone marrow samples of 148 patients were evaluated using immunohistochemistry. Evaluated genes were CRBN, Ikaros, Aiolos, IRF4 and Myc. All 148 patients received standard treatment in the HOVON-87/NMSG-18 trial: 70 patients (47%) were treated in the MPT-T arm and 78 patients (53%) in the MPR-R arm. Median age was 73 years [interquartile range (IQR) 70-77] and 54% of patients were male. Baseline demographics and disease characteristics are shown in Table 1. Comparison of disease characteristics of the subset used in the current analysis (n=148) and the total patient population in the trial (n=637) demonstrated no significant differences between these two groups (Suppl. table 1). Best response on protocol treatment is shown in Suppl. table 1. Nuclear and cytoplasmic CRBN was evaluable in 144/148 patients and IRF4 in 146/148 patients. For Ikaros, Aiolos and Myc 148/148 cases were available for analysis. Median H-scores were 171 (IQR, 140-203) for nuclear CRBN, 170 (IQR, 142-197) for cytoplasmic CRBN, 219 (IQR, 194-242) for Aiolos, 223 (IQR, 207-234) for Ikaros, 184 (IQR, 154-203) for IRF4 and 99 (IQR, 64-130) for Myc.

In the HOVON-87/NMSG-18 trial patients were treated with 9 cycles of MPT followed by thalidomide maintenance or MPR followed by lenalidomide maintenance. After cycle 1, 3, 5, 7 and 9, and after maintenance, response evaluation was available. Here we analyzed the relation between nuclear and cytoplasmic CRBN levels and response in both treatment arms and separately. First, CRBN and associated biomarker levels were assessed in relation to the best achieved response during the trial; secondly, CRBN levels were analyzed in relation to dynamic changes in response during the trial and thirdly, we analyzed CRBN in the context of development of progressive disease.

Comparison of nuclear CRBN levels in patients with sCR, CR, VGPR, PR and NC/PD indicated overall significant differences in nuclear CRBN levels between these response categories (Kruskal Wallis p-value = 0.03; Figure 2A). Analysis of all pairwise comparisons demonstrated higher CRBN levels in patients with CR vs NC/PD (CR: median H-score 199 (IQR 181-220; n=16) and NC/PD: median H-score 160 (IQR 129-185); n=21; adjusted p-value = 0.03; see supplemental methods). Comparison of cytoplasmic CRBN levels between patients with sCR, CR, VGPR, PR and NC/PD demonstrated a similar pattern as shown for nuclear CRBN, but only borderline significant (Kruskal-Wallis p-value =0.09). Cytoplasmic CRBN levels also differed most between patients with CR vs NC/PD, without reaching significance (CR: median H-score 188 (IQR 167-205; n=16) and NC/PD: median H-score 163 (IQR 117-189); p=0.1).

Comparison of response in two categories, i.e. ≥ VGPR (n=72, 50%) and ≤PR (n=72, 50%) showed a higher median H-score for nuclear CRBN of 185 (IQR 147-211) for ≥ VGPR compared to 159 (IQR 130-193) for ≤PR (p=0.02). For cytoplasmic CRBN the following levels were found: median H-score of 179 (IQR 153-205) for ≥ VGPR; median H-score of 165 (IQR 128-192) for ≤PR (p=0.02; Figures 2B and 2D, supp. Table 2).

Table 1. Patient characteristics

	Patients, n (%)
Age	73 (IQR 70-77)
Gender	
Male	80 (54)
Female	68 (46)
ISS	
1	41 (28)
2	67 (45)
3	37 (25)
unknown	3 (2)
R-ISS	
1	17 (11)
2	96 (65)
3	10 (7)
unknown	25 (17)
Cytogenetic abnormalities	
Del 17p	
Yes	14 (9)
No	104 (70)
Unknown	30 (20)
t4;14	
Yes	15 (10)
No	108 (73)
Unknown	25 (17)
t14;16	
Yes	2 (1)
No	110 (74)
Unknown	36 (24)
Treatment arm	
MPT-T	70 (47)
MPR-R	78 (53)

MPT-T=melphalan/prednisone/thalidomide, MPR-R=melphalan/prednisone/lenalidomide followed by lenalidomide maintenance

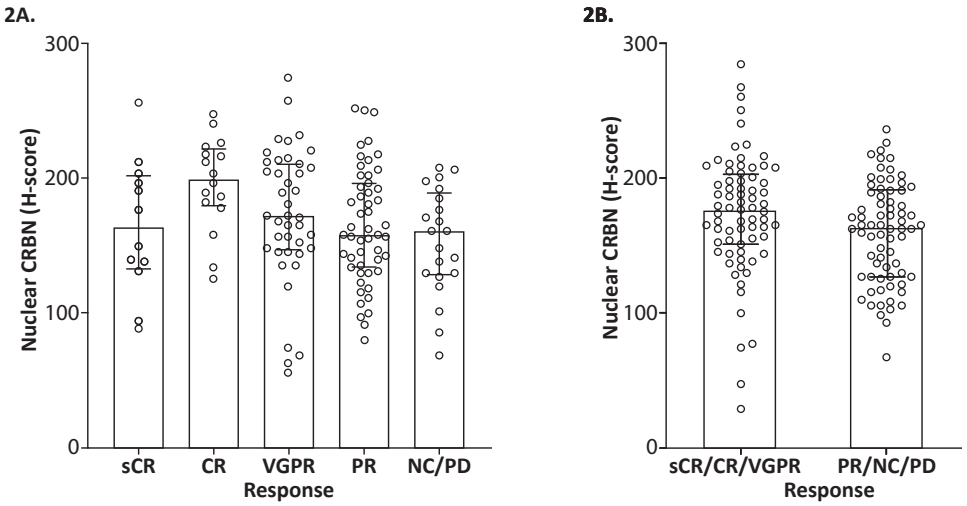


Figure 2. Relation between nuclear and cytoplasmic CRBN level and response. sCR stringent: complete response; CR: complete response; VGPR: very good partial response; PR: partial response; NC: no change. PD: progressive disease.

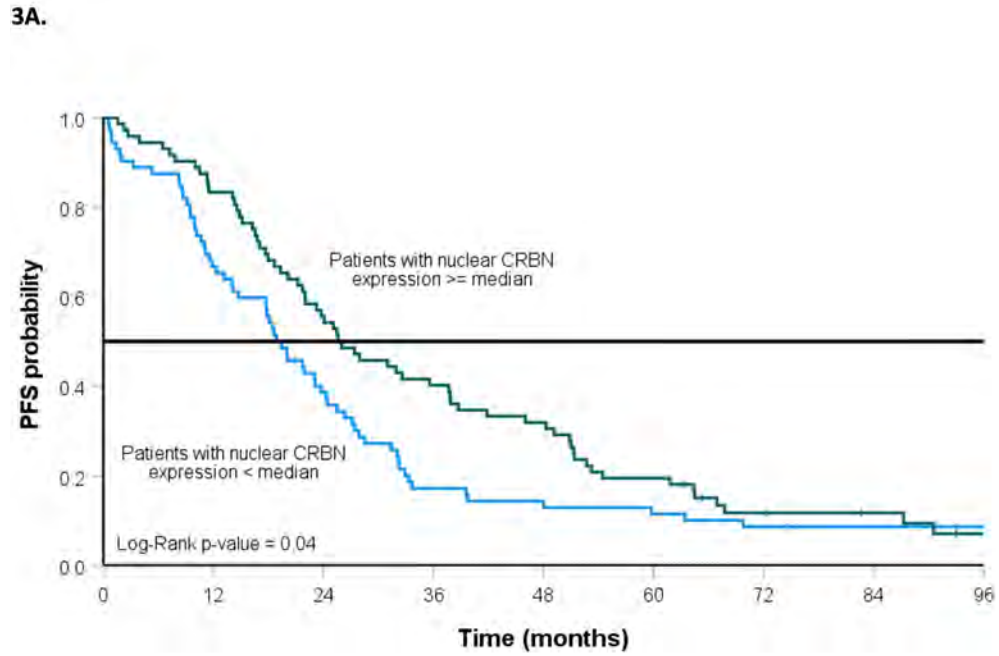


Figure 3. Nuclear CRBN levels in relation to PFS (A) and OS (B). Kaplan Meier plot for nuclear Cereblon (above median and below median) in relation to PFS and OS. PFS: progression-free survival. OS: overall survival.

Table 2. Univariable and multivariable analysis for PFS and OS

	Progression-free survival			Overall survival			Progression-free survival			Overall survival		
	Univariable			Univariable			Multivariable			Multivariable		
Covariate	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Cytogenetics												
del(17p)	1.31	0.73-2.34	0.37	1.31	0.68-2.55	0.42	1.10	0.59-2.02	0.77	0.92	0.46-1.85	0.81
t(4;14)	2.21	1.26-3.86	0.005	2.12	1.17-3.84	0.01	1.76	0.93-3.33	0.08	1.36	0.67-2.77	0.39
Nuclear CRBN	0.53	0.37-0.77	0.001	0.59	0.38-0.90	0.02	0.50	0.32-0.77	0.002	0.49	0.30-0.82	0.006
R-ISS												
R-ISS I	1			1			1			1		
R-ISS II	1.62	0.93-2.82	0.09	4.14	1.67-10.27	0.002	1.83	1.11-3.00	0.02	4.95	2.28-10.7	<0.001
R-ISS III	1.61	0.68-3.81	0.28	4.68	1.53-14.33	0.007	1.09	0.43-2.75	0.86	4.28	1.44-12.7	0.009
Treatment arm												
MPT-T	1			1			1			1		
MPR-R	0.66	0.47-0.93	0.02	0.61	0.41-0.91	0.02	0.71	0.49-1.03	0.07	0.62	0.41-0.94	0.02

Strikingly, the relation between response and CRBN levels appeared dependent on treatment arm. In MPT-T treated patients only, median nuclear CRBN level was significantly higher in patients with ≥ VGPR (median H-score 180 (IQR 156-205; n=29) as compared to ≤PR patients (p=0.01; median H-score: 156 (IQR 129-181; n=38); in contrast, in MPR-R treated patients, the difference between both categories was less clear, and not significant (median nuclear CRBN level 189 (IQR 145-214; n=43) for ≥ VGPR vs 170 (IQR 140-201; n=34) for ≤PR (p=0.37)). Also, when comparing nuclear CRBN level in patients with sCR, CR, VGPR, PR and NC/PD the association between response and CRBN appeared stronger in MPT-T treated patients vs MPR-R treated patients (Kruskal Wallis p=0.07 for MPT-T for nuclear CRBN vs 5 response categories, and p=0.56 for MPR-R for nuclear CRBN vs 5 response categories).

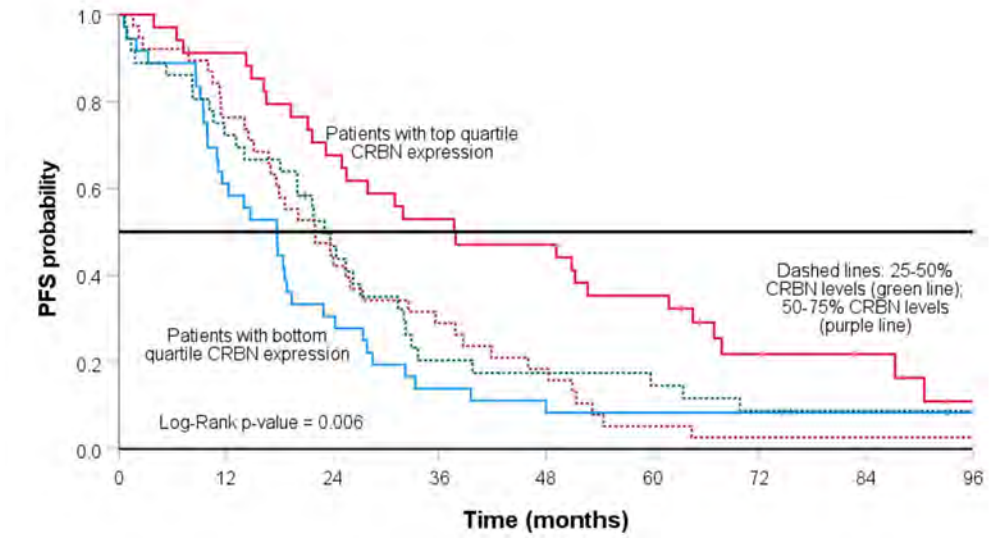
In 124 patients out of 144 with valid CRBN measurements, more than 1 response evaluation was available during induction and maintenance treatment. Patients were split into 4 categories based on whether response deepened from one timepoint to the next. The first category consisted of 24 patients without any improvement of response: 4 patients demonstrated consistent VGPR status, 9 PR status and 8 NC status. In addition, 4 patients demonstrated progressive disease after NC or PR, and were therefore also included in this category. The median H-score for nuclear CRBN was 145 (IQR 129-185) and for cytoplasmic CRBN: 164 (IQR 136-189). On the opposite end of the scale, 6 patients demonstrated 3 instances of improved response, with 5 out of 6 patients demonstrating response changing from NC to PR, from PR to VGPR and from VGPR to CR. The sixth patient demonstrated the sequence PR-VGPR-PR-VGPR-CR. In this category, higher levels of nuclear CRBN were found: median H-score 217 (IQR: 196-223) and of cytoplasmic CRBN (median H-score: 190 (IQR: 181-199).

In the two intermediate categories, patients demonstrated 1 and 2 instances of improved response during the course of the treatment (n=71, 1 improvement; n=22, 2 improvements). Comparison of the levels of nuclear and cytoplasmic CRBN in these 4 categories demonstrated significant difference overall (Kruskal Wallis analysis p=0.003 for nuclear and p=0.005 for cytoplasmic CRBN). Pairwise comparisons of each category to each other demonstrated clearly higher levels of nuclear CRBN in patients with either 2 (p=0.03) or 3 improvements (p=0.01) as compared to no improvement in response. For cytoplasmic CRBN, patients with 2 improvements in response demonstrated clearly higher levels than patients with no improvement (p=0.02). Other differences in cytoplasmic CRBN levels were not significant, after adjusting for multiple testing, possibly due to small group size (n=6, patients with 3 improved responses). The other protein markers also did not demonstrate differences between these dynamic response categories. In terms of improved response, a stronger relation was found for patients treated with MPT-T vs MPR-R. When patients with no improvement were analyzed as compared to patients with any improvement, nuclear CRBN was higher in patients with improved response (p=0.03) and MPT-T treatment but not in patients with improved response and MPR-R treatment (p=0.2).

In 14 patients progressive disease was noted during induction (n=8) or maintenance (n=6) treatment. Both nuclear and cytoplasmic CRBN levels were lower in patients with progressive disease, in particular for cytoplasmic CRBN (p=0.03). Split by study arm, the relation between CRBN and progressive disease was only seen in MPT-T patients, and not significantly in MPR-R treated patients (nuclear CRBN, MPT-T treated patients, p=0.004; cytoplasmic CRBN, MPT-T treated patients, p=0.001; nuclear CRBN, MPR-R, p=0.86; cytoplasmic CRBN, MPT-T, p=0.61). Please note the small sample set in PD patients.

Next we evaluated whether the level of the different proteins in the CRBN pathway correlates with survival, analyzing both study arms together and also separately. In patients treated with MPT-T or MPR-R (both study arms), using nuclear CRBN as a continuous marker, a higher level of nuclear CRBN staining was associated with longer PFS (HR = 0.53 (95% CI=0.37-0.77, p<0.001) and longer OS (HR = 0.59 (95% CI=0.38-0.90; p=0.02)). Next patients were divided into expression levels above or below median expression. Patients with high nuclear CRBN levels (top 50%) demonstrated a median PFS of 6.7 months longer than patients with low CRBN levels (bottom 50%). Median PFS for patients with high CRBN levels was 25.6 months (95% confidence interval (CI), 18.0-33.1), whereas median PFS for patients with low CRBN levels was 18.9 months (95% CI, 14.8-22.9; P=0.04, Figure 3). For OS, patients with high versus low nuclear CRBN levels had a median survival of 53.6 months (95% CI, 38.7-68.5) and 44.8 months (95% CI, 31.4-58.1) respectively (p=0.16). Similarly, continuous cytoplasmic CRBN staining was clearly associated with improved PFS (HR = 0.67 (95% CI=0.46-0.97; p=0.03)), however not with OS (HR = 0.75 (95% CI=0.49-1.15); p=0.19)). Median survival times are shown in Suppl. Table 3. Dividing CRBN levels in quartiles showed more clearly the association of survival with CRBN levels, both for PFS and for OS (log-rank p-values of 0.006 and 0.04, respectively) (Figure 4).

4A.



4B.

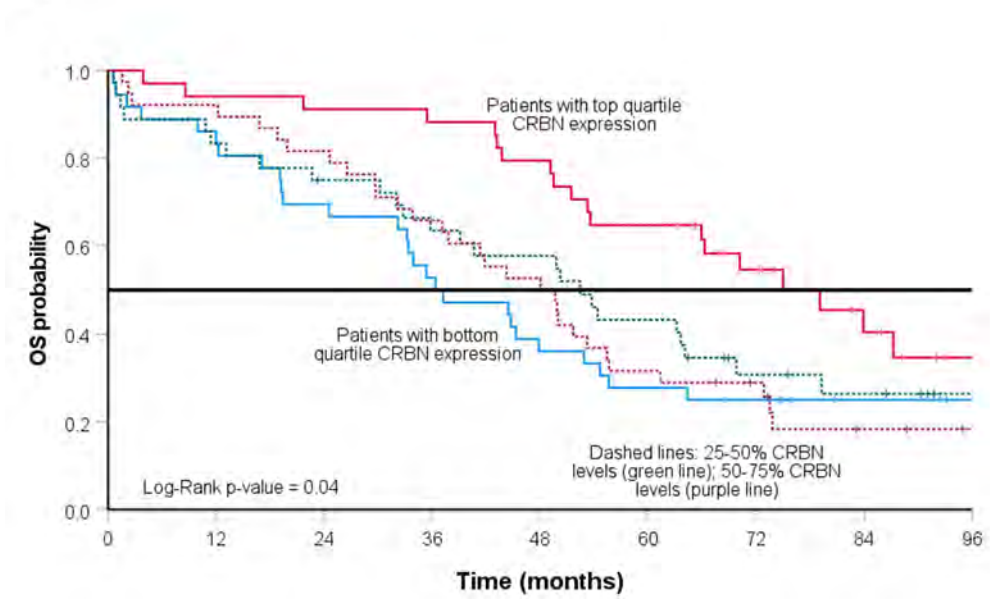


Figure 4. Nuclear Cereblon levels in relation to PFS (A) and OS (B). Nuclear Cereblon levels were divided into quartiles.

Despite difference in relation between response and CRBN levels in MPT-T as compared to MPR-R, as outlined above, the relation between CRBN and survival appeared to be only marginally different in MPT-T and MPR-R treated patients. For PFS, MPT-T (HR 0.49; 95% CI 0.26-0.90), p=0.02; MPR-R (HR 0.59; 95% CI 0.36-0.95), p=0.03; for OS, MPT-T (HR 0.50; 95% CI 0.25-1.00), p=0.05; MPR-R (HR 0.64; 95% CI 0.36-1.14), p=0.13).

Protein levels of Aiolos, Ikaros, Myc and IRF4 did not have an association with PFS or OS (Figure 3, Supp. Table 4).

In the multivariable Cox regression analysis, which included study arm (MPT-T vs MPR-R), nuclear CRBN, high-risk FISH abnormalities and R-ISS, nuclear CRBN remained statistically significant for PFS and for OS (Table 2).

Next, we assessed whether levels of CRBN pathway proteins affected the relation of nuclear CRBN with survival. We hypothesized that levels of CRBN pathway proteins would influence the value of CRBN as a prognostic factor, since IMiD action through CRBN has been linked to degradation of Ikaros and Aiolos, and downstream acts on levels of Myc and IRF4.

Indeed, IRF4 levels influenced the association of CRBN with OS. Using both markers as continuous parameters with an interaction term in the Cox regression analysis showed significance for the interaction term, highlighting this association. Using median IRF4 expression as a cut-off, CRBN levels were clearly associated with OS in patients with high IRF4 levels, whereas in patients with low IRF4 levels this association was notably absent. In patients with high IRF4, high CRBN resulted in a median overall survival of 61.4 months (95% CI 43.6-79.2), as compared to 33.2 months (95% CI 19.4-47.0) for patients with low CRBN levels (HR 0.48 (0.27-0.83; p=0.009). In patients with low IRF4, median overall survival of 50.3 months is seen in patients with low CRBN levels, compared to 50.0 months with high CRBN levels (Figure 5; p=0.88). The association of CRBN with survival does not vary with different levels of Ikaros, Aiolos and Myc, neither for OS, nor for PFS.

In order to allow future analyses in datasets where only mRNA samples are available, as bone marrow biopsies allowing protein analyses were often lacking, we compared mRNA levels (evaluated using microarray) and protein levels of CRBN. mRNA samples were available for 58 patients used in this analysis. This analysis showed a correlation between mRNA levels and protein levels of CRBN (Spearman's rank correlation 0.37 (p=0.005)). (Suppl. figure 2).

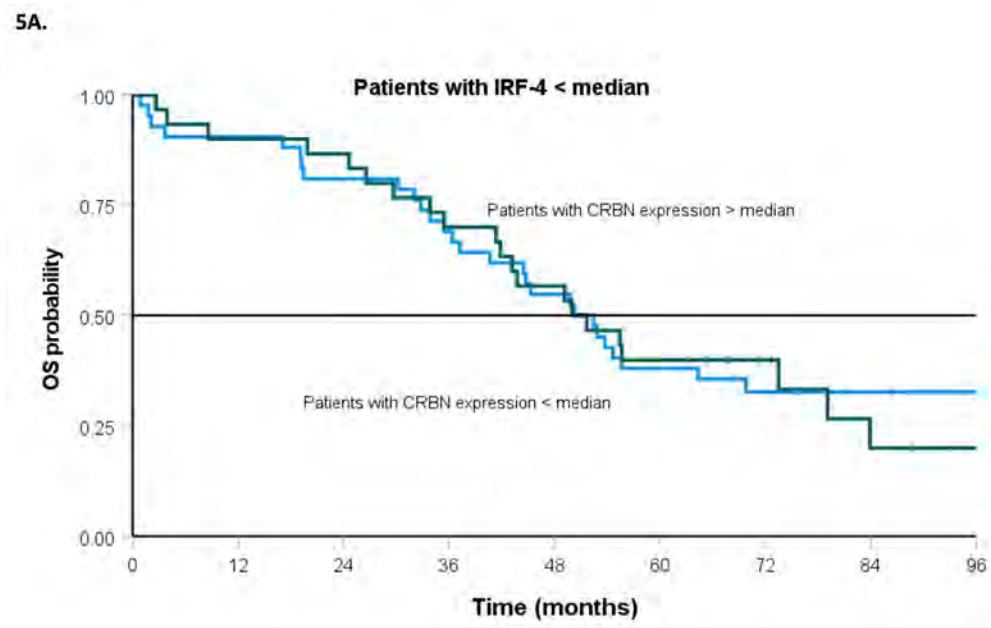


Figure 5. IRF4 in relation to nuclear Cereblon levels and OS. Figure A represents patients with IRF4 level below the median and figure B represents patients with IRF4 above the median. OS: overall survival.

DISCUSSION

This is the largest series of MM patients evaluated by immunohistochemistry and RNA expression for CRBN expression, assessed in CD138 positive cells in combination with IRF4, Myc, Ikaros and Aiolos. All patients were treated homogeneously, and a long clinical follow up was available which included cytogenetic investigation.[11]

We performed this analysis to investigate the effect of CRBN level and its downstream targets on response and survival. Hereby evaluating the value of CRBN as a potential biomarker in predicting outcome in patients treated with IMiDs. As mentioned previously, IMiDs act by several mechanisms. Central is the binding of IMiDs to the E3 ubiquitin ligase complex component CRBN which results in the degradation of proteins IKZF1 and IKZF3.[4-7] Hereby inducing immunomodulatory effects, such as secretion of cytokine IL-2 in T-cells.[8]

Evaluation of protein levels exclusively in MM cells does resolve a number of restrictions previously identified. Heintel et al for instance evaluated RNA levels by RT-PCR on both enriched and non-enriched MM samples.[21] Prior to that, our group evaluated RNA levels in enriched samples, using a microarray based method to assess expression level. This microarray method uses hybridization to multiple sequences to determine the expression level.[6] Our previous study as well as the study by Heintel et al. demonstrated improved outcome with higher CRBN expression. In terms of microarray detected RNA levels it is interesting to note the correlation we found here between RNA levels and protein levels in 58 patients. Earlier, a lack of correlation between protein and mRNA expression of CRBN was demonstrated.[15] This difference in findings may be due to differences in techniques, and subsequent studies also highlighted the relevance of looking at specific splicing variants, as absence of the IMiD binding site in exon 10 of CRBN would be expected to reduce IMiD efficacy.[15,21,22] Indeed, in terms of resistance to IMiDs, CRBN related mechanisms include copy number reduction of CRBN, mutation of the gene, and preferable splicing for the IMiD binding site lacking transcript.[14] Another mechanism of resistance was described by Gooding et al. They showed that copy loss of chromosome region 2q37 containing COP9 signalosome members COPS7B and COPS8 resulted in adverse outcome if the clonal fraction was high.[23] Recently it was suggested that patients with expression of CRBN splicing variants without exon 10 demonstrate a TNFalpha gene expression pattern, which may confer a specific sensitivity to Venetoclax.[24] A notable drawback of our immunohistochemical technique, therefore, is that these splicing variants are all detected equally, as the antibody is directed to amino acids 65-76 of CRBN (cf. exon 10: amino acids 340-383).[13] Moreover, immunohistochemistry is challenging for a number of additional reasons: this method requires biopsies, which are not routinely available and evaluation, despite the descriptive H-score, is prone to variability. The latter factor may also impede setting a universal cut-off. For this method to be applied widely, further optimization and standardization is required. The main results of this study are the association of CRBN level with outcome, both response and survival, suggesting a

role for CRBN as biomarker in MM treatment. Use of protein CRBN levels as a predictive biomarker can be useful if a non-IMiD alternative is available and if an alternative therapy results in better survival for this patient group. Currently, PFS between the two preferred treatment regimens for non-transplant eligible patients are quite disparate with median PFS for DRd of 62 months, compared to 35 months for D-VMP. [1,2] It is unclear whether survival outcomes of low CRBN expressors would indeed improve with an alternative therapy.

Comparison of the relation of CRBN with outcome in the different treatment arms is clearly of interest, as the drugs thalidomide and lenalidomide demonstrate clear differences in downstream effects, including differential effect in treatment of del(5q) MDS due to CK1alpha degradation by lenalidomide, and not by thalidomide.[25]

Our data also demonstrated that high CRBN levels at baseline were associated with multiple improvements in response. Indeed patients who demonstrated multiple improvements of response have higher median CRBN levels compared to patients who have none or only one event. Multiple improvements over time suggests that treatment benefit of IMiD have a longer lasting effect, which is corroborated by the choice of this type of treatment for maintenance.[26,27] In terms of this longer lasting effect, it is interesting that multiple studies have described the reduction of CRBN after treatment. Franssen et al. and Dimopoulos et al. demonstrated a decline in CRBN levels in patients with progression of disease during treatment with IMiDs.[11,12]

Other downstream targets in the CRBN pathway were not associated with improvement of response and survival. We observed that higher levels of CRBN combined with higher levels of IRF4 showed improvement of survival. This suggests that patients with both high levels of CRBN and IRF4 are more sensitive to treatment with IMiDs. IRF4 is central to MM biology, as inhibition is universally lethal to MM cells. [28] Furthermore targeting IRF4 may overcome IMiD resistance.[29]

In conclusion, this study demonstrates that higher expression of CRBN in patients treated with IMiDs is associated with improvement in response and survival. Therefore, CRBN could be a potential biomarker in predicting depth of response and PFS in patients treated with IMiDs.

Acknowledgements

This work was funded by grants from Celgene Corporation.

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SUPPLEMENTALS

Table 1. Patient and disease characteristics in HOVON-87/NMSG-18[16]

	All patients		CRBN set	
	Arm A: MPT-T	**Arm B: MPR-R**	**Arm A: MPT-T**	**Arm B: MPR-R**
Number	317	319	70	78
Median age, years (range)	72 (60-91)	73 (60-87)	73 (64-90)	73 (60-83)
FISH abnormality present if performed, N (%)				
17p13 loss	25/221 (11)	19/224 (8)	8/58 (14)	6/60 (10)
t(4;14)	21/225 (9)	19/241 (8)	8/58 (14)	7/65 (11)
t(14;16)	3/196 (2)	10/216 (5)	1/52 (2)	1/60 (2)
1q21 gain	64/168 (38)	67/188 (36)	21/44 (48)	19/52 (37)
Response rate				
CR	33 (10)	48 (15)	10 (14)	19 (25)
VGPR	117 (37)	99 (31)	19 (27)	22 (29)
PR	108 (34)	118 (37)	27 (39)	26 (34)
Overall response on protocol (≥PR)	258 (81)	265 (83)	56 (80)	67 (86)
Median PFS, months (95% CI)	20 (17-23)	21 (19-24)	20 (16-24)	26 (17-35)
OS at 2,3,4 years	73%, 63%, 53%	83%, 70%, 58%	73%, 60%, 47%	86%, 76%, 67%

Table 2. Expression of the proteins of the CRBN pathway in relation to response, combining both treatment arms.

	Response, median H score (IQR)		
Proteins	**sCR/CR/VGPR**	**PR/NC/PD**	**P-value**
CRBN (nuclear)	185 (147-211)	159 (130-193)	0.018
CRBN (cytoplasmic)	179 (153-205)	165 (128-192)	0.024
Ikaros	221 (207-233)	225 (208-237)	0.35
Aiolos	219 (192-242)	228 (201-243)	0.86
Myc	97 (61-135)	100 (62-127)	0.58
IRF4	185 (154-207)	183 (154-200)	0.64

sCR=stringent complete response, CR=complete response, VGPR-very good partial response, PR= partial response, NC=no change, PD=progressive disease

Table 3. A, Cox regression analysis of nuclear and cytoplasmic CRBN levels in relation to survival; B, Median survival of high and low CRBN levels.

A.

	Progression-free survival		Overall survival	
Proteins	**HR (95% CI)**	*P-value*	**HR (95% CI)**	*P-value*
CRBN (nuclear)	0.53 (0.37-0.77)	<0.001	0.59 (0.38-0.90)	0.02
CRBN (cytoplasmic)	0.67 (0.46-0.97)	0.03	0.75 (0.49-1.15)	0.19

B.

	Progression-free survival		Overall survival	
Proteins	**H score > median months (95% CI)**	**H score ≤ median months (95% CI)**	**H score > median months (95% CI)**	**H score ≤ median months (95% CI)**
CRBN (nuclear)	25.59 (18.04-33.14)	18.86 (14.84-22.87)	53.62 (38.71-68.53)	44.78 (31.44-58.12)
CRBN (cytoplasmic)	25.50 (21.64-29.35)	18.60 (16.43-20.77)	55.69 (44.40-66.97)	44.49 (32.65-56.32)

Table 4. Univariable Cox regression analysis of Ikaros, Aiolos, IRF4 and Myc levels in relation to survival

	Progression-free survival		Overall survival	
Proteins	**HR (95% CI)**	*P-value*	**HR (95% CI)**	*P-value*
CRBN (nuclear)	0.53 (0.37-0.77)	0.00082	0.59 (0.38-0.90)	0.015
CRBN (cytoplasmic)	0.67 (0.46-0.97)	0.033	0.75 (0.49-1.15)	0.19
Ikaros	1.00 (0.47-2.14)	1.00	0.99 (0.40-2.44)	0.98
Aiolos	0.91 (0.58-1.43)	0.69	1.21 (0.73-2.00)	0.46
IRF4	1.12 (0.69-1.82)	0.65	1.18 (0.67-2.10)	0.57
Myc	0.86 (0.57-1.29)	0.47	1.31 (0.84-2.02)	0.23

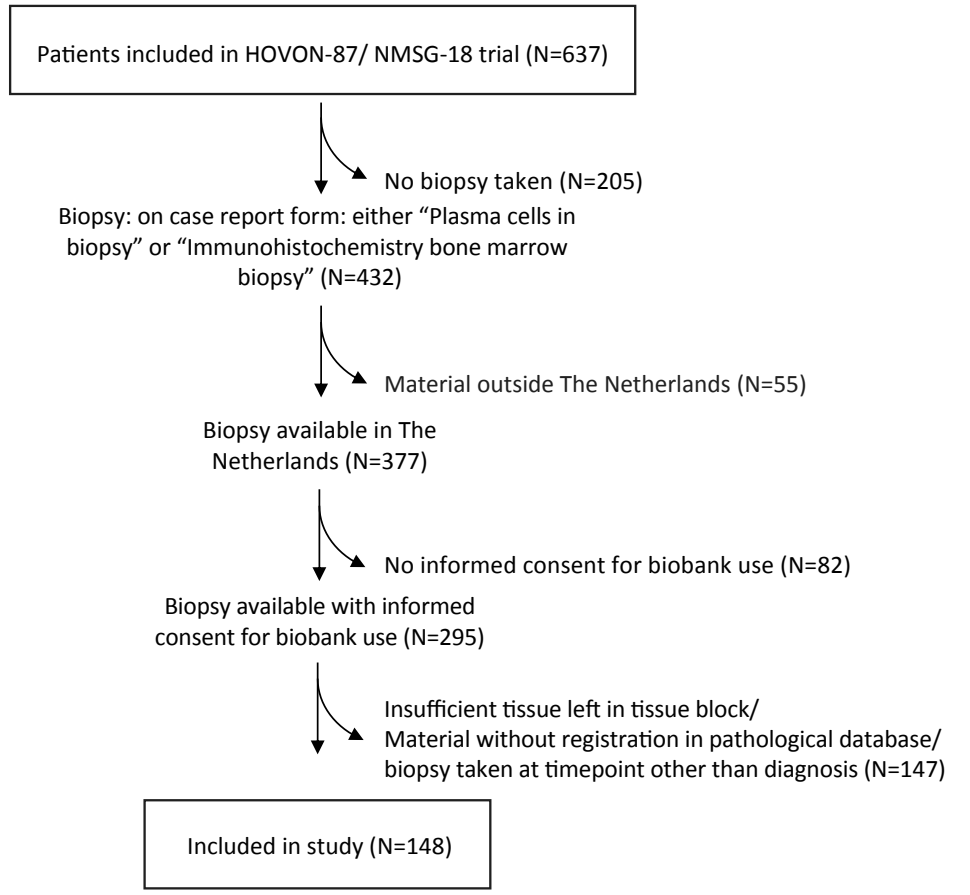

Figure 1. Selection of biopsies. Bone marrow samples of patients, included in the HOVON-87/NMSG-18 trial, were obtained before start of treatment. The selection of bone marrow samples for this analysis was based on informed consent status, availability and quality of biopsies at diagnosis.

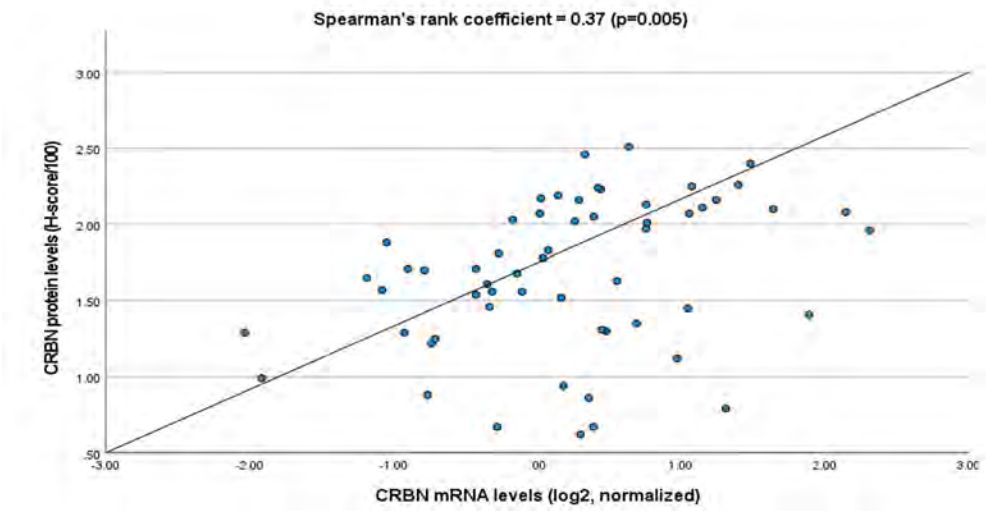

Figure 2. Correlation between mRNA levels and protein levels of CRBN.

METHODS

Pairwise comparisons were: sCR vs CR, sCR vs VGPR, sCR vs PR, sCR vs NC/PD, CR vs VGPR, CR vs PR, CR vs NC/PD, VGPR vs PR, VGPR vs NC/PD and PR vs NC/PD.

PART IV

Clinical benefit and implementation of treatment

EHA evaluation of the ESMO-Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1) for hematological malignancies

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Published in ESMO Open Cancer Horizons, November 2019

ABSTRACT

Objective Value frameworks in oncology have not been validated for the assessment of treatments in haematological malignancies, but to avoid overlaps and duplications it appears reasonable to build up experience on existing value frameworks, such as the European Society for Medical Oncology—Magnitude of Clinical Benefit Scale (ESMO-MCBS). Methods Here we present the results of the first feasibility testing of the ESMO-MCBS v1.1 for haematological malignancies based on the grading of 80 contemporary studies for acute leukaemia, chronic leukaemia, lymphoma, myeloma and myelodysplastic syndromes. The aims were (1) to evaluate the scorability of data, (2) to evaluate the reasonableness of the generated grades for clinical benefit using the current version and (3) to identify shortcomings in the ESMO-MCBS v1.1 that require amendments to improve the efficacy and validity of the scale in grading new treatments in the management of haematological malignancies. Results In general, the ESMO-MCBS v1.1 was found to be widely applicable to studies in haematological malignancies, generating scores that were judged as reasonable by European Hematology Association (EHA) experts. A small number of studies could either not be graded or were not appropriately graded. The reasons, related to the differences between haematological and solid tumour malignancies, are identified and described. Conclusions Based on the findings of this study, ESMO and EHA are committed to develop a version of the ESMO-MCBS that is validated for haematological malignancies. This development process will incorporate all of the usual stringencies for accountability of reasonableness that have characterised the development of the ESMO-MCBS including field testing, statistical modelling, evaluation for reasonableness and openness to appeal and revision. Applying such a scale will support future public policy decision-making regarding the value of new treatments for haematological malignancies and will provide insights that could be helpful in the design of future clinical trials.

INTRODUCTION

In recent years, rapid developments in haematology research resulted in a considerable expansion of treatment options. The development of instruments to measure clinical benefit is essential in the current scenario where increasing numbers of treatments for haematological malignancies (HMs) are becoming available, often targeting a small and defined subpopulation of patients. For this, several value frameworks have been published by different organisations and institutions taking into account or emphasising different aspects contributing to such an evaluation.[1] These frameworks vary in terms of their definition of value, target audience and methodology, and each of them has specific limitations, which should be taken into consideration when interpreting their outputs.[2] Until now, value frameworks developed in oncology have not been validated in the setting of HMs. The European Society for Medical Oncology (ESMO) has developed such a value framework called the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS).[3] Initially published in 2015, the scale is a validated and reproducible tool in solid tumour oncology with a particular focus on the *clinical benefit*. The ESMO-MCBS was developed to generate clear, valid and unbiased grading of the magnitude of clinical benefit demonstrated in therapeutic studies that could be used for a number of purposes including public health policy and health technology assessment (HTA), clinical decision-making, medical publication and journalism. The ESMO-MCBS grading highlights those treatments which substantially improve the duration of survival and/or the quality of life (QOL) of patients with cancer and aims to distinguish them from trials demonstrating more limited and sometimes even marginal benefits. The ESMO-MCBS was revised (version 1.1) in 2017, based on feedback and queries from clinicians, patients, researchers and representatives of the pharmaceutical industry, and a dynamic process of internal peer review.[4] Version 1.1 incorporates 10 revisions and most importantly allows also for scoring of single-arm studies. The ESMO-MCBS assigns categorical benefit scores to European Medicines Agency (EMA) approved drugs, based on results from 'positive' randomised clinical trials: (1) superiority trials that have demonstrated a statistically significant result for the primary endpoint of the study, or secondary in case of overall survival (OS) and (2) non-inferiority trials, reaching a conclusion of non-inferiority. Primary or secondary endpoints included in the scoring system are OS, progression-free survival (PFS), QOL, treatment toxicity or response rates. In developing the ESMO-MCBS scale, ESMO aspired to meet standards for 'accountability for reasonableness',[5,6] incorporating extensive field testing, statistical modelling[7] and peer review of the 'reasonableness' of the generated results into the development process. The ESMO-MCBS is currently incorporated in ESMO's clinical practice guidelines and is being used as part of HTA processes.[8,9] The European Hematology Association (EHA) and ESMO have developed a joint initiative to develop a version of the ESMO-MCBS that is validated for HMs. As a first step in this process, we have field tested the current version of the ESMO-

MCBS (version 1.1) across a wide spectrum of HMs. The aims of this evaluation were (1) to evaluate the scorability of data derived from contemporary clinical trials in HMs, (2) to evaluate the reasonableness of the generated grades for clinical benefit using the current version and (3) to identify shortcomings in the ESMO-MCBS v1.1 that require amendments to improve the efficacy and validity of the scale in grading new treatments in the management of HMs.

METHODS

Study selection

The corresponding disease-oriented EHA scientific working groups identified experts who selected representative treatments currently used in clinical practice with a focus on recently approved drugs and novel strategies, to be evaluated for each of the common haematological malignancies: acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML), Hodgkin and non-Hodgkin lymphomas, multiple myeloma (MM) and myelodysplastic syndromes (MDS). The treatments selected underwent a literature search to identify corresponding clinical trials and data.

ESMO-MCBS grading

Identified studies were graded by members of the EHA scientific working groups according to the ESMO-MCBS v1.1 forms[4] in accordance with the instructions provided by ESMO. Magnitude of clinical benefit scores range from A to C for treatment strategies with curative intent and 5-1 for treatments with non-curative intent, with scores of A–B and 5-4 relating to a substantial level of clinical benefit. Initial grading by the expert groups were reviewed by the ESMO-MCBS working group for applicability and correctness.

Evaluations

For each disease entity, we evaluated the scorability of the evaluated studies and the reasonableness of the derived scores. Based on these findings, we identified shortcomings in the current version of the ESMO-MCBS that either precluded scoring or which generated grading which was considered not to be a reasonable estimation of benefit when such studies were identified.

Results

The extensive research concluded in 80 studies, 5 of which had either more than two arms or different publications for the same trial presenting results after longer follow-up times (87 studies and/or comparisons in total). In detail, we have scored 7 studies for AML, 5 studies for ALL, 8 studies for CLL, 4 studies for CML, 23 studies for non-Hodgkin and Hodgkin lymphoma, 23 studies for MM and 10 studies for MDS. The ESMO-MCBS v1.1 tool was applied in all the 87 distinct studies and/or subgroups.

Acute myeloid leukaemia

Studies evaluated: Seven studies were evaluated,[10-16] three in a curative setting and four in a non-curative setting (table 1).

Scorability: All studies were published with endpoints and data applicable to the ESMO-MCBS v1.1.

Reasonableness: The separation of studies with curative/non-curative intent corresponds closely to the distinction between intensive versus non-intensive chemotherapy regimens which are the terms usually applied in the treatment of AML. Grading effectively distinguished between high benefit treatment strategies in a curative setting and stratified between higher and lower benefit treatments in a non-curative setting.

Shortcomings*:* None identified.

Acute lymphoblastic leukaemia

Studies evaluated: Five studies were evaluated,[17-23] and these included studies relating to three agents recently approved by EMA for relapsed and refractory ALL (table 2).[17-20,21]

Scorability: Four of the five studies were published with endpoints and data applicable to the ESMO-MCBS v1.1. The only not scoreable study was the single-arm study of ponatinib as add-on to standard of care upfront treatment with curative intent.[21]

Reasonableness: Both the first-in class bispecific antibody blinatumomab (TOWER trial)[17,18] and the antibody-drug conjugate inotuzumab ozogamicin (INO-VATEtrial)[19,20] reached high scores based on positive OS data and favourable QOL data for blinatumomab (ESMO-MCBS v1.1 scores 5 and 4, respectively). The chimeric antigen receptor (CAR) T-cell treatment in children/young adults with relapsed or refractory B-cell ALL was graded with maximal credit of 3 for a single-arm study in a non-curative setting.[22] The ponatinib treatment (single-arm PACE trial)[23] was assigned grade 2 based on the major molecular response (MMR) in the non-curative setting.

Reasonableness*:* Grading effectively distinguished between high benefit treatment strategies in a curative stetting and stratified between higher and lower benefit treatments in a non-curative setting.

Shortcomings*:* One shortcoming was identified:

1. The ESMO-MCBS v1.1 does not have a form to grade single-arm treatments with curative intent. This shortcoming precluded scoring in one study[21] and may also have been relevant to the grading of CAR T-cell salvage therapy which could also be considered as curative.[22]

Table 1 Feasibility testing of the ESMO-MCBS v1.1 for acute myeloid leukaemia (n=7)

Medication	Trial Name	Setting	Primary Outcome	PFS/EFS/ DFS Control	PFS/EFS/DFS Gain	PFS/EFS/DFS HR	OS Control	OS Gain	OS HR	RR (DOR)	QOL	Toxicity	ESMO-MCBS score	ESMO-MCBS form	Reference
SOC±midostaurin	RATIFY	Upfront, FLT3-mutated	OS	15.5 months (DFS)	11.2 months		**25.6 months**	**49.1 months**	**0.78 (0.63–0.96)**				A	1	[10]
SOC±gemtuzumab ozogamicin	ALFA-0701	Upfront, 50–70 years	EFS	**17.1% 2 years**	**23.7%**	**0.58 (0.43–0.78)**	41.9% 2 years	11.3%	0.69 (0.49–0.98) Immature			Increased	A	1	[11]
SOC±sorafenib (+maintenance)	SORAML	Upfront	EFS	**22% 3 years**	**18%**	**0.64 (0.45–0.91)**	56% 3 years	7%	Immature			Slightly increased	A	1	[12]
Azacitidine versus SOC	AZA-001	Upfront elderly, low blast count	OS				16 months	8.5 months	0.47 (0.28–0.79)			Benefit (+1 point)	5	2a	[13]
Decitabine versus SOC	DACO-016	Upfront, elderly, intermediate/poor risk	OS				5 months	2,7 months	0,82 (0.68–0.99)				2	2a	[14]
LDAC ±Volasertib		Upfront, unfit	ORR	2.3 months EFS	3.3 months	0.57 (0.35–0.92)	**5.2 months**	**2.8 months**	**0.63 (0.40–1.00)**	**31% vs 13%, gain 18%**		Slightly increased	3	2a	[15]
Enasidenib		IDH2 mutated, relapsed/refractory	ORR				3.3 months (historical)			**40.3% (5.8 months)**			2	3	[16]

Across all tables, in case there is reported information for multiple endpoints, the evaluated endpoint results are indicated with bold.
DFS, disease-free survival; DOR, duration of response; EFS, event-free survival;ESMO-MCBS v1.1, European Society for Medical Oncology—Magnitude of Clinical Benefit Scale, version 1.1; FLT3, *fms*-like tyrosine kinase 3; IDH2, isocitrate dehydrogenase 2; LDAC, low-dose cytarabine; ORR, overall response rate; OS, overall survival;PFS, progression-free survival; QOL, quality of life; RR, response rate; SOC, standard of care.

Table 2 Feasibility testing of the ESMO-MCBS v1.1 for acute lymphoblastic leukaemia (n=5)

Medication	Trial name	Setting	Primary outcome	PFS/EFS control	PFS/EFS gain	PFS/EFS HR	OS control	OS gain	OS HR	RR (DOR)	QOL	Toxicity	ESMO-MCBS score	ESMO-MCBS form	Reference (s)
Blinatumomab versus SOC	TOWER	Relapsed/refractory	OS	12% EFS 6 months	19%	0.55 (0.43–0.71)	**4 months**	**3.7 months**	**0.71 (0.55–0.93)**	44% vs 25% CRR, gain 19%	Improved (+1 point)		5	2a	[17,18]
Inotuzumab ozogamicin versus SOC	INO-VATE	Relapsed/refractory	OS/CRR	1.8 months	3.2 months	0.45 (97.5% CI: 0.34 to 0.61)	**6.7 months (10% gain in 2-year survival)**	**1 month (13% gain in 2-year survival)**	**0.77 (97.5% CI: 0.58 to 1.03) p=0.04**	81% vs 29% CRR, gain 52%	Improved	Veno-occlusive disease 11% in experimental arm	4*	2a	[19,20]
Hyper-CVAD +ponatinib		Philadelphia chromosome-positive, upfront. Phase II single arm	EFS	81% 2 years EFS			80% 2 years						Not scoreable		[21]
CAR T-cell tisagenlecleucel		Relapsed/refractory, age <21 years, single arm	ORR at 3 months				76% 1 year			81% ORR		>30% grade 3/4 cytokine release syndrome	3	3	[22]
Ponatinib	PACE	Philadelphia positive resistant to or side effects with dasatinib or nilotinib, or T315I mutation after TKI	Major haematological response within the first 6 months		7% at 12 months			40% at 12 months		Major haematological response: 41% (3 months)			2	3	[23]

*Based on >10% increase in 2 years of OS improvement.
CAR T- cell, chimeric antigen receptor T-cell therapy; CRR, complete remission rate; DOR, duration of response; EFS, event-free survival;ESMO-MCBS v1.1, European Society for Medical Oncology—Magnitude of Clinical Benefit Scale, version 1.1; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone; ORR, overall response rate; OS, overall survival;PFS, progression-free survival; QOL, quality of life; RR, response rate; SOC, standard of care; TKI, tyrosine kinase inhibitor.

Chronic lymphocytic leukaemia

Studies evaluated: Eight studies were evaluated (table 3).[24-35]

Scorability: CLL is generally a relatively indolent disease with a very long survival—often decades long—and many patients do not need intervention for many years and when treatment is initiated it commonly generates very long periods of remission. For these reasons, PFS is generally the most relevant and measurable primary endpoint. Since CLL is generally not considered to be a curable disease, all scoring was performed using scales for non-curative disease. One study[27] could not be scored because the primary objective of non-inferiority with regard to PFS was not met. Moreover, the published results limited to a subcohort of patients older than 65 years, which are relevant for clinical practice (particularly in view of presented toxicity data) did not show non-inferiority and they were derived from a post hoc exploratory analysis.

Reasonableness: Overall scoring was considered reasonable with the highest grades being achieved by studies demonstrating either mature OS data[24-26] or PFS gains with long-term plateauing of PFS[33], or compelling PFS gains.[28,29] Grading of the phase III study of ibrutinib versus ofatumumab (RESONATE trial)[31,32] was considered to be low; it was credited for PFS advantage including gain in the tail of the curve but was penalised for toxicity associated with the more prolonged drug exposure in continuous treatment (ESMO-MCBS v1.1 score 3). However, the 9% improvement in OS at 12 months was not credited as these results are deemed immature by the ESMO-MCBS criteria. The benefit of novel agents in populations with high unmet need, like relapsed and refractory patients with CLL carrying deletion in chromosome 17 p, was graded reasonably using form 3 for single-arm studies in a non-curative setting.[34,35]

Shortcomings: One shortcoming was identified:

1. The EHA scientific working group members felt that compelling immature survival benefit ought to be credited even when the median survival of the control arm has not been reached.

Table 3 Feasibility testing of the ESMO-MCBS v1.1 for chronic lymphocytic leukaemia (n=8)

Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	RR	QOL	Toxicity	ESMO-MCBS score	ESMO-MCBS form	Reference(s)
FC±R	CLL8	Upfront, chemofit	PFS	32.9 months	23.9 months	0.59 (0.50–0.69)	**86 months (66.9% 5 years)**	**>10% gain at 5 years**	**0.68 (0.54–0.89)**		No difference	Increased	4	2a	[24]
FC-R versus R-bendamustine	CLL10	Upfront, focus elderly subgroup >65 years	Non-inferiority in PFS	55.2 months	−13.5 months	Non-inferiority not met neither overall, nor in the >65 years post hoc subgroup			Not significant			Less toxicity in experimental arm	Not significant, not eligible for scoring	2c	[27]
Ibrutinib versus chlorambucil	RESONATE-2	Upfront elderly	PFS	**18.9 months**	**8 months**	**0.16 (0.09–0.28)**	85% at 24 months	13%	0.16 (0.05–0.56) Immature		Improved (abstract only)		3	2b	[28,29]
Obinutuzumab± chlorambucil	CLL11	Upfront elderly not eligible for fludarabine	PFS	**11.1 months**	**15.6 months**	**0.18 (0.13–0.24)**	NR	NA	0.41 (0.23–0.74) Immature			Increased but not meeting criteria for downgrading	3	2b	[30]
Ibrutinib versus ofatumumab	RESONATE	Relapsed/refractory (cross-over allowed)	PFS	**8.1 months**	**4+ months (>10% gain at 12 months with plateau)**	**0.11 (0.08–0.15)**	81% at 12 months	9% at 12 months	0.43 (0.24–0.79) Immature		Pending	>10% SAE increase (−1 point)	3	2b	[31,32]
R-Venetoclax versus R-bendamustine	MURANO	Relapsed/refractory	PFS	**17 months**	**6+ months (>10% gain at 12 months with plateau)**	**0.17 (0.11–0.25)**	87% at 24 months	5.30%	0.48 (0.25–0.90) Immature				4	2b	[33]
Ibrutinib	RESONATE-17	Relapsed/refractory with del17p	ORR	63% at 24 months			75% at 24 months			64%		No new safety flags	3	3	[34]
Venetoclax	M13-982	Relapsed/refractory with del17p	ORR	72% at 12 months			87% at 12 months			79%		No new safety flags	3	3	[35]

del17p, 17 p deletion;ESMO-MCBS v1.1, European Society for Medical Oncology—Magnitude of Clinical Benefit Scale, version 1.1; FC, fludarabine, cyclophosphamide; NA, not applicable; NR, not reached; ORR, overall response rate; OS, overall survival;PFS, progression-free survival; QOL, quality of life; R, rituximab; RR, responserate; SAE, serious adverse event.

Chronic myeloid leukaemia

Studies evaluated: Four landmark trials addressing the use of tyrosine kinase inhibitors imatinib, nilotinib, dasatinib and bosutinib upfront for chronic phase CML were graded.[36-43] Only one of these had mature OS data (table 4).[38]

Scorability: CML is generally considered an incurable disease, but in a small proportion of cases with deep molecular responses the disease may be eradicated. Thus, when mature survival data were available, CML was scored for both curative and non-curative intent.[36-38] Contemporary studies in CML treatments are conventionally evaluated using molecular response evaluations.[44,45] This differs from the concepts of 'pathological complete response' or 'response rate' which are terms used in the ESMO-MCBS v1.1. Scoring of these studies was only possible by interpreting deep molecular responses (MMR 4–5) as pathological complete responses (form 1) or major responses (form 2 c).[39-43] In one study,[36-38] PFS/event-free survival (EFS) gains could not be credited because the PFS of the control arm was very long and had not reached median PFS after 11 years of follow-up.

Reasonableness: In the IRIS study of imatinib versus former standard interferon plus cytarabine, initial scoring at 18 months was credited on the basis of complete cytogenic response for curative intent with a grade of C and improvement in molecular response rate with grade 2.[36-38] At 10-year follow-up, the imatinib scores B for curative intent based on survival improvement. While the grades for curative intent were considered reasonable, the EHA working group considered the ESMO-MCBS grade of 2 for non-curable intent to be too low for the benefits observed. The remaining studies of nilotinib, dasatinib and bosutinib show minor improvements in complete molecular response rates when compared with imatinib (grade 2) in a non-curative setting.[39-43] None of these agents had mature data beyond 5 years and consequently they were not graded for curative intent.

Shortcomings: These relatively low scores for imatinib in the non-curative grading appear to indicate two shortcomings in the ESMO-MCBS v1.1:

1. When PFS (or EFS) is very long, there is no mechanism to credit strong interim gains when the median PFS of the control arm has not yet been reached.
2. The surrogacy of complete cytogenic response and level 4–5 MMR, defined as 4 to 5-log reduction in *BCR–ABL1* transcript levels from a standardised baseline, are much stronger surrogates for survival than pathological complete response and response rate in solid tumours.[44,45] Consequently, form 2 c needs to be amended to incorporate evaluation of deep molecular responses.

Table 4 Feasibility testing of the ESMO-MCBS v1.1 for chronic myeloid leukaemia (n=4)

Medication	Trial name	Setting	Primary outcome	EFS/PFS control	EFS/PFS gain	PFS/EFS HR	OS control	OS gain	OS HR	Major CytRR/MMR	Complete CytRR	MMR	MR4	MR4.5	QOL	Toxicity	ESMO-MCBS score	ESMO-MCBS form	Reference(s)
Imatinib versus interferon/ cytarabine	IRIS	Newly diagnosed chronic phase (cross-over allowed)	Initial: PFS/EFS long term: OS												Improved	Less toxicity			
			18 months PFS	73.5%	18.6%					**87% vs 35%, gain 52%**	**76% vs 15%, gain 62%**						**C/2**	1/2c	
			10 years EFS	56.6%	23%		**78.8%**	**4.5%**	**0.74 (0.56–0.99)**								**B/2**	1/2c	
Nilotinib 600 or 800 mg versus imatinib	ENESTnd	Newly diagnosed chronic phase	Initial primary: MMR at 12 months, secondary: complete cytRR													More cardiovasc. events for nilotinib 800 mg			
			12 months 600 mg								80% vs 65%, gain 15%	**44% vs 22%, gain 22%**					**2**	2c	
			12 months 800 mg								78% vs 65%, gain 13%	**43% vs 22%, gain 21%**					**2**	2c	
			5 years 600 mg	92.6%	2.4%	NS	91.7%	2.0%	NS			77% vs 60%, gain 17%	**66% vs 42%, gain 24%**	**54% vs 31%, gain 22%**			**2**	2c	
			5 years 800 mg		4.3%	0.37 (0.15–0.88)		4.5%	0.44 (0.21–0.93)				**63% vs 42%, gain 21%**	**52% vs 31%, gain 21%**			**2**	2c	
Dasatinib versus imatinib	DASISION	Newly diagnosed chronic phase	Complete cytRR																
			12 months								**77% vs 66%, gain 11%**	46% vs 28%, gain 18%					**1**	2c	
			5 years				90%	1%	NS			76% vs 64%, gain 12%	42% vs 33%, gain 9%						
Bosutinib versus imatinib	BFORE	Newly diagnosed chronic phase	MMR at 12 months								77% vs 66%, gain 11%	**47% vs 37%, gain 10%**					**1**	2c	

cardiovasc., cardiovascular; CytRR, cytogenetic response rate;EFS, event-free survival;ESMO-MCBS v1.1, European Society for Medical Oncology–Magnitude of Clinical Benefit Scale, version 1.1; MMR, major molecular response; MR, molecular response; NS, not significant; OS, overall survival; PFS, progression-free survival; QOL, quality of life.

Indolent non-Hodgkin's, relapsed/refractory setting of nondiffuse large B-cell lymphoma (non-DLBCL) and Hodgkin's lymphoma

Studies evaluated: Twelve studies of recently approved drugs for indolent non-Hodgkin's, relapsed/refractory setting of non-DLBCL and Hodgkin's lymphoma were evaluated (table 5).[46-62]

Scorability: In one of the studies,[46] PFS/EFS gains could not be graded because the PFS of the control arm was very long, the median PFS was not reached and only interim gains were reported. The BRIGHT study could not be scored because form 2 c makes no provision for scoring of non-inferiority studies based on response rates.[49,50] The remaining 10 studies were published with endpoints and data applicable to the ESMO-MCBS v1.1 and were all evaluable.

Reasonableness: The grading was applicable and was judged by the EHA working group to be reasonable in the evaluated trials, endorsing relatively high benefit grades, that is, ESMO-MCBS v1.1. scores of 4–5 for 7 of the 10 evaluable studies.

Shortcomings: Two shortcomings were observed:

1. The ESMO-MCBS v1.1 has no mechanism for scoring non-inferiority studies based on response rate.
2. When PFS (or EFS) is very long, there is no mechanism to credit strong interim gains when the median PFS of the control arm has not yet been reached.

Table 5 Feasibility testing of the ESMO-MCBS v1.1 for indolent non-Hodgkin and relapsed/refractory setting of non-DLBCL and Hodgkin's lymphoma (n=12)

Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	RR (DOR)	QOL	Toxicity	ESMO-MCBS score	ESMO-MCBS form	Reference(s)
Obinutuzumab-Chemo versus R-Chemo	GALLIUM	Follicular lymphoma, first line	PFS	73% (3 years)	7%	0.66 (0.51–0.85)							Not scoreable	2b	[46]
VR-CAP versus R-CHOP	LYM-3002	Mantle cell lymphoma first line, not eligible for transplant	PFS	14.4 months	10.3 months	0.63 (0.5–0.79)	**55.7 months**	**35 months (7 year survival gain >5% with plateau)**	**0.66 (0.51–0.85)**			Increased in experimental arm	A/4	1/2a	[47,48]
R-Bendamustine versus R-CHOP/R-CVP	BRIGHT study	Indolent and mantle cell lymphoma, first line	Non-inferiority in CRR (margin: 0.88)							Non-inferiority met 1.26 (0.93–1.73) 31% versus 25%, 6% gain	Improved		Not scoreable	2c	[49,50]
R-Bendamustine versus R-CHOP	STiL Trial NHL 1-2003	Indolent and mantle cell lymphoma, first line	Non-inferiority in PFS (margin: 1.32)	31.2 months	38.3 months	0.58 (0.44–0.74) Non-inferiority met						Less adverse events in experimental arm	4	2c	[51]
Bendamustine± Obinutuzumab	GADOLIN	Rituximab-refractory indolent non-Hodgkin's lymphoma	PFS	14.9 months	NA	0.55 (0.40–0.74)	**NR**	**>10% at 5 years**	**0.67 (0.47–0.96)**		Delayed deterioration in QOL		5	2a	[52,53]
Ibrutinib versus Temsirolimus		Relapsed/refractory mantle cell lymphoma	PFS	6.2 months	8.4 months	0.43 (0.32–0.58)					Improved (+1 point)		4	2b	[54]
Lenalidomide versus Investigator's choice	MCL-002 SPRINT	Relapsed/refractory mantle cell lymphoma	PFS	5.2 months	3.5 months	0.61 (0.44–0.84)					Improved (+1 point)		4	2b	[55]
Ibrutinib	PCYC-1104-CA	Relapsed/refractory mantle cell lymphoma	ORR	13.9 months						68%			3	3	[57]
Ibrutinib		Relapsed/refractory marginal zone lymphoma	ORR	14.2 months						48%		Relevant toxicity but not meeting criteria for downgrading	3	3	[58]
Idealisib	DELTA (101-09)	Relapsed/refractory indolent lymphoma	ORR	11 months						57% (12.5 months)			3	3	[59]
Pembrolizumab	KEYNOTE-087	Relapsed/refractory Hodgkin lymphoma	ORR							69%	Improved (+1 point)		4	3	[60]
Nivolumab	Check Mate 205	Relapsed/refractory Hodgkin lymphoma	ORR	14.7 months						69%	Improved (+1 point)		4	3	[61,62]

chemo, chemotherapy; CRR; complete response rate;DLBCL, non-diffuse large B-cell lymphoma; DOR, duration of response;ESMO-MCBS v1.1, European Society for Medical Oncology—Magnitude of Clinical Benefit Scale, version 1.1; NA, not applicable; NR, not reached; ORR; overall response rate; OS; overall survival;PFS, progression-free survival; QOL, quality of life; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CVP, rituximab, cyclophosphamide, vincristine and prednisone; RR, responserate; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone.

Diffuse large B-cell lymphoma

Studies evaluated: Eleven studies were evaluated [63-75]; two in the first-line setting with curative intent,[63-66] two intensified therapies for first-line and salvage setting, respectively, with both curative and non-curative intent,[67,68] two single-arm studies of CAR T-cell salvage therapy [70,71] and five in a non-curative setting for relapsed and refractory disease (table 6).[69,72-75]

Scorability: All studies incorporated required data for evaluation using the ESMO-MCBS v1.1. Single-arm studies of CAR T-cell therapy for refractory or resistant disease [70,71] could not be evaluated for curative intent. The NCIC-CTG LY12 trial could not be graded in the non-curative setting because non inferiority was evaluated on the basis of overall response rate.[68]

Reasonableness: The grading was applicable and was judged by the EHA working group to be reasonable in the evaluated trials, endorsing high benefit grades for first-line therapies with curative intent.[63-67] Lower benefit scores for trials in the relapsed and refractory therapies were considered reasonable.

Shortcomings: One shortcoming was identified:

1. The ESMO-MCBS v1.1 does not have a form to grade single-arm treatments with curative intent and this shortcoming does not allow for the representation of the full potential benefit of CAR T-cell salvage therapy.[70,71]

Table 6 Feasibility testing of the ESMO-MCBS v1.1 for DLBCL (n=11)

Medication	Trial name	Setting	Primary outcome	PFS/EFS/DFS control	PFS/EFS/DFS gain	PFS/EFS/DFS HR	OS control	OS gain	OS HR	RR (DOR)	QOL	Toxicity	ESMO-MCBS score	ESMO-MCBS form	Reference(s)
CHOP±R	MInT study	First-line DLBCL, stage II–IV or I with bulky disease, IPI 0–1	EFS	55.8% (6 years)	18.5%	p<0.0001	**80% (6 years)**	**10.1%**	**p=0.0004**				A	1	
CHOP±R	LNH-98.5	First-line DLBCL, stage II–IV, age 60–80	PFS	20% at 10 years	16.5%	p<0.0001	**27.6% (10 years)**	**15.9%**	**p<0.0001**				A	1	
			EFS	38% at 2 years	19%	p<0.001									
R-CHOP ±lenalidomide maintenance	REMARC	First-line DLBCL, stage II–IV, age 60–80	PFS	58.9 months	4+ months	0.71 (0.54–0.93)			NS				A/3	1/2b	
R-GDP+ASCT versus R-DHAP +ASCT	NCIC-CTG LY12	Relapsed/refractory aggressive lymphoma	Non-inferiority (ORR) (margin: −10%)			No difference			No difference	ORR difference: −1.2 (-9, 6.7) 44% vs 45% (non-inferiority met)	Improved		B/not scoreable	1/2c	
Pixantrone versus investigators' choice		Relapsed/refractory aggressive lymphoma	CRR	**2.6 months**	**2.7 months** **>10% gain at 12 months, no plateau**	**0.60 (0.42–0.86)**				20% vs 6%, gain 14%			3	2b	
CAR T-cell Axicabtagene ciloleucel	ZUMA-1	Relapsed/refractory aggressive non-Hodgkin's lymphoma	ORR							82%		Toxicity but not meeting criteria for downgrading	3	3	
CAR T-cell Tisagenlecleucel	JULIET	Relapsed/refractory DLBCL	ORR							52% (not reached, >10 months)		Toxicity not meeting criteria for downgrading	3	3	
Lenalidomide versus investigators' choice	DLC-001	Relapsed/refractory DLBCL	ORR	**2 months**	**1.4 months**	**0.64 (0.41–0.99)**				28% vs 12%, gain 16%		More PFS-improvement in ABC subtype	2	2b	
Panobinostat with or without R		Relapsed/refractory DLBCL	ORR							28% (15 months)			3	3	
Brentuximab vedotin		Relapsed/refractory DLBCL	ORR	4 months						44%			2	3	
Ibrutinib		Relapsed/refractory DLBCL, subgroup ABC subtype	ORR	2 months						37% (4.8 months)			1	3	

ASCT, autologous stem cell transplantation; CART- cell, chimeric antigen receptor T-cell therapy; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CRR, complete response rate; DFS, disease-free survival; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; EFS, event-free survival;ESMO-MCBS v1.1, European Society for Medical Oncology—Magnitude of Clinical Benefit Scale, version 1.1; IPI, International Prognostic Index; NS, not significant; ORR, overall response rate; OS, overall survival;PFS, progression-free survival; QOL, quality of life;R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine and cisplatin; R-GDP, rituximab, gemcitabine, dexamethasone and cisplatin; RR, response rate.

Multiple myeloma

Studies evaluated: Table 7 describes results from eight studies in the first-line setting.[76-84] Of these, three were conducted for autologous stem cell transplantation (ASCT) eligible [76-78] patients and five are for ASCT ineligible patients.[79-84] Table 8 describes the results of a further 15 studies with relapsed or refractory myeloma.[85-104]

Scorability: Most studies incorporated required data for evaluation using the ESMO-MCBS v1.1. The PETHEMA/GEM study comparing VTD (bortezomib, thalidomide and dexamethasone) to TD (thalidomide and dexamethasone) or VBMCP/VBAD/B (vincristine, BCNU, melphalan, cyclophosphamide, prednisone/vincristine, BCNU, doxorubicin, dexamethasone/bortezomib) as induction therapies did not report HRs for the PFS, resulting in precluded scoring with non-curative intent using form 2b.76 The GIMEMA 2005 study could not be scored for non-curative intent because the median PFS of the control arm had not yet been reached.[77] The MM5 non- inferiority study [78] could not be scored for non-curative intent because non-inferiority was based on response rate.

Reasonableness: First-line treatments for patients who are ASCT eligible are graded both for curative and non-curative intent. The relatively low grades of C for curative intent achieved in two of the ASCT eligible studies [76,77]

reflect the prevailing consensus that MM is rarely cured. In most studies evaluated, the scale was feasible and the results were consistent with clinical practice.

Shortcomings: Three previously described shortcomings influenced scoring for a small number of these studies.

1. The ESMO-MCBS v1.1 has no mechanism for scoring non-inferiority studies in a non-curative setting based on response rate.
2. When PFS (or EFS) is very long, the ESMO-MCBS v1.1 has no mechanism to credit strong interim gains when the median PFS of the control arm has not yet been reached.
3. The EHA working group members felt that the capitation of PFS at a maximal preliminary grade of 3, with provision for an upgrade based on tail of the curve only if there is a plateau in the study medication PFS with gain of >10% at 12 months, may have undervalued some MM treatments.[96,97] The plateau requirement for this adjustment precludes credit for substantial prolonged gains in PFS in this disease entity.

Table 7 Feasibility testing of the ESMO-MCBS v1.1 for first-line multiple myeloma (n=8)

Medication	Trial name	Setting	Primary outcome	PFS/DFS control	PFS/DFS gain	PFS/DFS HR	OS control	OS gain	OS HR	RR	QOL	Toxicity	ESMO-MCBS score	ESMO-MCBS form	Reference(s)
VTD versus TD or VBMCP/VBAD/B	GEM2005-less65 PETHEMA/GEM	ASCT eligible	CR post ASCT (PFS)									More neuropathy but not meeting criteria for downgrading		1/2b	
			TD	28.2 months	28.0 months	p=0.01	65% at 4 years	9%	NS	**CRR 46% vs 24%, gain 22%**			C/not scoreable		
			VBMCP/VBAD/B	35.3 months	20.9 months	p=0.01	70% at 4 years	4%	NS	**CRR 46% vs 38%, gain 8%**			NEB/not scoreable		
VTD versus TD	GIMEMA 2005	ASCT eligible	CR post induction (PFS)	**56% at 3 years**	**12%**	**0.63 (0.45–0.88)**	84% at 3 years	2%	NS	(near) CRR 31% vs 11%, gain 20%		More neuropathy but not meeting criteria for downgrading	C/not scoreable	1/2b	[75]
VCD versus PAD	MM5	ASCT eligible	Non-inferiority of ≥VGPR rates (margin: −10%)							VGPR difference: 2.6% (−6.8% to 12.3%) non-inferiority met		SAEs higher in the control arm	Not scoreable	1/2c	[78]
VMP versus MP	VISTA	ASCT ineligible	TTP	16.6 months	7.4 months	0.48 (p<0.001)	**43.1 months**	**13 months**	**0.70 (0.57–0.85)**				4	2a	[79,80]
VMPT versus VMP	GIMEMA VMPT	ASCT ineligible	PFS	**27 months 41% at 3 years**	**>13 months 15%**	**0.67 (0.50–0.90)**	87% at 3 years	2%	NS		–	Vascular and cardiac events increased in experimental arm (−1 point)	2	2b	[81]
Lenalidomide-d continuous versus x18 or MPT x12	FIRST	ASCT ineligible	PFS												[82]
			Len-d x18	20.7 months	4.8 months	0.70 (0.60–0.82)	**56% at 4 years**	**3% gain at 4 years**	**NS**				3	2b	
			MPT	21.2 months	4.3 months	0.72 (0.61–0.85)	**47 months 51% at 4 years**	**7 months 8% gain at 4 years**	**0.78 (0.64–0.96)**				4	2a	
VMP ±daratumumab	ALCYONE	ASCT ineligible	PFS	18 months 50% at 18 months	9+ months 21% at 18 months	0.50 (0.38–0.65)						More infections but not meeting criteria for penalty	3	2b	[83]
Lenalidomide-d ±bortezomib	SWOG S07777	ASCT ineligible	PFS	30 months	13 months	0.71 (0.56–0.91)	**64 months**	**11 months**	**0.71 (0.52–0.96)**			Slightly increased	4	2a	[84]

ASCT, autologous stem cell transplantation; CR, complete remission; CRR, complete remission rate; d, dexamethasone; DFS, disease-free survival;ESMO-MCBS v1.1, European Society for Medical Oncology—Magnitude of Clinical Benefit Scale, version 1.1; Len-d, lenalidomide-d; MP, melphalan and prednisone; MPT, melphalan, prednisone and thalidomide; NEB, no evaluable benefit; NS, not significant; OS, overall survival; PAD, bortezomib, doxorubicin, dexamethasone;PFS, progression-free survival; QOL, quality of life; RR, response rate; SAE, serious adverse event; TD, thalidomide and dexamethasone; TTP, time to progression; VBMCP/VBAD/B, vincristine, BCNU, melphalan, cyclophosphamide, prednisone/vincristine, BCNU, doxorubicin, dexamethasone/bortezomib; VCD, bortezomib, cyclophosphamide, dexamethasone; VGPR, very good partial response rate; VMP, bortezomib, melphalan and prednisone; VMPT, bortezomib, melphalan, prednisone and thalidomide; VTD, bortezomib, thalidomide and dexamethasone.

Table 8 Feasibility testing of the ESMO-MCBS v1.1 for relapsed/refractory multiple myeloma (n=15)

Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	RR (DOR)	QOL	Toxicity	ESMO-MCBS score	ESMO-MCBS form	Reference(s)
Dexamethasone ±lenalidomide	CC-5013- MM-010	Relapsed/refractory	TTP	**4.7 months**	**6.6 months**	**0.35 (0.27–0.46)**	20.6 months	NA	0.66 (0.45–0.96)				3	2b	[redacted]
Lenalidomide-d ±carfilzomib	ASPIRE	Relapsed/refractory	PFS	17.6 months	8.7 months	0.69 (0.57–0.83)	**40.4 months**	**7.9 months**	**0.79 (0.67–0.95)**		Improved (+1 point)	Slightly increased	4	2a	[redacted]
Lenalidomide-d ±ixazomib	TOURMALINE-MM1	Relapsed/refractory	PFS (interim)	14.7 months	5.9 months	0.74 (0.59–0.94)			Immature		Not improved		3	2b	[redacted]
Lenalidomide-d ±daratumumab	POLLUX	Relapsed/refractory	PFS (interim)	18.4 months	16+months	0.37 (0.27–0.52)			Immature			Higher haematological toxicities	3	2b	[redacted]
Lenalidomide-d ±elotuzumab	ELOQUENT-2	Relapsed/refractory	Coprimary PFS and ORR (interim)	14.9 months 57% at 12 months	4.5 months 11% at 12 months	0.70 (0.57–0.85)	**39.6 months**	**8.7 months**	**0.78 (0.63–0.96)**		No difference	Slightly higher SAEs	3	2a	[redacted]
Dexamethasone ±bortezomib	APEX	Relapsed/refractory	TTP	**3.5 months**	**2.7 months**	**0.55 (p=0.001)**	23.7 months	6.1 months	0.77 (p=0.027)				3	2b	[redacted]
Carfilzomib-d versus bortezomib-d	ENDEAVOR	Relapsed/refractory	PFS	9.4 months	9.3 months	0.53 (0.44–0.65)	**40 months**	**7.6 months**	**0.79 (0.65–0.96)**		Improved (abstract only)	Slightly higher SAEs	3	2a	[redacted]
Bortezomib-d ±daratumumab	CASTOR	Relapsed/refractory	PFS	7.1 months 26.9% at 12 months	9.6 months 33.8% at 12 months	0.31 (0.24–0.39)			Immature			Higher haematological toxicity	3	2b	[redacted]
Bortezomib-d ±panobinostat	PANORAMA1	Relapsed/refractory	PFS	**8.1 months**	**3.9 months**	**0.63 (0.52–0.76)**	30.4 months	3.25 months	Immature			3% increase in PN grade ≥3 (~1 point)	2	2b	[redacted]
Dexamethasone ±pomalidomide	MM-003	Relapsed/refractory	PFS	1.9 months	2.1 months	0.48 (0.39–0.60)	**8.1 months**	**4.6 months**	**0.74 (0.56–0.97)**				4	2a	[redacted]
Pomalidomide-d ±cyclophosphamide	MMC-16705	Relapsed/refractory ≥2 prior lines of treatment	ORR	4.4 months	5.1 months	NS				64.7% vs 38.9%, gain 25.8%			2	2c	[redacted]
Daratumumab	SIRIUS	Relapsed/refractory	ORR	3.7 months						29% (7.4 months)			2	3	[redacted]
Daratumumab	GEN501	Relapsed/refractory (16 mg/kg)	Safety	5.6 months						36% (NR)			2	3	[redacted]
Daratumumab +pomalidomide + d	MMY1001	Relapsed/refractory ≥2 prior lines of treatment	Safety	8.8 months			17.5 months			60% (>13 months)			3	3	[redacted]
Pomalidomide +bortezomib + d	MC1082	Relapsed/refractory	ORR	13.7 months						86%			3	3	[redacted]

d, dexamethasone; DOR, duration of response;ESMO-MCBS v1.1, European Society for Medical Oncology—Magnitude of Clinical Benefit Scale, version 1.1; NA, not applicable;NR, not reached; NS, not significant; ORR, overall response rate; OS, overall survival;PFS, progression-free survival; PN, polyneuropathy; QOL, quality of life; RR, responserate; SAEs, serious adverse events; TTP, timeto progress.

Myelodysplastic syndrome

Studies evaluated: Ten studies were evaluated in this setting.[105-114] Of these, two studies were evaluated based on OS or PFS and the remaining eight studies were evaluated based on response rate (table 9).

Scorability: All studies incorporated required data for evaluation using the ESMO-MCBS v1.1. Clinical benefit measure was, however, partly confounded by the heterogeneity of the available definitions of haematological response and their clinical meaningfulness.

Reasonableness: In the two studies evaluating hypomethylating agents in intermediate-risk/high-risk patients,[105,106] the ESMO-MCBS v1.1 graded them with substantial benefit based on either PFS gain or OS gain with improved QOL. In lower risk patients, the remaining eight studies included randomised trials investigating erythropoietin-stimulating agents, lenalidomide in MDS with del(5q) or non-del(5q) and immunosuppressive therapy with antithymocyte globulin plus cyclosporine, compared with best supportive care.[107-114] All studies were evaluated based on response rates, but they used a range of different and inconstant criteria, some using International Working Group, or modifications thereof, and other study-specific criteria such as transfusion requirements. All these studies resulted in a final ESMO-MCSB v1.1 score of 2. In one of these studies [108] QOL was evaluated and demonstrated to have improved but this was not reflected in grading since there is no QOL bonus for studies in which response rate is the primary outcome.

Shortcomings: The EHA working group identified one shortcoming derived from these evaluations:

1. In studies evaluating response rate as a primary endpoint, there is no provision of QOL bonus if improved QOL is demonstrated as a secondary outcome.

Table 9 Feasibility testing of the ESMO-MCBS v1.1 for myelodysplastic syndrome (n=10)

Medication	Trial name	Setting	Primary outcome	PFS control	PFS gain	PFS HR	OS control	OS gain	OS HR	RR (DOR)	QOL	Toxicity	ESMO-MCBS score	ESMO-MCBS form	Reference
Azacitidine versus SOC	AZA-MDS-001	High-risk MDS	OS				15 months	9.5 months	0.58 (0.43–0.77)				4	2a	
Decitabine versus SOC		MDS FAB (IPSS ≥0.5)	Coprimary ORR and PFS	7.8 months	4.3 months	0.58 (0.37–0.91)					Improved (+1 point)	4	4	2b	
Lenalidomide (10 mg/5 mg) versus SOC	LEN-MDS-004	Transfusion-dependent patients with low-risk/intermediate-risk MDS del5q (IPSS ≤1)	RR (RBC-TI) 10 mg 5 mg							56% vs 6%, gain 50% 43% vs 6%, gain 37%			2 2	2c 2c	
Lenalidomide versus SOC	LEN-MDS-005	MDS-WHO (IPSS ≤1)	RR (RBC-TI at ≥8 weeks)							26.9% vs 2.5%, gain 24.4%	Improved	2	2	2c	
Antithymocyte globulin versus SOC	SAKK 33/99	MDS <10% bone marrow blasts	RR at 6 months							29% vs 9%, gain 20%		2	2	2c	
rHuEPO versus SOC	ICSG	MDS <10% bone marrow blasts	RR (TI)							37% vs 11%, gain 26%		2	2	2c	
rHuEPO versus ±GCSF		MDS-FAB (IPSS ≤0.5)	RR (TI)							73% vs 40%, gain 33%		2	2	2c	
EPO versus SOC	E1996	MDS <10% bone marrow blasts	RR (IWG 2000 modified)							36% vs 10%, gain 26%		2	2	2c	
rHuEPO +GCSF versus SOC	GFM	MDS <10% bone marrow blasts	RR (IWG 2006 stringently modified)							42% vs 0%, gain 42%		2	2	2c	
Darbepoetin versus SOC		MDS-WHO IPSS ≤1	RBC transfusion incidence							59% vs 36%, gain 23%		2	2	2c	

del5q, 5q deletion; DOR, duration of response;ESMO-MCBS v1.1, European Society for Medical Oncology—Magnitude of Clinical Benefit Scale, version 1.1; FAB, French–American–British classification for MDS; GCSF, granulocyte-stimulating factor; IPSS, international Prognostic Scoring System; IWG, International Working Group; MDS, myelodysplastic syndrome;ORR, overall response rate; OS, overall survival;PFS, progression-free survival; QOL, quality of life; RBC-TI, red blood cell transfusion independency; rHuEPO, recombinant human erythropoietin; RR, responserate; SOC, standard of care; TI, transfusion independency.

DISCUSSION

The EHA with currently more than 5000 members is the largest European-based haematology association. In addition to its educational mission, it has a public policy and advocacy role that engages stakeholders, including patient representatives, to improve patient care and to raise awareness for haematology as a distinct medical discipline with specific needs.[115] Reflecting these goals, EHA has observed the development of the ESMO-MCBS and its broad utility in solid tumour oncology with great interest, and in the absence of a value tool validated for malignant haematology, we sought to investigate the applicability of the ESMO-MCBS v1.1 as a first step to the development of a version validated for HMs. There are several major differences in the behavior of HMs as compared with solid tumour cancers. These differences arise largely from the more variable natural history of HMs which can range from fulminant (acute leukaemia and high-grade lymphomas) to almost benign (low-grade MDS). Furthermore, many of these malignant haematological diseases, even when they are not cured, they are characterised by very long PFS and OS that are rarely seen among incurable solid tumour malignancies. Finally, the endpoints used in the studies of treatments for HMs are sometimes different to those used in solid tumours and in some instances, such as CML, they are even disease-specific. Consequently, at the outset of this project we did not know if ESMO-MCBS v1.1 could be applied to studies in HMs, and if the grading of studies would generate grades considered reasonable by experts in the relevant diseases. This evaluation of the behaviour of the ESMO-MCBS v1.1 in the grading of 80 studies across the full spectrum of HMs has demonstrated that the ESMO-MCBS v1.1 is widely applicable for the overwhelming majority of analysed studies (90% scoreable studies) and that the generated scores were generally adjudicated by clinical experts to reasonably accord with their evaluation of the magnitude of clinical benefit. In 5 of the 80 studies (6%), the ESMO-MCBS could not be applied at all [21,27,46,49,50,78] and in 3 more studies (4%), it could not be applied to one of the evaluable parameters.[68,76,77] In the evaluation of imatinib in CML,[36-38] it generated scores that were considered to under-represent the true value of the intervention in the opinion of experts in the evaluated diseases. Based on the analysis of the scorability of studies and the reasonableness of the generated results, this field testing identified six shortcomings in the current version of the ESMO-MCBS that will require redress to improve the applicability and reasonableness of ESMO-MCBS scoring for malignant haematological conditions.

1. Regarding single-arm studies with curative intent, such as CAR T-cell salvage therapies, the ESMO-MCBS v1.1 does not have a form to grade single-arm treatments with curative intent.
2. Regarding relatively indolent conditions with a very long PFS (or EFS) or OS such as CLL, CML, indolent lymphoma and MM, there is no mechanism to credit strong interim gains when the median of the control arm has not yet been reached.

3. The capitation of PFS at a maximal preliminary grade of 3, with provision for an upgrade based on tail of the curve only when there is a plateau in the arm with the study medication, may undervalue treatments with substantial late PFS gain but with no plateauing of the curves.
4. Regarding the standard molecular surrogate endpoints used for CML, the surrogacy of complete cytogenic response and level 4–5 MMR must be acknowledged and incorporated.
5. The scale does not make provision for the grading of non-inferiority studies based on response rate criteria.
6. In studies evaluating response rate as a primary endpoint, there is no provision of QOL bonus if improved QOL is demonstrated as a secondary outcome. Finally, it must be acknowledged that the results of the scale may not be reasonable for some of the least malignant of the HMs such as low-risk MDS. Most of the studies for MDS were evaluated based on response rates, but there was heterogeneity of the available definitions of haematological response and their clinical meaningfulness. This underlines the need for a stand-alone form regarding studies with such heterogeneity in their response rates. ESMO and the EHA are committed to the development of a version of the ESMO-MCBS that is validated for HMs. Based on the findings of this study, a revised version of the ESMO-MCBS will be developed to address the identified shortcomings in the current version of the scale regarding the assessment of HMs. This development process will incorporate all the usual stringencies for accountability of reasonableness that have characterized the development of the ESMO-MCBS. This, thus far, included field testing, statistical modelling, evaluation for reasonableness and openness to appeal and revision. Applying such a scale will support future decision-making and will provide insights that could be helpful in the design of future clinical trials.

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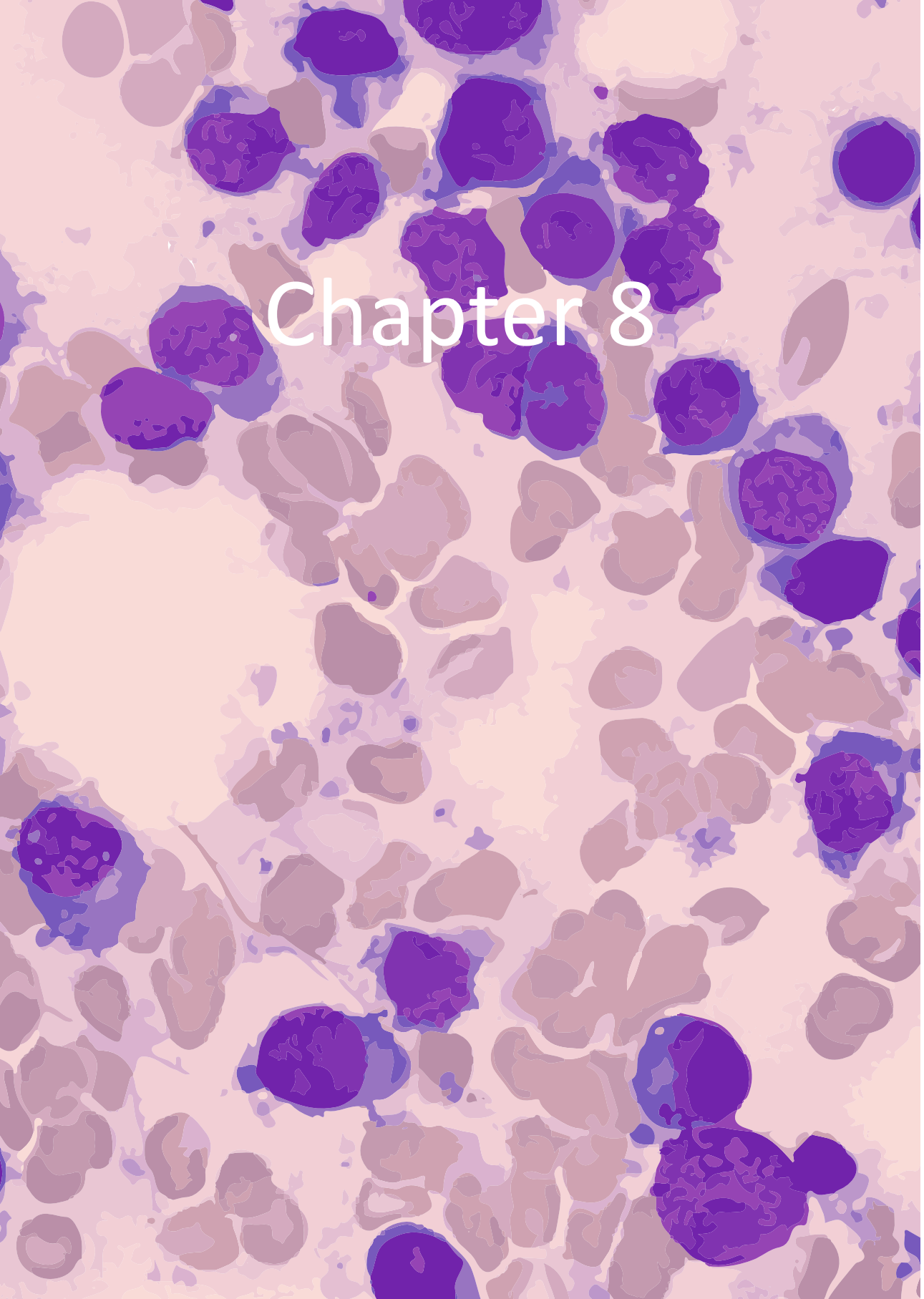

Chapter 8

Biases in study design, implementation, and data analysis that distort the appraisal of clinical benefit and ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) scoring

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Published in ESMO Open Cancer Horizons, April 2021

ABSTRACT

The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) is a validated, widely used tool developed to score the clinical benefit from cancer medicines reported in clinical trials. ESMO-MCBS scores assume valid research methodologies and quality trial implementation. Studies incorporating flawed design, implementation, or data analysis may generate outcomes that exaggerate true benefit and are not generalisable. Failure to either indicate or penalise studies with bias undermines the intention and diminishes the integrity of ESMO-MCBS scores. This review aimed to evaluate the adequacy of the ESMO-MCBS to address bias generated by flawed design, implementation, or data analysis and identify shortcomings in need of amendment. Methods: As part of a refinement of the ESMO-MCBS, we reviewed trial design, implementation, and data analysis issues that could bias the results. For each issue of concern, we reviewed the ESMO-MCBS v1.1 approach against standards derived from Helsinki guidelines for ethical human research and guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the Food and Drugs Administration, the European Medicines Agency, and European Network for Health Technology Assessment. Results: Six design, two implementation, and two data analysis and interpretation issues were evaluated and in three, the ESMO-MCBS provided adequate protections. Seven shortcomings in the ability of the ESMO-MCBS to identify and address bias were identified. These related to (i) evaluation of the control arm, (ii) crossover issues, (iii) criteria for non-inferiority, (iv) substandard post-progression treatment, (v) post hoc subgroup findings based on biomarkers, (vi) informative censoring, and (vii) publication bias against quality-of-life data. Conclusion: Interpretation of the ESMO-MCBS scores requires critical appraisal of trials to understand caveats in trial design, implementation, and data analysis that may have biased results and conclusions. These will be addressed in future iterations of the ESMO-MCBS. Key words: ESMO-MCBS, bias, clinical trial design, clinical trial implementation, clinical trial reporting, clinical trial analysis.

INTRODUCTION

The European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) was first published in 2015 and revised in 2017.[1,2] With a growing recognition that many cancer medicines provided modest benefits disproportionate to their high costs, the oncology community needed a tool that could objectively assess the clinical benefit from cancer medicines, assist in comparison with other similar medicines, and guide regulatory and reimbursement decisions. The ESMO-MCBS was established to address these needs.[1,2] To reduce bias and error in grading, the scale has been developed in close adherence to the principles of 'accountability for reasonableness', [3] a standard for ethical public health decision-making processes. The ESMO-MCBS aims to highlight treatments with a substantial level of clinical benefit for patients and distinguish those from studies demonstrating only moderate, minor, or marginal clinical benefit. Within ESMO, the ESMO-MCBS is used in clinical practice guidelines and provides a structured approach to evaluate clinical research data. On its website, ESMO has an open access searchable portal detailing >230 clinical studies (Scorecards) assessed using the ESMO-MCBS.[4] Internationally, a high ESMO-MCBS score is currently valued and adopted by the World Health Organization Essential Medicines List (WHO EML) and Health Technology Assessment bodies worldwide. These global health applications underscore the importance of the ESMO-MCBS commitments to 'accountability for reasonableness' and continual efforts to improve the scoring process's validity. ESMO-MCBS scores assume valid research methodologies and high-quality trial implementation. Studies that incorporate flawed design, implementation, and/or data analysis may generate biased outcomes and conclusions that exaggerate real benefit and are not generalisable. This subverts the intention of the ESMO-MCBS to give representative grading to the benefit observed in generalisable data and compromises its integrity. Therefore, as part of the ongoing commitment to improving the validity of the scoring process, we undertook a review of trial design, implementation, and analysis issues that could bias the results and reviewed the adequacy of the ESMO-MCBS v1.1 to address these issues and identify shortcomings to redress in future revisions.

METHODOLOGY

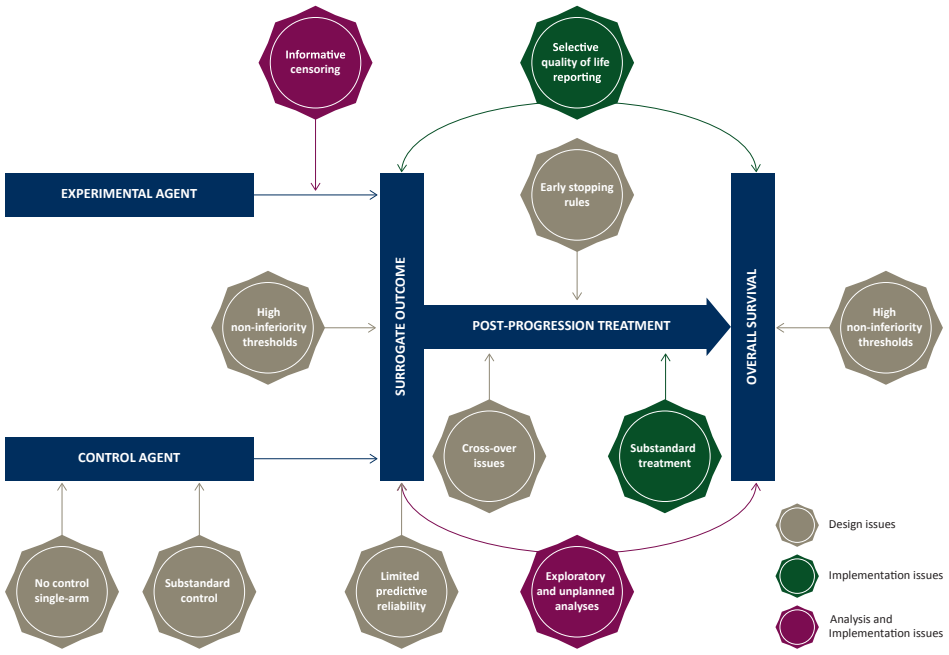
Based on experience in evaluating the magnitude of benefit in clinical studies, ESMO-MCBS Working Group and Extended Working Group members (all listed in authorship) identified issues in study design, implementation, and data analysis that may influence study outcomes and compromise the veracity of the ESMO-MCBS scores. We conducted a review for each of these issues, including definitions, relevant policy documents derived from regulatory authorities, relevant literature, and illustrative studies. The policy documents included the

World Medical Association Helsinki Declaration for Ethical Principles for Human Research,[5] and guidelines from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),[6-8] the Food and Drugs Administration (FDA),[9-11] the European Medicines Agency (EMA),[12-14] and the European Network for Health Technology Assessment.[15-19] For each issue we reviewed the ESMO-MCBS v1.1 approach to identify shortcomings of the scale to adequately address and document the corresponding sources of bias.

RESULTS

Design issues Six issues in study design that could bias benefit evaluation were considered (Figure 1).

Figure 1. Issues in study design, implementation, and data analysis that may influence study outcomes and compromise the ESMO-MCBS scores. HR, hazard ratio; NI, non-inferiority; QoL, quality of life.



Substandard control arm

Rationale: Data derived from studies with a comparator (control) arm inferior to the standard of care (SOC), may bias the outcome by generating a larger benefit than if SOC had been used.[8,10,12,16] *Regulations*: According to the Helsinki Declaration,[5] the comparator arm of a randomized, clinical trial (RCT) must be 'the best-proven intervention(s)'. The ICH guidelines

emphasize the importance of using appropriate dosing and scheduling of the control.[8] The Helsinki Declaration allows two exceptions[5] : (i) when no proven intervention exists and (ii) when there are compelling and scientifically sound methodological reasons for using a less than best-proven control therapy. The Helsinki Declaration allows the use of placebo, no intervention, or a lesser SOC if deemed necessary to determine an intervention's efficacy or safety. However this is only permitted on the condition that subjects receiving the control arm will not be subject to additional risks of serious or irreversible harm. The guidelines add the admonition that 'extreme care must be taken to avoid abuse of this option.' For non-inferiority (NI), the ICH emphasizes that the control arm should comprise 'a drug acceptable in the region to which the studies will be submitted (for licensing) for the same indication'. [6] Therefore, it is incumbent upon researchers to demonstrate that the control arm is consistent with the SOC at study initiation or that any deviation is adequately justified. The justification must present compelling and scientifically sound methodological reasons for the deviation and that participants will not be subject to serious harm. Institutional Review Boards (IRBs) are responsible for ensuring compliance with these conditions.[5] For registration trials, this adjudication is often guided by the regulatory agencies themselves.

***Illustrative case*:** The NEMO study in treatment-naive or pretreated patients with advanced NRAS-mutated melanoma randomized 402 participants in a 2 : 1 ratio, between August 2013 and April 2015, to receive binimetinib or dacarbazine.20 Seventy-nine percent of the participants were treatment-naive. Dacarbazine, the control arm for treatment-naive patients, was already proven to be inferior to ipilimumab immunotherapy plus dacarbazine.[21] Ipilimumab monotherapy was subsequently licensed as first-line treatment in 2011 by both the EMA22 and FDA.[23] Consequently, patients in the control arm were deprived of the best, licensed upfront treatment, and in the first-line setting the marginal benefit of binimetinib was only demonstrated relative to a suboptimal comparator.

ESMO-MCBS v1.1: ESMO-MCBS relies on the integrity of the IRB and regulatory agencies to evaluate the control arm's adequacy.

***Shortcoming**:* The ESMO-MCBS does not independently evaluate the control arm's appropriateness, nor does it have a mechanism to either indicate or penalize studies with a substandard control arm.

The predictive reliability of surrogate endpoints

Definitions: Surrogate outcome endpoints provide an indirect measurement when direct measurement of clinical effect is not feasible or practical.[8] While they aim to predict clinical benefits such as prolonged survival or improved quality of life (QoL), the reliability and strength of surrogates' predictive capacity vary.[24] The effect of an improved surrogate endpoint may not directly benefit the patient.[24] Commonly used surrogate outcomes in cancer trials include a decrease in tumour size response rate (RR) and delays in tumour progression [progression-free survival (PFS); disease-free survival (DFS)].[10,12,19]

***Limitations of surrogate outcomes**:* The validity of a surrogate outcome depends on its reliability as a predictor of true clinical benefit, i.e. longer survival or improved QoL.[8,10,12,19] Hitherto, no outcome measure in oncology has been found to have absolute surrogacy for true clinical benefit across diseases and treatments.[25-29] As stated by the ICH, there is concern that they may not reliably predict clinical benefit.[7] Evaluation of DFS as a surrogate for overall survival (OS) in adjuvant therapy studies, found that predictive reliability is variable across diseases and, overall, it is at best characterised as moderate.[25,27,30,31] Even within the same tumour type, there may be differences in predictive reliability of DFS based on tumour subtypes: for example, DFS is a better surrogate for OS in HER2-positive breast cancer than for other breast cancer subtypes.[30] In studies evaluating therapies in non-curative settings, PFS and time to progression provide information about the biological activity and may indicate the possibility of benefit to patients.[29,32] However, they are not reliable surrogates for improved OS [31-36] or QoL [36,37] in all patients. RR and pathological complete response (pCR) rate are also weak predictors of improved OS.

***ESMO-MCBS v1.1**:* ESMO-MCBS v1.1 considers surrogacy in its weighting. Using ESMO-MCBS form 1, DFS scores are only creditable in the adjuvant setting if OS data are immature. If mature OS results do not demonstrate benefit, surrogacy is not confirmed, and the study is considered to not provide evaluable benefit (labelled 'No evaluable benefit'). Studies showing benefit based on pCR are credited at the lowest level, C, and only if a relatively high threshold marginal benefit is demonstrated. In the non-curative setting, when the primary endpoint is PFS or RR, several stringencies are applied. The preliminary grades are capped: for studies using PFS as primary endpoint at 3 and for RR at 2, with penalties for adverse effects. Furthermore, when PFS is the primary endpoint a non-significant OS gain at mature follow-up and QoL evaluation indicating neither improvement nor delayed deterioration is considered as refutation of surrogacy, and the score is downgraded by one point.

Shortcoming: Hitherto, in v1.1, it was assumed that DFS did not confer patient benefit independent of OS. The approach of ESMO-MCBS v1.1 to the grading of DFS was recently reviewed and considered unreasonable.[38] Patients and other stakeholders appealed that the ESMO-MCBS approach to DFS does give credit to the benefit of added time without treatment or the burden of disease for a proportion of patients independent of any impact (or lack thereof) on mature OS.[39] This is illustrated by the meta analysis of trastuzumab in HER2 overexpressed, hormone receptor-negative early breast cancer with less than two involved nodes. After a median of 8 years follow-up, there was a 5.9% gain in DFS, but the OS gain was not significant.[40] The ESMO-MCBS Working Group has concluded that DFS is an intermediate endpoint (i.e. a surrogate endpoint that may also directly have some patient benefits) that is worthy of a lower but persistent credit if OS benefit is not achieved. This consideration is incorporated in the draft revision of the ESMO-MCBS v2, and it is currently undergoing field testing and review.

Crossover

Definitions: In an RCT, crossover implies patients randomised to the control arm of the trial get the intervention allocated to the experimental arm upon disease progression. Crossover has methodological and ethical implications, depending on the medicine and line of therapy.[41,42] When a medicine has already been approved, is the SOC for later lines, and is being evaluated for an earlier line, the trial design should incorporate crossover. This is called appropriate or desirable crossover.[41,43] In such situations, since the experimental therapy is part of subsequent standard care, the clinical question is whether using the same drug earlier improves OS versus using it later in the disease course. Failure to incorporate crossover in this setting harms participants on the control arm by not ensuring that they receive optimal post-progression therapy and may exaggerate the observed OS benefits. If a medicine, never approved for a condition, is being tested in a trial, then crossover design is generally undesirable.[41-43] Since the new medicine's efficacy is unknown, there is no ethical mandate for the control arm patients to receive the medicine upon relapse.[42] Furthermore, crossover in this setting undermines the ability to determine the impact of the intervention on OS, and if crossover delays initiation of proven subsequent therapies, it may adversely impact patient well-being. For these reasons, crossover in this setting is discouraged by the EMA and FDA.[10,12]

Illustrative cases: Failure to incorporate appropriate crossover. Abiraterone acetate was approved for use in patients with chemotherapy-naive metastatic castrationresistant prostate cancer (CRPC) in 2012 and has become the SOC in that setting based on the COU-AA-302 trial showing prolonged OS.[44,45] Between 2013 and 2014, abiraterone was tested versus placebo in chemotherapy-naive patients with castration-sensitive prostate cancer in the LATITUDE trial.[46] In that study, only 11% of patients on the placebo arm received abiraterone upon progression to CRPC. A substantial OS benefit {hazard ratio (HR) 0.66 [95% confidence interval (CI): 0.56-0.78]} generated a high ESMO MCBS score of 4. However, due to the lack of crossover, we do not know whether using abiraterone earlier while the tumour is castration-sensitive is better than using the same drug while castration-resistant. Furthermore, since abiraterone had improved OS for patients with CRPC, the control arm patients were potentially harmed by not receiving a proven post-progression therapy.

***Incorporation of undesirable crossover**:* In the IMPACT trial, which randomised patients with low volume metastatic CRPC to the autologous dendritic cell therapeutic vaccine sipuleucel-T, or placebo,47 patients who progressed on the control arm were allowed a frozen version of the vaccine, even though its efficacy had not been proven. Outside the trial, these patients would have immediately received docetaxel chemotherapy that had previously demonstrated survival advantage and improved QoL in this setting.[48] In the study, treatment with sipuleucel-T did not affect RR or PFS compared with placebo, but it was associated with improved OS. The crossover of 64% patients in the control arm to the frozen vaccine version confounded interpretation of the findings since it was uncertain whether

prolonged survival was because of treatment efficacy in the experimental arm or delayed access to docetaxel in the control arm.[49]

ESMO-MCBS v1.1: ESMO-MCBS Scorecards indicate whether crossover is allowed or not allowed.

Shortcoming*:* The ESMO-MCBS does not have a mechanism to either indicate or penalise studies with inappropriate or inadequate crossover.

Early stopping of clinical trials

Definition*:* Early stopping rules allow for a study to terminate earlier than planned, with all patients crossing to the superior therapy, because of the result of an interim analysis showing larger than expected benefit or harm of the experimental intervention that adequately undermines equipoise.[8,12] These stopping boundaries are stringent and based on solid statistical methodology.[8,12] Cancer drug trials may be stopped early based on an interim analysis of time-to-event probability (DFS, PFS, or OS) when the HR crosses the stopping boundary.

Concern*:* Under the statistical rules applied, trials that are stopped early may overestimate the magnitude of benefit. The sooner the trial is stopped, the more impressive the HR will look since the stopping criteria are more stringent early in the trial course.[50] Hence, although the medicine is likely effective, the true benefit may be smaller in magnitude. Such over-estimations of the treatment effect's magnitude are particularly important when the primary endpoint is not a definitive endpoint like OS but a surrogate endpoint such as PFS.[50]

ESMO-MCBS v1.1: In solid tumours, PFS is scorable only if the median PFS of the control arm has been reached. Consistent with EMA guidance,[12] there is no extra credit for early stopping based on PFS. If, however, early stopping is triggered by interim analysis of OS gain meeting prespecified statistical criteria, the gain already credited for PFS in the preliminary score is upgraded by one point.

Shortcoming*:* None identified.

Inflated RRs and durations in single-arm trials

Definitions: In settings where there is no available therapy and where measurable reduction in tumour size meeting the RECIST criteria [51,52] can be attributed to the tested medicine, regulatory authorities often accept overall RR (ORR) and duration of response (DoR) derived from single-arm studies as adequate evidence supporting accelerated approval,*[10,12,17]* and occasionally full (regular) approval.

Limitations of single-arm studies: Studies have shown that ORR and DoR in single-arm trials are higher than the ORR and DoR when the same medicine for the same indication is tested in an RCT.[53,54] Furthermore, ORR is a poor surrogate for OS or QoL.[25,30]

ESMO-MCBS v1.1: The scoring of single-arm studies using the ESMO-MCBS form 3 applies two stringencies. The preliminary score for single-arm studies is capped at 3, and penalties are applied for adverse events. The score may be upgraded by one point if the findings are confirmed in a phase IV study or cancelled if accelerated approval is subsequently withdrawn.

Shortcoming: None identified.

NI design trials

Definition*:* In some cases, an investigational product is tested not to show superiority over the SOC but to demonstrate that for the primary outcome, the new agent is not worse than the active control by more than a prespecified small amount, known as an NI margin.[8,10-12] Benefit from the novel agent is demonstrated if it is less burdensome, less expensive, if it has less adverse effects, or if associated with improved QoL.[53] Defining the NI margin is critical. According to ICH standards, the NI margin, expressed by an upper limit of the 95% CI for the relevant endpoint, is the largest difference that can be judged as clinically acceptable. Moreover, it should be less than the gain observed in superiority trials of the active comparator.[8]

Non-adherence to the assigned treatment is particularly problematic in NI studies since it will bias the study toward concluding NI.[11] Consequently, monitoring treatment adherence by investigators and by the independent datamonitoring committee is crucial in these studies. Therefore, unlike superiority studies, both an intention-to-treat (ITT) analysis and a per-protocol analysis are required by the FDA and EMA for NI studies.[8,11,14,55,56]

Concerns regarding NI margin: If the defined NI margin is too lenient, there is a concern that treatments with true inferiority may seem non-inferior. Regretfully, the biostatistical rules for defining NI have not been standardised.[57] A recent analysis showed that cancer medicine trials used an NI threshold as high as 1.[33] for the upper limit of the 95% CI for the HR of OS.53 Consequently, it is plausible that if NI definitions are too lenient, NI may be credited even when substantial differences in the treatment arms exist. If a previous superiority trial has demonstrated gains, a substantial percentage of these gains must be preserved.

ESMO-MCBS v1.1: ESMO-MCBS relies on IRB processes' integrity to evaluate the validity of the NI thresholds. NI studies can be scored using the ESMO-MCBS form 1 in the adjuvant setting (grade B) and form 2c in the advanced setting (grade 4). The ESMO-MCBS v1.1 only credits NI design trials if NI is confirmed according to pre-specified statistical criteria and if the study demonstrates benefits of reduced costs, adverse effects, or benefits in global QoL. NI alone is not the basis for any credit of benefit.

Shortcoming: ESMO-MCBS does not have rules to determine the validity of the pre-specified NI margin. Study implementation issues Two issues of study implementation and reporting were considered: (1) the impact of post-progression subsequent treatments on OS and (2) the publication bias in the reporting of QoL data (Figure 1).

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Shortcoming: ESMO-MCBS does not have rules to determine the validity of the pre-specified NI margin.

Study implementation issues

Two issues of study implementation and reporting were considered: (1) the impact of post-progression subsequent treatments on OS and (2) the publication bias in the reporting of QoL data (Figure 1).

Post-progression subsequent therapies

Definition: Most RCTs involve evaluating a single period of randomisation between a novel treatment and an active control. In studies of first- or second-line therapies in solid tumours, most patients will subsequently receive one or more lines of post-progression treatment,

which influences OS.[58] In some settings, such as hormone-responsive breast cancer, it is not uncommon for patients to receive more than five subsequent therapy lines.[59] When patients receive optimal post-progression therapy, any advantage gained by the experimental treatment may be impacted by subsequent therapies.[58] When the PFS gain is maintained or even improved after optimal post progression therapies and reflected in an OS gain, the benefit is recognized as being important. However, when PFS gains are diluted after optimal post-progression therapies and reflected in no significant OS gain, the benefits may be relatively trivial. This, however, is not the case when patients also derived qualitative benefits such as delayed deterioration or improvement in QoL.[33]

Regulations: The ICH guidelines state that efforts should be made to collect all data pertinent to the relevant outcomes, including the occurrence and timing of intercurrent events.[7] They emphasise that clinical trials are less generalizable if the sponsor tries to avoid or minimize these issues. Post-progression treatments constitute an intercurrent event that is pertinent to OS.[58] While some degree of attrition may be expected post-progression, the acceptable thresholds should be judged based on previous experiences from real-world studies.

Concerns regarding post-progression treatments: Failure to provide optimal post-progression treatment can exaggerate the impact of a PFS gain on OS even when both arms receive the same suboptimal therapies.[41,58,60] This underscores the importance of documenting post-progression subsequent treatments until death as part of routine follow-up data.[58]

Illustrative case*:* The MONALEESA-7 study evaluated hormonal therapy with ribociclib or placebo in the first- or second-line treatment of premenopausal women with estrogen receptor-expressing breast cancer.[61] Patients receiving ribociclib had a PFS gain of 10.8 months. A planned interim analysis of OS at 76% of anticipated deaths showed a large OS gain that met pre-specified significance thresholds. Applying ESMO-MCBS v1.1, the MONALEESA-7 study achieved a preliminary score of 4, which was upgraded to 5 after QoL data demonstrated delayed deterioration in global QoL.[62] The paper indicated that 26.8% of the patients in the control arm and 31.1% of patients in the ribociclib arm received no further subsequent treatments at disease progression after the first line of therapy.[61] Although some degree of attrition is expected with each subsequent line of therapy, nearly one-third of patients not getting any subsequent therapy post first-line is an astoundingly aberrant figure given that most women with estrogen receptor positive HER2-negative breast cancer routinely survive for >2 years after first progression and generally receive four subsequent lines of therapy or more.[59] This major divergence from SOC for a substantial proportion of patients renders the OS data from this study non-generalisable. Indeed, it is plausible that the failure to provide subsequent standard therapy to more than a quarter of the patients who progressed on the study may have exaggerated the OS gain from ribociclib compared with placebo.

Shortcoming*:* The ESMO-MCBS does not indicate or penalise studies in which OS benefit may have been exaggerated by substandard post-progression treatment.

Publication bias in the reporting of QoL data

Definition*:* Publication bias occurs when the outcome of an experiment or research study influences the decision to publish or otherwise distribute it.[63]

Publication bias in QoL results*:* QoL data remain missing for many trials.[64] Most QoL data from trials go unpublished or are substantially delayed, even when the primary study results are positive.[65]

ESMO-MCBS v1.1: When QoL is evaluated as a secondary outcome in clinical studies, the generated results impact ESMO-MCBS scoring. When the QoL benefits are reported in studies applying a valid scale, with an adequately complete dataset and using valid statistical criteria, ESMO-MCBS scores are upgraded one point for evaluations in the non-curative setting. When the primary outcome is PFS with secondary outcomes of OS and QoL, and the subsequent mature OS does not demonstrate any survival advantage, the surrogacy of the PFS finding is dependent on the QoL results. In this scenario, a negative QoL finding without improvement or delayed deterioration in global QoL results in readjusting the score with a one point downgrade. Failure to publish negative QoL results or substantial publication delay subverts this important score adjustment.

Shortcoming*:* ESMO-MCBS does not address nonpublication or delayed publication of QoL data.

Issues related to analysis of trial data

Two issues related to the analysis and interpretation of trial data were considered: (1) conjectural findings from exploratory and unplanned analyses and (2) informative censoring (Figure 1).

Conjectural findings from exploratory and unplanned analyses

Definition: A conjecture is an unproven proposition suspected to be true based on preliminary supporting evidence. 'Conjectural findings' relate to the evaluation of efficacy based upon incomplete or suboptimal data. These include findings from post hoc subgroup analyses or exploratory analyses outside of the statistical plan. 'Conjectural findings' contrast with 'confirmatory finddings' derived from primary analysis in a study with a prespecified and justified statistical plan and a significant positive outcome.[8] In many instances, subgroup analyses with appropriate adjustment for multiplicity of testing and alpha splitting are part of the planned confirmatory analysis and are incorporated into the statistical plan.[8] The EMA guideline on the investigation of subgroups in confirmatory clinical trials[13] describes two types of conjectural analyses: (i) when the evidence of benefit in the primary analysis population is statistically significant but of small magnitude, it is of post hoc interest to identify and to distinguish between subgroups more or less likely to derive clinically meaningful benefit, and (ii) when a study fails to establish statistically significant evidence of benefit in the primary analysis population, and there is interest in identifying a subgroup where the treatment may be effective.

Concerns: Conjectural findings increase the probability of false-positive findings, i.e. the magnitude of clinical benefit is falsely concluded to be greater than in the primary analysis population.[9,13] False-negative conclusions, in which a subgroup is inaccurately identified as being unlikely to benefit, are equally important.

Regulations: The ICH guidelines,[8] endorsed by FDA and EMA, exhort that findings from post hoc subgroup analyses should be interpreted cautiously. The EMA guideline outlines a structured approach to conjectural evaluation based on (i) external evidence that the subgroup of interest is well defined and clinically relevant, (ii) plausible explanation for different efficacy (or risk benefit) in a sub-population and its complement, (iii) substantially different results and, when possible (iv) replication of similar subgroup findings from other relevant trials.[13] In a draft guideline that is not yet ratified,[9] the FDA expresses the concern that investigators' or sponsors' incentives can influence the choice of analyses to identify one or more positive findings.[9]

ESMO-MCBS v1.1: The ESMO-MCBS v1.1 distinguishes confirmatory findings, based on the pre-specified endpoints and statistical plan, and conjectural findings, based on post hoc and exploratory analyses. Confirmatory findings of clinical benefit, including pre-specified subgroups, are scored. The ESMO-MCBS v1.1 constrains the number of pre-specified subgroups (no more than 3) and allows separate subgroups grading when adjusted for multiplicity. Conjectural findings based on post hoc subgroup analyses and exploratory endpoints are not eligible for scoring by the ESMO-MCBS v1.1. An exception is made for studies that incorporate tissue samples collection to enable restratification based on plausible new genetic or other biomarkers. When conjectural findings form the basis for regulatory approval, the ESMO Clinical Practice Guidelines and E-Updates' approach is to present the ITT and planned subgroup data and scoring in the tables. The relevant conjectural data relating to the regulatory approval are discussed in the text and annotated below the ESMO-MCBS tabulations.

Illustrative cases: The APHINITY trial[66] tested adjuvant pertuzumab in patients with HER2-positive breast cancer and showed marginal gains in DFS for the ITT population. The publication, however, reported the findings of 12 post hoc subgroup analyses and highlighted better outcomes among patients who had node-positive disease. In this case, the ESMO-MCBS v1.1 scored only the ITT (score B) results and not the post hoc subgroup findings. More recently, atezolizumab was tested combined with nab-paclitaxel in triple-negative breast cancer in the IMpassion130 trial.[67] The median PFS was improved by 1.7 months in the ITT population and by 2.5 months in patients with programmed death-ligand 1 (PD-L1)-positive tumours compared with nab-paclitaxel alone. There was no difference in OS in the ITT population. The statistical plan incorporated hierarchical testing, which allowed evaluation of OS in the PD-L1-positive subgroup only if there was OS benefit in the ITT population. An exploratory analysis of the PD-L1- positive subgroup found an OS improvement of 10 months. The ESMO-MCBS v1.1 only scored the PFS result of the PDL1-positive subgroup, since the OS data were derived from an exploratory analysis outside of the statistical plan. Two examples illustrate the importance of the ESMO-MCBS exception for post hoc subgroup findings based on enabling restratification based on plausible new genetic or other biomarkers. The IPASS trial identified the importance of the EGFR mutation status for treatment with gefitinib,[68] and the PRIME [69,70] and CRYSTAL[71] studies identified the importance of RAS/RAF status for anti-EGFR therapy in metastatic colorectal cancer.

Shortcoming: The ESMO-MCBS does not explicitly state that the exception for post hoc subgroup findings based on plausible new genetic or other biomarkers is restricted to findings resulting into a modification in licensed indication.

Informative censoring

Definition: In clinical trials, the term 'censoring' refers to patients who do not complete the study in full and drop out without further measurements.[72] When dropouts are balanced between the two arms of a comparative superiority study, it is assumed that this does not impact the results. This is called 'uninformative censoring'. When patients discontinue for reasons related to the study drug, including lack of effect or side-effects, this assumption does not hold, and this is referred to as 'informative censoring.' [72]

The problem of informative censoring: In studies using the surrogate outcomes of DFS and PFS, patients who stop treatment before documentation of disease progression for reasons other than death are at risk of no longer being evaluated. When censoring is greater in patients receiving the experimental therapy than in the control arm, censoring poorly performing patients may exaggerate the benefit seen in these outcome measures.[72-74] Four approaches to mitigate this bias are described, including (i) encouraging OS rather than surrogates as the primary endpoint, (ii) comparing PFS/DFS gains with time-to-treatment-failure (TTF) differences, which includes discontinuations as failures, (iii) listing the reasons for censoring, and (iv) providing best-case (assuming all censored patients do not have disease progression) and worst-case (assuming all censored patients have progressed) sensitivity analyses.[72-74]

Regulatory requirements: The ICH guidelines address this issue, stating that 'the frequency and type of protocol violations, missing values, and other problems should be documented in the clinical study report and their potential influence on the trial results should be described'.[8]

Illustrative cases: The BOLERO-2 study of exemestane combined with everolimus or placebo in hormone-positive advanced breast cancer[75] reported a 6.5 months benefit in median PFS with HR 0.36 (95% CI, 0.27-0.47) for patients receiving everolimus. This result was reasonably impacted by informative censoring since 19% patients in the everolimus arm discontinued treatment due to adverse effects versus 4% in the placebo arm (since treatment discontinuation due to adverse effects does not count as a PFS event). Reanalysing the study data using TTF which considers progression or discontinuation as well as death, the median gain in TTF was only 1.1 months[76] and the difference in OS, which is based on ITT analysis, was not significant.[77]

ESMO-MCBS v1.1: ESMO-MCBS v1.1 does not evaluate the causes and rates for censoring when evaluating trials with DFS or PFS primary endpoint. The draft revision of the ESMO-MCBS v2, currently undergoing field testing and review, incorporates a 1-point downgrade for PFS studies where there is a difference of 10% in prevalence of treatment discontinuations for adverse effects.

Shortcoming: The ESMO-MCBS does not account for the impact of informative censoring on scores based on DFS.

DISCUSSION

The ESMO-MCBS scores assume valid research methodologies and high-quality trial implementation, and freedom from publication bias. To promote the integrity of the ESMO-MCBS scoring, there is a need to discern valid and biased research. Consequently, new approaches are needed to indicate or penalise studies with deficiencies in their research methodologies, trial implementation, analysis or publication strategy that may contribute to biased outcomes and conclusions.

Table 1. The necessary preconditions for a valid study

1. Clinically relevant and appropriate hypothesis (primary outcome, targeted magnitude of benefit, secondary outcomes, type I and II errors)
2. Appropriate study design
3. In comparative studies: an adequate control arm that is consistent with the contemporaneous standard of care at the time of trial initiation
4. Inclusion and exclusion criteria that optimise the balance between generalisability and participant safety
5. Completeness of data collection
6. Valid statistical plan and adherence to that plan
7. When overall survival is either a primary or secondary outcome, postprogression treatment demonstrably consistent with the contemporaneous standard of care
8. Analysis of data that clearly distinguishes between confirmatory findings and conjectural conclusions

The necessary preconditions for a valid study are outlined in Table 1. The ESMO-MCBS already addresses some of these issues in version 1.1 and its upcoming revisions. The ESMO-MCBS only scores studies with a clinically relevant hypothesis and statistically significant findings consistent with a valid pre-specified statistical plan. When indirect surrogate outcomes are used, the scale incorporates additional precautions and caps to minimise the risk of exaggerated claims of benefit unless surrogacy is verified. Regarding the QoL data, the Working Group is collaborating with partners in the European Organization for Research and Treatment of Cancer (EORTC) to refine new strategies to restrict credits to findings based on robust methodology and adequately complete datasets.

This review has identified seven shortcomings in the ESMO-MCBS approach to potential sources of bias in clinical studies that will need to be addressed in the future development of the scale:

1. The ESMO-MCBS does not independently evaluate the control arm's validity, nor does it have a mechanism to identify to either indicate or penalise studies with a substandard control arm. This is relevant to all ESMO-MCBS forms evaluating comparative studies.
2. The ESMO-MCBS does not evaluate crossover, its appropriateness, and when appropriate, its adequacy. This is relevant to scores derived from OS data using form 2a.
3. The ESMO-MCBS does not have discriminatory rules to determine the pre-specified NI margin validity. This is relevant to form 2c.

4. The ESMO-MCBS does not indicate or penalise studies in which OS benefit may have been exaggerated by substandard post-progression treatment. This is relevant to scores derived from OS data using form 2a.
5. The ESMO-MCBS exception for post hoc subgroup findings based on enabling restratification based on plausible new genetic or other biomarkers is not explicitly restricted to biomarkers generating a modification in licensed indications. This is relevant to the instructions regarding the use of forms 1 and 2.
6. The ESMO-MCBS does not indicate or penalise trials with differential rates of informative censoring in studies graded based on DFS. This is relevant to form 1.
7. ESMO-MCBS does not address non-publication or delayed publication of QoL data. This is particularly relevant to form 2b.

These issues will be addressed in future iterations of the ESMO-MCBS. The ESMO-MCBS Working Group will consider all potential options and would appreciate stakeholder feedback in this process. Options include developing a checklist for evaluating these issues, using annotations to indicate flawed studies, or possibly applying a downgrade to ESMO-MCBS scores.

Nevertheless, the appropriate interpretation of the ESMO-MCBS scores requires the critical appraisal of trials to understand these issues in trial design, implementation, and data analysis that may have biased the results and conclusions. The ESMO-MCBS facilitates unbiased evaluation of the magnitude of clinical benefit from cancer medicines, however, like all tools, its utility lies in the hands of the user. The ESMO-MCBS does not obviate the need to think critically about cancer medicine trial designs, and users should consider all these issues when appraising and scoring any clinical trial.

Acknowledgements

The authors wish to acknowledge the editorial and organisational support provided by Nicola Latino ESMO Head of Scientific Affairs and Martina Galotti ESMO Scientific Affairs Specialist.

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PART V

Discussion

Chapter 9

General discussion and future perspectives

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

The prognosis of multiple myeloma (MM) has improved considerably during the last decades. This improvement has been achieved by the development of new treatment modalities, such as immunomodulating agents (IMiDs), proteasome inhibitors (PI's), monoclonal antibodies and recently the introduction of chimeric antigen receptor T (CAR-T) cell therapy and treatment with bispecific T-cell engagers (BiTEs). Despite this major improvement in prognosis, MM remains an incurable disease and relapse almost always occurs. Moreover, treatment in patients with MM is accompanied by side effects which may have a permanent character. Therefore, the need for improvement of treatment remains. The objectives of this thesis were to evaluate several recent aspects of MM treatment:

1. Prospective clinical trials:
   a. To investigate dosing regimens of carfilzomib and the role of treatment duration in transplant eligible (TE) newly diagnosed MM (NDMM)
   b. To evaluate the value of addition of consolidation treatment in TE NDMM
2. To investigate different treatment regimens in patients with relapsed/refractory MM (RRMM) with emphasis on IMiDs.
3. To outline the underlying mechanism of action of IMiDs.
4. The development of a tool to determine the true value of new treatment modalities.

PART II: PROSPECTIVE CLINICAL TRIALS

In chapter 2 and 3 the Carthadex trial was presented. Patients were treated with the combination of carfilzomib, thalidomide and dexamethasone (KTd).[1-3] Carfilzomib is a second generation PI, already approved in combination with dexamethasone or lenalidomide and dexamethasone in RRMM. In the ASPIRE trial patients were randomized between treatment with carfilzomib, lenalidomide and dexamethasone (KRd) or lenalidomide and dexamethasone (Rd).[4] In this trial a longer PFS and OS was reported for patients treated with KRd. Median progression free survival (PFS) was 26.1 months (95% CI, 23.2 to 30.3 months) in the KRd group versus 16.6 months (95% CI, 14.5 to 19.4 months) in the Rd group (HR, 0.66; 95% CI, 0.55 to 0.78; (P=0 .001).[4] In the ENDEAVOR trial, patients were randomized between treatment with carfilzomib and dexamethasone (Kd) or treatment with bortezomib and dexamethasone (Vd), demonstrating a a longer PFS and overall survival (OS) in patients treated with Kd. Median PFS was 18.7 months (95% CI 15·6–not reached) for Kd versus 9.4 months (8·4–10·4) for Vd (hazard ratio [HR] 0·53 [95% CI 0·44 –0·65]; p<0·0001).[5] Moreover, in Kd rates of polyneuropathy (PNP) were lower. Based on these results, carfilzomib was approved as second line treatment in patients with RRMM. Besides response and survival, side effects are an important factor in developing new treatment modalities. The main clinical adverse effects with carfilzomib are dyspnea, hypertension and cardiac toxicities.[6] However, with adequate management and selection of patients, treatment with carfilzomib is well tolerated.

Carfilzomib has not yet been approved in NDMM. Moreover, the optimal dose of carfilzomib was never prospectively investigated and different dose levels were used in several trials. Jakubowiak et al. performed a phase 1/2 study treating patients with KRd with carfilzomib dosage of 27 mg/m2 or 36 mg/m^2.[7] Treatment was well tolerated with limited dose modifications, even at the higher dosage of 36 mg/m^2. In the ENDURANCE trial, patients were randomized between treatment with KRd (with carfilzomib dosage of 36 mg/m2) versus bortezomib, lenalidomide and dexamethasone (VRd).[8] The KRd regimen did not improve PFS compared with the VRd regimen. Moreover, patients treated with KRd experienced more toxicity (mainly cardiotoxicity). In the FORTE trial patients with NDMM were treated with the combination of carfilzomib, cyclophosphamide and dexamethasone (KCd) or KRd (with carfilzomib dosage of 36 mg/m2) with or without autologous stem cell transplantation (ASCT).[9] Toxicity and especially cardiac toxicity was lower in this trial compared to the cardiac toxicity in the ENDURANCE trial, possibly due to the inclusion of patients not intended for ASCT in the ENDURANCE trial, which is a population of older age. However cross comparison between trials should be interpreted with caution.

The Carthadex trial is the only trial which investigated different dose levels of carfilzomib in NDMM patients. In this trial efficacy was observed to be higher with all three dose levels above 27 mg/m^2 of carfilzomib, while toxicity remained the same. Therefore, we

recommended a minimum dosage of carfilzomib of 36 mg/m2 twice a week. However, because of the limited number of patients and the fact that this was not a randomized trial the discussion about the optimum dose level of carfilzomib remains. For this reason, EMA has not approved Carthadex in first-line treatment of patients with NDMM. This is unfortunate, because carfilzomib generates high response rates accompanied with less polyneuropathy than can be observed with bortezomib treatment, even in combination with thalidomide and dexamethasone. When we compare data from carthadex versus the landmark study of Cavo et al., in which patients were treated with bortezomib, thalidomide and dexamethasone (VTd) versus thalidomide/dexamethasone (Td), PFS in patients treated with KTd was higher than with VTd.[10] Again, cross comparison between trials should be interpreted with caution. It is expected that this regimen will combine higher efficacy with less adverse effects such as polyneuropathy than what is observed with standard VTd.

Currently, ongoing studies combine carfilzomib with a number of other agents in patients with NDMM. In the EMN24/ISKIA trial, patients with NDMM were randomized to receive treatment with KRd with or without isatuximab, a CD38 antibody. This trial has completed accrual and results are expected in the coming years. The efficacy of Isa-KRd in high-risk TE NDMM was demonstrated in the phase II GMMG-CONCEPT trial. The interim analysis of the first 50 patients showed a two-year PFS rate of 75.5% with a median PFS not reached.[11] Moreover, Tan et al. performed a retrospective analysis in patients with high-risk NDMM treated with KRd versus VRd. The median PFS for HR-NDMM patients treated with VRd induction was 42.6 months (95%CI, 32.8-62) and was NR (95%CI, 45.5-NR) for the KRd group (HR=1.84; 95%CI, 1.11-3.06; P=0.02).[12]Therefore, carfilzomib may be specifically effective in the treatment of patients with high-risk NDMM.The second clinical trial described in chapter 4 of this thesis is the HOVON95/EMN02 trial. This trial investigated two important questions. The first question adressed the role of high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT) versus continuous treatment without HMD/ASCT. The second question concerns the additive efficacy of consolidation treatment. In this thesis we focused on the role of consolidation. While many treatment regimens have incorporated consolidation therapy already as a standard treatment, there are no prospective trials comparing consolidation versus no consolidation in a well defined population. Therefor, the important question is whether consolidation therapy improves PFS in NDMM.

In the HOVON95/EMN02 trial, patients were randomized to be treated with continuous conventional therapy versus high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT). Hereafter, after a second randomization patients received two cycles of VRD consolidation versus no consolidation. All patients received lenalidomide maintenance.[13, 14] The impact of consolidation treatment on PFS and survival was investigated. In this trial an improvement in PFS and OS in patients with consolidation treatment was demonstrated; median PFS was 59.3 months versus 42.9 months in patients

with no consolidation treatment([HR] = 0.81; 95% CI, 0.68 to 0.96; *P* = 0.016). At 6 years OS was 76% (95% CI, 71 to 79) with consolidation and 69% (95% CI, 64 to 73) without consolidation. [14] In the STAMINA trial patients were randomized to either treatment with double ASCT versus single ASCT and consolidation or single ASCT without consolidation. In the as treated analysis, 6 years PFS were 49.4%, 39.7% and 38.6% respectively (p=0.01). [15, 16] In the HOVON 95/EMN02 trial flow cytometry was used to analyze minimal residual disease in a specific subset of 226 patients who had achieved either complete response, stringent complete response, or very good partial response prior to starting maintenance treatment. The results revealed that 74% of patients treated with VRD showed no evidence of minimal residual disease. Nowadays consolidation has become an integrated part of the initial therapy in NDMM patients. Most clinical trials implement consolidation therapy and they all show an improvement in depth of response resulting in improvement of survival. [15, 17-20] Currently the Dutch guidelines advise to give two cycles of consolidation therapy based on the improvement in response and PFS.

PART III: REGISTRY AND CORRELATIVE STUDIES IN TREATMENT WITH IMIDS

The novel drug class of IMiDs, including thalidomide, lenalidomide and pomalidomide, has contributed to the marked improvement in outcome for patients with MM. IMiDs are widely used in the treatment of NDMM and in the relapsed/refractory setting. In chapter 5 and 6 of this thesis a registry study of pomalidomide and a translational study on the effect of IMiDs on the CRBN pathway were presented.

The registry study with pomalidomide was performed in cooperation with HOVON and with the nationwide Netherlands Cancer Registry. Registry studies are important to generate a perspective on the effectiveness of treatment in the real world clinical practice within a heterogeneous population. In clinical trials usually a selection of patients is included with strict inclusion and exclusion criteria, which are often not representative for the population treated in routine clinical practice. For instance, severe renal insufficience is an important prognostic factor in patients with MM and is also an exclusion criterium in many clinical trials. Real-world evidence may be useful in identifying groups of patients who will benefit from a specific treatment regimen. For example, Cherniawsky et al. performed a retrospective study in patients treated with lenalidomide maintenance in the real world, demonstrating similar improvement in terms of PFS and OS as shown in clinical trials.[21]

We performed a prospective analysis in a large group of heavily pretreated patients who were treated with pomalidomide/dexamethasone (Pd) as a last line of therapy which demonstrated a median PFS of 3.6 months.[22] This PFS is slightly worse compared to the PFS shown in the STRATUS trial, the MM-002 and the MM-003 registration trial.[23-25] Probably due to the fact that overall, patients treated within trials have less comorbidities and a better performance status compared to patients treated outside of clinical trials. In patients with RRMM, Pd, especially when a third drug is added, remains a good and well tolerated treatment regimen.

One of the questions is whether to treat patients with a pomalidomide containing regimen at a time when other new treatment modalities also emerge, bearing in mind that triple therapy is more effective than a two-drug regimen. However, for the great majority of patients these new regimens are not available and Pd remains the practical option. Pd was EMA approved from third line of treatment or later. In current practice most patients are treated with lenalidomide containing regimens in first or second line of treatment. Therefore, the question arises if these patients may still respond to pomalidomide as a later line of treatment. At the time of the current population study, Kastritis et al. had performed an analysis in patients treated with Pd after exposure to lenalidomide.[26] They showed comparable survival in these patients compared to clinical trials, although cross comparison between trials should be interpreted with caution.

Another important question is whether Pd is sufficient or whether adding a third drug such as cyclophosphamide to Pd improves survival in this setting. Several trials showed that adding a third drug to treatment with Pd improves response and survival. Larocca et al. performed a phase 1/2 trial, treating patients with pomalidomide, cyclophosphamide and prednisone. They showed a median PFS of 10.4 months.[27] In the PERSPECTIVE trial cyclophosphamide was added to treatment with Pd if response to Pd alone was insufficient, hereby improving ORR and PFS.[28] Baz et al. also showed an improvement in PFS by adding cyclophosphamide to Pd 4.4 months (95% CI, 2.3-5.7) in Pd versus 9.5 months (95% CI,4.6-14) in PCd.[29] Currently, the combination of Elotuzumab and Pd (EPd) is EMA approved from 3rd line of treatment based on data from the ELOQUENT-3 trial.[30] In this phase 3 trial, patients were randomized between treatment with EPd versus Pd, with a PFS of 10.3 months for EPd. Even more interesting is adding anti CD38 therapy to Pd. In the APOLLO trial daratumumab was added to Pd, improving PFS from 6.9 months to 12.4 months.[31] This regimen is now EMA approved, however not yet reimbursed in the Netherlands. Pd combined with isatuximab is approved from 3rd line of treatment based on data from the Ikaria trial showing a PFS of 11.5 months.[32] Based on these results from large clinical trials, pomalidomide has a place in the treatment landscape of MM, and preferably Pd should be combined with a third drug. Which drug this should be depends on previous therapy and development of resistance and patients choice.

Due to the fact that patients develop resistance to drugs in earlier lines of treatment, limited options remain in adding a third drug to Pd. Currently a phase 3 trial is ongoing comparing treatment with EloPd to selinexor Pd (SPd). Selinexor is a selective inhibitor of nuclear export (SINE) that inhibits XPO1.[33] XPO1 is overexpressed in MM cells.[34] The level of XPO1 is correlated to poor prognosis and therapy resistance.[35, 36] Selinexor is FDA approved in penta-refractory RRMM based on results from the STORM trial.[37] In this phase 2 trial patients were treated with selinexor and dexamethasone. Median PFS was 3.7 months. In the phase 3 BOSTON trial selinexor was combined with Vd (SVd) versus Vd alone.[38] Median PFS was 13.93 months (95% CI 11·73-not evaluable) for SVd and 9.46 months (95% CI 8.11-10.78) for Vd. Therefore selinexor may be a potent oral option for patients with RRMM.

In chapter 6 the results of a correlative study regarding IMiDs and the effect on their main target the Cereblon (CRBN) pathway were discussed. This analysis was performed by analyzing bone marrow biopsies of patients treated in the HOVON87 trial. Advantages of this study is the large series of included patients and the homogenous treatment with IMiDs. We tried to identify a practical clinical marker to better predict which patient will have a durable response and/or improvement of survival with IMiD treatment. Central to the efficacy of IMiDs is the binding to the E3 ubiquitin ligase complex component CRBN which results in the degradation of proteins Ikaros and Aiolos.[39-42] Hereby it induces immunomodulatory effects, such as secretion of cytokine IL-2 in T-cells.[43] In our study, protein expression in

the CRBN pathway (Ikaros, Aiolos, cellular myelocytomatosis oncogene (*c-MYC)*, interferon regulatory factor 4 (IRF4) and CRBN) was analyzed in primary clinical bone marrow samples obtained from patients in the clinical trial using a standardized immunohistochemical staining and scoring system.[44, 45] Previous studies showed conflicting results concerning the clinical utility of CRBN and its downstream proteins as a clinical biomarker.[46, 47] In those studies a lower CRBN level was not always associated with worse prognosis. However, other studies showed that higher CRBN expression is associated with a better response to treatment with thalidomide, lenalidomide or pomalidomide.[41, 48, 49] Our data demonstrated that a higher nuclear CRBN protein level was associated with an improvement of both PFS and OS. The question remains if CRBN is a reliable and practical biomarker in predicting response and outcome in patients with MM treated with IMiDs in clinical practice. The staining and scoring technique of CRBN is time-consuming and should be carried out in a central laboratory. In addition, previous studies showed conflicting results concerning the effect of the level of CRBN on survival. Especially because IMids are almost always combined with new agents such as anti-CD38 therapy, it is unlikely that CRBN will be used as a biomarker in guiding therapy in clinical practice. It will be challenging to determine the use of CRBN as biomarker during maintenance due to the scarcity of plasma cells at that time. Therefore, CRBN may not be useful as a practical biomarker in guiding therapy.

Another interesting and important issue is the development of resistance to IMiDs. Eventually most patients with MM develop resistance during treatment. Several mechanisms are thought to play a role in the development of IMiD resistance. IRF4 may play an important role in resistance to IMiDs. It is already known that IRF4 has an important role in the survival of myeloma cells. In vitro inhibition of IRF4 was toxic to myeloma cells.[50] Therefore, direct targeting of IRF4 may overcome lenalidomide resistance.[51] In this study we demonstrated that higher levels of IRF-4 in combination with higher levels of CRBN were associated with better survival. This should be validated in a larger cohort and in comparison with other prognostic factors such as genetic mutations which have an impact on drug resistance.

PART IV: CLINICAL BENEFIT AND IMPLEMENTATION OF TREATMENT

In chapter 7 and 8 the impact of the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) was investigated. This scale was developed initially for solid tumors. It is a validated and reproducible tool to evaluate the magnitude of clinical benefit of new and effective treatment in solid tumors and may be used as a clinical framework in assessing the clinical benefit of new treatment options.[52-54] The ESMO-MCBS grading system aims to highlight treatments that significantly improve patients' survival duration and/or quality of life (QOL) in comparison to other treatments. Its objective is to distinguish such treatments from those that demonstrate limited or minimal benefits. The scale assigns categorical benefit scores to drugs approved by the European Medicines Agency (EMA) using results from positive randomized clinical trials. These trials demonstrate statistical significance for the primary endpoint or secondary endpoints like overall survival, progression-free survival, quality of life, treatment toxicity, or response rates. The development process of the ESMO-MCBS followed rigorous standards, including field testing, statistical modeling, and peer review.[55] The question is whether this scale is also applicable in hematological diseases.

During the last two decades rapid development in research resulted in incredible expansion in therapeutic options for hematological diseases, especially for MM. These new treatment modalities often improve survival in patients but are mostly very expensive.This leads to a delay in approving these treatment modalities. Next, it is important to critically review results from clinical trials to evaluate the real impact on survival and clinical benefit in patients which explains the need for the development of a scale evaluating clinical benefit for hematological malignancies (HM). In chapter 7 we investigated the applicability of the ESMO-MBSC in HM,by extensive field testing of this scale in different HM, coordinated by EHA. This evaluation revealed that the ESMO-MBSC is applicable in most analyzed studies in a wide variety of HM. However there are differences in the behavior between oncological and HM effecting the implementation of this scale. HM behave more variable than oncological diseases with sometimes a large variability in PFS. Another issue is that the scale does not make a provision for the grading of non-inferiority studies based on response rate criteria. Therefore, it is necessary to make some changes to the scale to make it better applicable in HM. EHA and ESMO together will develop a new version of this ESMO-MCBS scale that is validated for HM. The principle of the scale is that it will be a dynamic tool and the ESMO-MCBS working group will revise it when necessary. In the future, this scale may play an important role in decision making regarding the effect of new treatment in HM, not only concerning survival but also taking into account quality of life. Another important issue is the upcoming use of surrogate markers to predict outcome, for example MRD measurement in patients with MM. If this will be used in the future as surrogate marker than it should also be incorporated within this tool.

Chapter 8 consists of a review with the aim to evaluate the adequacy of the ESMO-MCBS to address bias generated by flawed design, implementation, or data analysis and identify shortcomings in need of amendment with the aim of optimizing this scale. Seven shortcomings in the ability of the ESMO-MCBS to identify and address bias were identified. These related to evaluation of the control arm, crossover issues, criteria for non-inferiority, substandard post-progression treatment, pos hoc subgroup findings based on biomarkers, informative censoring and publication bias against quality-of-life data. Therefore, in the following version of this tool, these shortcomings will be taken into consideration. Like all tools, the critical use of this tool is the responsibility of the user. As user, a critical appraisal of the different clinical trials is necessary to use this tool in the best way.

In conclusion, in current practice, due to the wide availability in treatment options, a critical appraisal with regard to efficacy is important. Quality of life may be influenced by therapy, sometimes with only minor improvement of survival and with high costs. On the other hand this tool could have an important function in accelerating the process of registration and reimbursement of new treatment modalities. Therefore, it is important to modify the tool to make it applicable to HM.

CONCLUSIONS AND FUTURE PERSPECTIVES

In this thesis several aspects in the treatment of patients with MM were evaluated. We showed the impact of novel treatment in patients with NDMM as shown in the Carthadex trial. The major advantage of treating patients with carfilzomib instead of bortezomib is the lower incidence of invalidating PNP. Carfilzomib is now being used more frequently as a first-line treatment in combination with anti-CD38 monoclonal antibody (MoAb) therapy in clinical trials, and it is likely to become the primary therapy alongside bortezomib-based induction treatment, particularly for high-risk patients.

Additionally, in chapter 4, the impact of consolidation treatment was discussed. This is one of the few trials randomizing patients between consolidation versus no consolidation. Nowadays, in patients with NDMM, 2 cycles of consolidation treatment after HDM and ASCT is standard of care whereas in most ongoing studies in NDMM even longer consolidation, as well as light consolidation is investigated.
Currently, trials are ongoing investigating CAR-T cell therapy and/or BITEs as part of first line treatment. This will probably further improve outcome in NDMM patients.

Clinical trials are necessary to investigate the effectiveness of new treatment modalities and to improve treatment options outside of clinical trials. However, it remains important to investigate the effect of these novel treatment options in real world. Patients treated in clinical trials are probably not representative of patients treated in real world. Registry studies are important in giving perspective on the effectiveness of treatment in the real world within a heterogeneous population. In this thesis we evaluated the effect of treatment with Pd or PCd in patients treated outside of clinical trials, and showed comparable results as observed in clinical trials. In order to demonstrate the efficacy of new treatment combinations in real-world population, it is crucial to validate the results obtained from clinical trials in real-world settings.

Another major issue in treating patients with MM is the development of resistance and sometimes the initial lack of response to treatment. In this thesis we evaluated the impact of CRBN as a potential biomarker. We showed that there is a correlation with improvement of survival with high CRBN. However, it will be necessary to standardize the test in order to use CRBN as a biomarker in guiding treatment, since the test is time consuming and susceptible to inter observer variation. The question remains if treatment will be guided by the level of CRBN due to the fact that overall IMiDs are a powerful treatment option, especially in combination with other drugs. Several factors, other than CRBN, are also important determinants of resistance, including the micro-environment. The fact that lenalidomide is currently used as a backbone treatment and quadruplet therapy is often administered makes it complicated to determine the role of CRBN in response to IMiDs such as lenalidomide.

Finally, the ESMO-MCBS was included in this thesis. Application of this tool in HM showed that this tool may be feasible if some modifications will be applied. Implementation of this kind of tools is necessary in current practice due to the wide availability of treatment, impact on quality of life and high costs. This tool may accelerate the process of registration and reimbursement of new and effective treatment modalities. On the other hand, the ESMO-MCBS also emphasizes the importance of evaluating the effectiveness of new treatment with regard to the effect on quality of life.

Particularly for MM, there is a rapid increase in the development of new treatment modalities. Currently CAR-T cell therapy and treatment with teclistamab (BITE) is EMA approved in RRMM. However, due to high costs CAR-T cell therapy is not yet reimbursed in the Netherlands. The ESMO-MCBS could contribute to speeding up the reimbursement process for these new treatment modalities.

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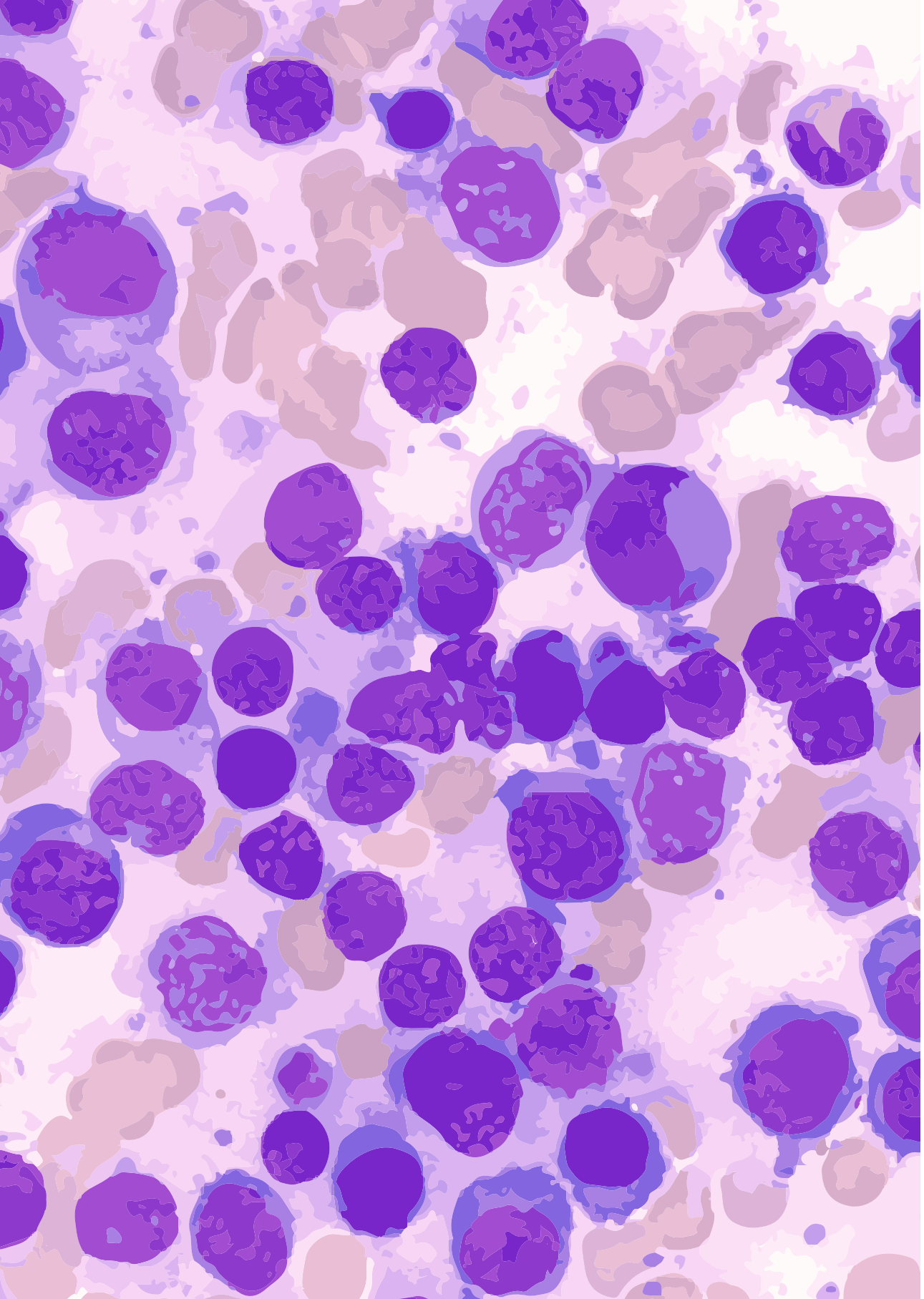

Appendices

ENGLISH SUMMARY

Multiple myeloma (MM) is a malignant plasma cell disorder and is the second most common hematological malignancy. It is characterized by the clonal proliferation of malignant plasma cells in the bone marrow. These malignant plasma cells secrete a monoclonal protein (M-protein). Typical organ damage caused by this malignant plasma cell clone includes osteolytic bone lesions, renal failure, anemia, and hypercalcemia, and are the result of the accumulation of plasma cells in tissues and due to the production of cytokines by the plasma cells.

Survival in patients with MM has significantly improved during the last decades due to the introduction of novel therapeutic agents, i.e. high dose melphalan (HDM) followed by autologous stem cell transplantation (ASCT), immune modulating agents (IMiDs), proteasome inhibitors (PI), monoclonal antibodies and most recently CAR T cell therapy and bispecific antibodies. Despite these major improvement in therapeutic options, MM remains an incurable disease.

In this thesis outcome in patients with MM was evaluated using different treatment strategies with emphasis on treatment with IMiDs.

In chapter 2 and 3 the results of the Carthadex trial were described. In this trial patients with newly diagnosed MM (NDMM) were treated with different dose levels of carfilzomib combined with thalidomide and dexamethasone (KTd) as induction and consolidation treatment. This is the only clinical trial evaluating different dose levels of carfilzomib. This trial demonstrated that higher doses of carfilzomib (minimal 36 mg/m2 twice a week) had better efficacy with similar toxicity in patients with NDMM. However, due to the limited number of patients and the absence of randomization, a definitive answer about the optimum dose level remains unclear. Currently, carfilzomib is not yet approved as first line treatment in NDMM due to lack of randomized trials using carfilzomib in this patient population.

In Chapter 4 we showed the results of the HOVON 95/EMN02 trial. This trial randomized patients between continuous therapy and HDM with ASCT, followed by randomization between consolidation and no consolidation, with all patients receiving lenalidomide maintenance. Patients who received consolidation therapy after HDM and ASCT experienced an improvement in progression-free survival (PFS) compared to those who did not receive consolidation, which is considered the standard of care nowedays.

In chapter 5 a registry study with pomalidomide was presented. In this chapter we emphasize the importance of performing registry studies due to strict inclusion criteria for patients included in clinical trials. We demonstrated that response and survival in patients treated with pomalidomide and dexamethasone (Pd) in real world is comparable to survival shown in clinical trials. Pomalidomide is effective in treating patients with MM, however preferably a third drug is added. Which drug is depended on previous therapy, development of resistance and patients choice.

In chapter 6 the results of a correlative study regarding IMiDs and the effect on the CRBN pathway were demonstrated, by analyzing bone marrow biopsies of patients treated in the HOVON87. In this study protein expression of cereblon (CRBN) and its downstream targets (Ikaros, Aiolos, *c-Myc* and IRF-4) were analyzed with the aim to investigate if one of these targets may act as a practical clinical marker to predict which patient will have a durable response and improvement of survival with IMiD treatment. The study found that higher CRBN protein levels were associated with an improvement in survival, and if used as a predictive marker, it is best to use a standardized technique for staining and scoring. However, the technique is time-consuming and may not be used in clinical practice. The study also discusses the development of resistance to IMiDs, where IRF4 may play an important role, and higher levels of IRF-4 in combination with higher levels of CRBN were associated with better survival. However, other factors such as genetic and chromosomal changes may have a larger impact on the development of resistance.

In chapter 7 and 8 the European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) was described. This is a validated tool used to evaluate the clinical benefit of new treatments in solid tumors. However, its applicability in hematological diseases (HM) is being questioned due to the differences in behavior between oncological and HM. Despite this, the ESMO-MCBS is still applicable in most analyzed studies of HM, with some shortcomings that need to be addressed. EHA and ESMO will work together to develop a new version of the scale that is validated for HM, taking into account the shortcomings found. A critical appraisal of clinical trials is necessary to use this tool effectively, as it can play an important role in decision making regarding the effect of new treatments on survival and quality of life.

NEDERLANDSE SAMENVATTING

Multipel myeloom (MM) is een kwaadaardige plasmacelaandoening en is de tweede meest voorkomende hematologische maligniteit. Het wordt gekenmerkt door de klonale proliferatie van maligne plasmacellen in het beenmerg. Deze maligne plasmacellen produceren een monoklonaal eiwit (M-proteïne). Typische kenmerken veroorzaakt door deze maligne plasmacelkloon bestaan uit osteolytische botlaesies, nierinsufficiëntie, anemie en hypercalciëmie. Deze kenmerken zijn het resultaat van de accumulatie van plasmacellen in weefsels en door de productie van cytokines door de plasmacellen.

De overleving van patiënten met MM is de afgelopen decennia aanzienlijk verbeterd dankzij de introductie van nieuwe therapeutische middelen, dat wil zeggen hoge dosis melfalan (HDM) gevolgd door autologe stamceltransplantatie (ASCT), immuunmodulerende middelen (IMiD's), proteasoomremmers (PI), monoklonale antilichamen en recent CAR T-celtherapie en bispecifieke antilichamen. Ondanks deze verbetering in therapeutische opties, blijft MM een ongeneeslijke ziekte.

In dit proefschrift wordt de uitkomst bij patiënten met MM geëvalueerd met behulp van verschillende behandelstrategieën met de nadruk op behandeling met IMiD's.

In hoofdstuk 2 en 3 worden de resultaten van de Carthadex trial beschreven. In deze studie werden patiënten met nieuw gediagnosticeerde MM (NDMM) behandeld met verschillende doses carfilzomib gecombineerd met thalidomide en dexamethason (KTd) als inductie en consolidatie behandeling. Dit is de enige klinische trial die verschillende doses carfilzomib onderzoekt binnen 1 trial. Deze studie toonde aan dat hogere doses van carfilzomib (minimaal 36 mg/m2, twee keer per week) een betere werkzaamheid had met vergelijkbare toxiciteit bij patiënten met NDMM. Door het beperkte aantal patiënten en het ontbreken van randomisatie blijft een definitief antwoord over het optimale dosisniveau echter onduidelijk. Momenteel is carfilzomib nog niet goedgekeurd als eerstelijnsbehandeling bij NDMM vanwege een gebrek aan gerandomiseerde trials in deze patiëntenpopulatie.

In hoofdstuk 4 tonen we de resultaten van de HOVON 95/EMN02 trial. Deze studie randomiseerde patiënten tussen continue therapie en HDM met ASCT, gevolgd door randomisatie tussen consolidatie en geen consolidatie, waarna alle patiënten behandeld werden met lenalidomide onderhoud. Deze studie toonde aan dat er sprake was van verbetering in PFS bij patiënten die werden behandeld met consolidatietherapie na HDM en ASCT, wat momenteel volgens de huidige richtlijnen standaard behandeling is bij patiënten met NDMM.

In hoofdstuk 5 wordt een registry trial gepresenteerd waarin patiënten buiten studie verband behandeld werden met pomalidomide en dexamethason (Pd). In dit hoofdstuk benadrukken we het belang van het uitvoeren van registry studies, vanwege het feit dat in klinische studies een selectie van patiënten wordt behandeld welke mogelijk niet representatief zijn voor de algehele populatie. Resultaten betreffende respons en overleving

met Pd in deze trial lijkt vergelijkbaar met resultaten vanuit klinische trials. Desalniettemin is pomalidomide effectief gebleken bij de behandeling van patiënten met MM, maar bij voorkeur wordt een derde geneesmiddel toegevoegd. Welk geneesmiddel is afhankelijk van eerdere therapie, ontwikkeling van resistentie, keuze van de patiënt en comorbiditeit.

In Hoofdstuk 6 worden de resultaten getoond van een correlatieve studie met betrekking tot IMiD's en het effect op de cereblon (CRBN) pathway door analyse van beenmergbiopten van patiënten behandeld in de HOVON 87. In deze studie werd eiwitexpressie van CRBN en de overige eiwitten in deze pathway (Ikaros, Aiolos, *c-Myc* en IRF4) geanalyseerd met als doel te onderzoeken of een van deze eiwitten kan fungeren als klinische marker om te voorspellen welke patiënt een duurzame respons en verbetering van overleving zal hebben met IMiD behandeling. Uit de studie bleek dat hogere CRBN-eiwitniveaus geassocieerd waren met een verbetering van de overleving. Echter, indien gebruikt als voorspellende marker, dan is het noodzakelijk om een gestandaardiseerde techniek voor kleuring en scoren van de samples te hanteren. De techniek is echter tijdrovend en zal daarom waarschijnlijk niet gebruikt worden in de klinische praktijk. De studie bespreekt ook de ontwikkeling van resistentie tegen IMiD's, waarbij IRF4 een belangrijke rol kan spelen. In deze studie werden hogere niveaus van IRF4 in combinatie met hogere niveaus van CRBN geassocieerd met een betere overleving. Andere factoren, zoals genetische en chromosomale veranderingen, hebben mogelijk een grotere invloed op de ontwikkeling van resistentie.

In hoofdstuk 7 en 8 wordt de European Society of Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) besproken welke gebruikt kan worden als leidraad om het klinische voordeel van nieuwe behandel opties voor solide tumoren te beoordelen. De toepasbaarheid van deze schaal bij hematologische ziekten werd echter bemoeilijkt vanwege de verschillen in gedrag tussen oncologische ziekten en hematologische maligniteiten (HM). Desondanks blijkt de ESMO-MCBS toepasbaar te zijn in de meeste geanalyseerde studies van HM in deze studie. EHA en ESMO zullen samenwerken om een nieuwe versie van de schaal te ontwikkelen die is gevalideerd voor HM, rekening houdend met de gevonden tekortkomingen. Een kritische beoordeling van klinische onderzoeken is nodig om dit instrument effectief te gebruiken, omdat het een belangrijke rol kan spelen bij de besluitvorming over het effect van nieuwe behandelingen op overleving en kwaliteit van leven.

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Ruth Wester was born on May 4th, 1983 in Hengelo (Overijssel), the Netherlands. In 2001 she completed the Gymnasium at the Ichthus College in Enschede. From 2003 to 2009 she studied medicine at Radboud University Nijmegen, the Netherlands. In this period she performed a scientific training in Denver on autosomal dominant kidney and liver disease. In 2010 she started her residency in internal medicine at Rijnstate hospital Arnhem, the Netherlands under supervision of dr. V. Matthijssen. She continued her residency internal medicine at the Erasmus MC on January 2013 under the supervision of dr. J. van Saase. April 2014 she started her hematology training under supervision of prof. dr. J.J. Cornelissen and dr. P. te Boekhorst. In 2016 she started her PhD research on multiple myeloma under supervision of prof. dr. P. Sonneveld and dr. A. Broijl. In October 2017 she finished her hematology training and started as chef the Clinique at Erasmus MC at the department of Hematology. January 2020 she became a permanent staff member at Erasmus MC with special interest in multiple myeloma.

In 2015 she married Chiel Smit. They have three children: Ruben (2016), Thomas (2018) and Elise (2018).

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A summary of PhD training and teaching activities

PhD candidate: Ruth Wester
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Research school: Molecular Medicine
Period: 2016-2023
Promotor: Prof. P. Sonneveld

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- Endnote	2016
- Microsoft excel basic	2016
- Systematic literature retrieval in Embase	2016
- Microsoft excel advanced	2016
- Basic introduction course on SPSS	2016
- EWP24 Survival analysis for clinicians	2016
- BROK	2020

Workshops

- Erasmus Hematology Lectures	2016-2017
- Regionale Nascholing Hematologie	2019-2023

Scientific meetings

- AIO/post-doc meetings at the Department of Hematology, Erasmus MC	2016-2017
- Journal club at the Department of Hematology, Erasmus MC	2016-2017

Oral presentations

- American Society of Hematology, San Diego	2016
- 21e regionale nascholing hematologie, Rotterdam	2019
- 22e regionale nascholing hematologie, Rotterdam	2020
- 23e regionale nascholing hematologie, Rotterdam	2022
- Dutch Hematology Congress	2023
- 4th European myeloma network meeting, Amsterdam	2023

Poster presentations

- European Hematology Association, Madrid	2017
- American Society of Hematology, Atlanta	2017
- 17th International Myeloma Workshop, Boston	2019
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LIST OF PUBLICATIONS

This thesis

Wester R., van der Holt B., Asselbergs E., Zweegman S., Kersten MJ., Vellenga E., van Marwijk Kooy M., de Weerdt O., Minnema M., Lonergan S., Palumbo A., Lokhorst H., Broijl A., Sonneveld P. Phase 2 study of carfilzomib, thalidomide, and low-dose dexamethasone as induction and consolidation in newly diagnosed, transplant eligible patients with multiple myeloma, the carthadex trial. *Haematologica. 2019 Nov;104(11):2265-2273.*

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Other publications

Hoevenaren IA, Wester R. Schrier RW, McFann K, Doctor RB, Drenth JP, Everson GT. Polycystic liver: clinical characteristics of patients with isolated polycystic liver disease compared with patients with polycystic liver and autosomal dominant polycystic kidney disease. *Liver int. 2008 Feb;28(2):264-7.*

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LIST OF ABBREVIATIONS

ASCT	Autologous stem cell transplantation
BCMA	B Cell Maturation Antigen
AE	adverse event
ALL	acute lomphoblastic leukaemia
AML	acute myeloid leukaemia
BiTEs	bispecific T-cell engagers
BM	bone marrow
BMSC	Bone marrow stromal cells
CA	Cytogenetic abnormalities
CAR-T	Chimeric antigen receptor T
CI	confidence interval
CLL	chronic lymphocytic leukaemia
CML	chronic myeloid leukaemia
c-Myc	cellular myelocytomatosis oncogene
CR	Complete response
CRAB	Hypercalcemia, renal failure, anemia, bone lesions
CRBN	Cereblon
daraKRd	Daratumumab with KRd
daraVMP	Daratumumab, bortezomib, melphalan, prednisone
daraVRD	Daratumumab, bortezomib, lenalidomide, dexamethasone
daraVTD	Daratumumab, bortezomib, thalidomide, dexamethasone
DFS	disease-free survival
DKd	Daratumumab, carfilzomib, dexamethasone
DLT	dose limiting toxicities
DoR	duration of response
DRd	Daratumumab, lenalidomide, dexamethasone
DVd	Daratumumab, bortezomib, dexamethasone
EFS	event-free survival
EHA	European hematology association
EMA	European Medicines Agency
EMA	European Medicines Agency
Epd	Elotuzumab, pomalidomide, dexamethasone
ESMO	European Society for Medical Oncology
ESMO-MCBS	ESMO-Magnitude Clinical Benefit Scale
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drugs Administration
FISH	fluorescence in situ hybridization

FLC	Free light chains
GCS-F	granulocyte-stimulating factor
GPRC5D	G protein-coupled receptor family C group 5-member D
HDM	High dose melphalan
HM	hematological malignancies
HR	Hazard ratio
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFM	Intergroupe Francophone du Myélome
IGF-1	Insulin-like growth factor-1
IgH	Immunoglobulin heavy chain
IL	Interleukin
IMiDs	Immunomodulating agents
IMWG	International Myeloma Working Group
IQR	interquartile range
IRBs	Intitutional Review Boards
IRF4	Interferon regulatory factor 4
isaKR	Isatuximab, carfilzomib, lenalidomide
isaKRd	Isatuximab with KRd
isaPd	isatuximab, pomalidomide, dexamethasone
ISS	International staging system
ITT	intention-to-treat
KCd	Carfilzomib, cyclophosphamide, dexamethasone
Kd	Carfilzomib, dexamethasone
Kd	Carfilzomib, dexamethasone
KRd	Carfilzomib, lenalidomide, dexamethasone
KTd	carfilzomib, thalidomide, dexamethasone
KTd	carfilzomib, thalidomide, dexamethasone
MDS	myelodysplastic syndromes
MDSC	Myeloid-derived suppressor cells
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MP	Melphalan prednisone
M-protein	Monoclonal protein
MPR-R	melphalan, prednisone, lenalidomide and lenalidomide maintenance
MPT-T	melphalan, prednisone, thalidomide and thalidomide maintenance
MRD	Minimal residual disease
MTD	maximum tolerated dose
NCR	Netherlands Cancer Registry
NDMM	Newly diagnosed multiple myeloma
NI	non-inferiority
NTE NDMM	Transplant ineligible newly diagnosed multiple myeloma
ORR	Overall response rate
OS	Overall survival
PAD	Bortezomib, doxorubicin, dexamethasone
PCd	Pomalidoide, cyclophosphamide, dexamethasone
PCd	pomalidomide, cyclophosphamide, dexamethasone
Pd	Pomalidomide, dexamethasone
PFS	Progression-free survival
PI	Proteasome inhibitors
PNP	Polyneuropathy
PR	Partial response
PVd	pomalidomide, bortezomib, dexamethasone
QoL	quality of life
RCT	randomized controlled trial
Rd	Lenalidomide, dexamethasone
R-ISS	Revised international staging system
RRMM	Relapsed/refractory multiple myeloma
RRMM	response rate
SAE	serious adverse event
sCR	stringent complete response
SD	Stable disease
SINE	selective inhibitor of nuclear export
SLAMF7	Signaling lymphocytic activation molecule F7
SMM	Smoldering multiple myeloma
SOC	standard of care
Td	Thalidomide, dexamethasone
TE NDMM	Transplant eligible newly diagnosed multiple myeloma
TTP	thrombocytopenic purpura
VAD	Vincristine, adriamycine, dexamethasone
VCD	Bortezomib, cyclophosphamide, dexamethasone
Vd	Bortezomib, dexamethasone
VGPR	Very good partial response
VMP	Bortezomib, melphalan, prednisone
VRD	Bortezomib, lenalidomide, dexamethasone
VTD	Bortezomib, thalidomide, dexamethasone
WHO EML	World Health Organization Essential Medicines List

DANKWOORD

Na 8 jaar is het boekje dan eindelijk af! Vele mensen hebben mij hierbij geholpen en ik ben hen zeer dankbaar voor de steun, feedback en opbouwende kritiek. Een aantal mensen wil ik daarom graag in het bijzonder bedanken.

Allereerst dank aan alle patiënten die hebben deelgenomen aan de klinische studies die weergegeven zijn in dit proefschrift. Zonder uw medewerking was dit niet tot stand gekomen.

Graag wil ik prof.dr. Sonneveld, Pieter, bedanken voor alle steun, vertrouwen en geduld tijdens dit promotie traject. Bedankt ook voor alle mooie kansen die je me hebt gegeven de afgelopen jaren. Ik kan mij nog goed onze eerste ontmoeting herinneren, dat was het sollicitatie gesprek in de Daniel den Hoed voor de opleiding tot hematoloog. Al snel wist ik dat ik mij verder wilde verdiepen in het multipel myeloom en klopte ik weer bij je aan, ditmaal om te vragen of ik onderzoek bij je kon gaan doen. En dit kon, in de vorm van een promotie traject. Dank voor de kritische blik op de manuscripten en voor het vertrouwen in mij.

En dan natuurlijk dr. Broijl, Annemiek, ik ben je allereerste PhD! Hoe bijzonder is dat! Bedankt voor je enorme inzet en betrokkenheid bij mijn promotie traject. Ik kon altijd bij je terecht als ik vragen had of als het schrijven weer eens niet wilde lukken. Dank ook voor de fijne samenwerking als collega's binnen de hematologie. We gaan er mooie jaren van maken.

Leden van de leescommissie, prof.dr. H.M.W. Verheul, prof.dr. J. Cloos en prof.dr. M. Delforge, hartelijk dank voor het lezen en beoordelen van mijn proefschrift. Ook bedank ik de leden van de grote commissie, prof. Dr. P.C. Huijgens, prof. dr. P.H.M. van der Kuy, prof.dr. S. Zweegman en prof. Dr. F.W.G. Leebeek voor jullie deelname in de oppositie.

Dr. Van Duin, Mark, dank voor al je hulp en inzet bij het cereblon project. Wat een geduld heb je met mij gehad. Bedankt voor alle input en hulp bij de analyses. Dank ook voor alle tijd die je hebt genomen om mij alles uit te leggen en het manuscript naar een hoger niveau te tillen.

Natuurlijk wil ik ook Dr. Lam, King, ontzettend bedanken. Heel wat maandag avonden hebben we samen achter de microscoop zitten turen naar plasmacellen! De oreo koekjes waren onmisbaar hierbij. Heel erg bedankt voor je tijd en geduld met het tellen van alle plasmacellen. Ik zal al je verhalen niet vergeten!

Dr. Dinmohamed, beste Avinash, dank voor je waardevolle input. Oneindig veel geduld heb je gehad om mij alle kneepjes te leren van Stata! Ontzettend bedankt voor je hulp rondom het pomalidomide project en je kritische blik op het manuscript. Hierbij ook dank aan IKNL voor het vergaren en leveren van de data.

Ook veel dank aan Dr. Van der Holt, Ronnie. Ontzettend bedankt voor je hulp en kritische blik bij de analyses van de Carthadex trial. Mede dankzij jou zijn hier een aantal mooie manuscripten uit voorgekomen.

Celgene, especially dr. Wang, dr. Couto, dr. Ren and dr. Thakurta, thank you for your help with the staining of the bone marrow samples regarding the cereblon project.

Co-auteurs van alle manuscripten, dank voor jullie waardevolle input waardoor de manuscripten naar een hoger niveau werden getild.

De myeloom groep op de 13e, Tom Cupedo in het bijzonder, dank voor jullie waardevolle inbreng.

Secretaresses, Jos en Els in het bijzonder, bedankt voor al het regelwerk en het organiseren van afspraken.

En natuurlijk Egied, bedankt voor de vormgeving van het boekje. Dank voor je creativiteit en je geduld als ik toch weer wat wilde veranderen!

Collega onderzoekers, Tim, Sophie en Aniko, het was van korte duur op de 13e maar wat hebben we het gezellig gehad in onze kamer. Op een gegeven moment konden jullie de opmerking ‘ik heb geen zin meer’ niet meer horen!

Lieve stafleden hematologie (Erasmus MC), dank voor alle steun en interesse gedurende de afgelopen jaren. Het is eindelijk af! Dank ook Simone voor al het werk wat je me altijd uit handen neemt. Het samen begeleiden van onze myeloom patiënten is super fijn.

Lieve vrienden, jullie zorgden ervoor dat ik naast werken en onderzoek doen ook nog toekwam aan ontspanning. Bedankt voor jullie interesse en oneindige steun en trouwe vriendschap.

Lieve Julia, dank je wel dat je onderdeel wilt zijn van ons gezin en ons zoveel uit handen neemt. En dank ook voor de vele keren dat je extra bent gekomen zodat ik nog even verder kon werken aan dit proefschrift!

Lieve schoonfamilie, Piet, Diny, Lieke, Matthijs, Dorien en Gerben. Dank voor jullie medeleven en steun, niet alleen bij mijn promotie onderzoek maar juist ook daarbuiten!

Inge en Marlies, mijn paranimfen! Onze vriendschap gaat terug naar onze studententijd in Nijmegen. Wat hebben we een fijne tijd gehad in ons studentenhuis. Ik denk nog graag terug aan al onze chocolade fondue feestjes en het binge watchen van foute films. Onze tijd in Nijmegen is de basis geweest voor een prachtige vriendschap. Dank dat jullie mijn paranimfen willen zijn en dank voor alle steun de afgelopen jaren.

Lieve Elke en Maarten en natuurlijk ook Jeroen en Marloes. Dank dat jullie er altijd voor me zijn. Het is fijn om te weten dat ik altijd op jullie steun kan rekenen. We hebben het goed met elkaar!

Lieve pap en mam, ja hoor het is dan eindelijk gelukt. Het boekje is af. Bedankt voor jullie ondersteuning tijdens goede gesprekken maar ook bij de hulp thuis met alle kleintjes en de drukte die dat met zich meebracht. Een tijd lang zijn jullie iedere donderdag geweest zodat ik verder kon werken aan dit proefschrift. Wat was dat fijn! Dank dat jullie me altijd alle kansen hebben gegeven om mezelf te ontwikkelen. Pap, voor jou is het ongeveer 40 jaar geleden dat je ook hier in het Erasmus promoveerde en nu doe ik dat. Hoe bijzonder is dat!

En dan mijn lieve, lieve kinderen. Lieve Ruben, Thomas en Elise, wat houd ik veel van jullie, van de maan en weer terug. Mijn wereld draait om jullie. Blijf zoals je bent!

Lieve, lieve Chiel, ik hou van jou. Zonder jouw niet aflatende steun en toewijding aan mij en onze kinderen had ik dit niet allemaal kunnen doen. Dank dat je er altijd voor me bent en me altijd zal steunen in de keuzes die ik maak. Ik houd van je!