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1 Drug description

Generic/Brand name/ATC code:

Bortezomib (formerly known as PS-341) / Velcade® / L01XX32

bortezomib (Velcade®)

Developer/Company:

USA: Millenium Pharmaceuticals; Europe: Janssen-Cilag International NV

Description:

The antineoplastic agent bortezomib is a first-in-class proteasome inhibitor [1]. Particularly, bortezomib is a dipeptide boronic acid analogue whose anti-tumour activity leads to cell cycle arrest, apoptosis and inhibition of angiogenesis by disrupting various cell signalling pathways [2].

a proteasome inhibitor leading to cell cycle arrest, apoptosis and inhibition of angiogenesis

Velcade® is currently approved as an intravenous (i.v.) infusion of 1.3mg per square meter body surface area. Bortezomib is approved as monotherapy in progressive MM and in combination with other agents as first-line therapy in transplant ineligible patients. When given together with melphalan and prednisone, bortezomib is given twice weekly on weeks 1, 2, 4 and 5 of a six-week cycle. This cycle is given 4 times followed by 5 weeks of once-weekly injections. When bortezomib is given as a single-agent, it is recommended twice weekly in weeks 1 and 2 of a three weeks cycle. Complete responders should receive 3 cycles; partial responders should receive up to eight treatment cycles [3].

approved at a dose of 1.3mg/m² i.v. infusion

Currently, the mode of administration – subcutaneous (s.c.) vs. i.v. – is investigated in clinical trials. The objective is to establish if s.c. administration maintains efficacy while simultaneously improving the safety profile, foremost in terms of a lower incidence of peripheral neuropathy, an adverse event (AE) caused by bortezomib and impairing the quality of life of multiple myeloma (MM) patients [4].

i.v. vs. s.c. administration

2 Indication

Bortezomib as consolidation or maintenance therapy after high-dose therapy (HDT) with autologous stem-cell transplantation (ASCT) in patients with newly diagnosed multiple myeloma.

bortezomib as consolidation or maintenance therapy after ASCT

3 Current regulatory status

in Europe approved for the treatment of transplant-ineligible MM patients

In Europe, Velcade® is approved

- as monotherapy for the treatment of patients with progressive MM who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation (since April 2004),
- and in combination with melphalan and prednisone for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant (since September 2008) [3, 5].

2008: approval for the treatment of MM patients

In May 2003, the US Food and Drug Administration (FDA) approved bortezomib (Velcade®)

- for the treatment of MM patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy [6]; this indication was later on revised to failure of at least one prior therapy in 2005 [7] and then to treatment of patients with MM regardless of prior therapy in 2008 [8].

2006: approved for the treatment of mantle cell lymphoma

- In 2006, the indication of bortezomib was extended to patients with mantle cell lymphoma who have received at least one prior therapy [9].

4 Burden of disease

MM accounts for ~10% of haematologic malignancies

MM is a malignant neoplasm of plasma cells that belongs to the type of B-cell lymphoma. MM accounts for about 10% of all haematological malignancies and is after non-Hodgkin's lymphoma (NHL) the second most common hematologic malignancy [10, 11]. The incidence of MM is estimated to be 4-6 per 100,000 habitants with a median age of 70 years at time of diagnosis and men being more often affected than women. About 20% of patients are symptom-free at time of diagnosis [12, 13]. MM is often referred to as a disease of the elderly with only about 35% of MM patients being younger than 65 years [4, 14]. Raised erythrocyte sedimentation rate (ESR), plasma viscosity, serum protein or globulin lead to incidental detection of MM. Clinical features of MM present at time of diagnosis are bone disease, impaired renal function, anaemia, hypercalcaemia, recurrent or persistent bacterial infection and hyperviscosity [15].

incidence: 4-6 per 100,000 habitants

median age at diagnosis: 70 years (35% of MM patients are <65 years)

tests to confirm diagnosis, estimate tumour burden and prognosis

If MM is suspected, a range of investigations and tests are indicated to confirm diagnosis, estimate tumour burden and prognosis and to assess myeloma-related organ impairment. Further, these tests aim to differentiate between patients with active and symptomatic MM that requires systemic therapy and monoclonal gammopathy of undetermined significance (MGUS), smouldering or indolent lymphoma or solitary plasmocytoma, all of which not requiring systemic therapy in the first instance [10, 13, 15].

heterogeneous natural history

The natural history of MM is very heterogeneous. Initially, the Durie and Salmon system [16] was the staging system of choice until it was superseded by the International Staging System (ISS) for MM [17]. The ISS defines 3 risk categories (stages I, II and III) with a corresponding median survival time of 62, 45 and 29 months in stages I, II and III, respectively. Especially biological parameters (e.g., β2-microglobulin, C-reactive protein, lactate dehydrogenase and serum albumin) are of prognostic relevance and thus incorporated in the determination of the ISS stages [13, 15]. Though, the ISS is valid for prognostic purposes, its use to determine choice of therapy for individual patients is still unproven [15].

3 risk categories according to ISS: stage I, II and III

factors for poor prognosis: genetic abnormalities = high-risk patients

Factors associated with poor prognosis are genetic abnormalities such as t(4;14), t(14;16) and deletion 17p (del(17p)) demonstrated by fluorescence in situ hybridisation (FISH) [15]. Patients presenting these prognostic factors are generally referred to as "high-risk" MM patients. Preliminary data suggest that the adverse prognosis of these factors may be abrogated by newer agents, but to confirm this observation further prospective evaluation is required [15].

100 newly diagnosed patients <65 years with symptomatic MM in Austria per year

According to clinical treatment guidelines only patients younger than 65 years are eligible for ASCT. With an incidence of 4 per 100,000 habitants [12, 13], there are about 360 patients newly diagnosed with MM in Austria per year. Applying the above mentioned estimates, there are about 100 patients younger than 65 years diagnosed with symptomatic disease and thus, eligible for first-line therapy with ASCT. In 2011, there were 120 MM transplantations overall in Austria. These 120 transplantations were 6 allogeneic SCTs, 99 first-line ASCTs and 15 second- or third-line transplantations [18].

5 Current treatment

watch-and-wait for asymptomatic MM

In the first instance, choice of therapy depends on the stage of disease and on presence or absence of symptoms. For MM of ISS stage I or indolent myeloma immediate treatment is not recommended [13].

symptomatic MM:

1st-line therapy is HDT with ASCT support in patients <65 years

For patients with advanced stages (stage II or III) or symptomatic myeloma choice of first-line therapy depends on age, or at least on the overall condition of the MM patient. For younger patients (<65 years) or patients in good clinical condition the current standard of care is high-dose therapy (HDT) with melphalan (HDM) supported by ASCT. The arbitrary age limit of 65 years is not a strict limit; the decision whether MM patients are eligible for HDT with ASCT mainly depends on their overall performance status and co-morbidities (e.g. serious heart, lung, renal or liver dysfunction) [19, 20]. In clinical practice the age limit for ASCT is between 65 to 70 years.

1st-line therapy for patients eligible for HDT supported by ASCT

this approach is currently discussed because of the availability and promising results of novel agents

Prior to HDT and ASCT, eligible patients receive a limited number (3-6 cycles) of induction therapy in order to reduce tumour cell mass and bone marrow plasma cell infiltration before the collection of peripheral blood stem cells [4, 15]. Prior to the introduction of novel agents such as thalidomide, lenalidomide and bortezomib, the standard induction regimen was VAD (vincristine, doxorubicin and dexamethasone) yielding overall response rates of 55% to 84% and complete response rates (CR) of 8% to 28% [15]. In recent years, however, novel agents have been incorporated in doublet and triplet induction regimens in order to enhance the depth of re-

sponse prior and post ASCT [4]. Due to promising results no commonly accepted standard induction regimen currently exists.

induction with novel agents: not all are approved as induction treatment yet

Another issue is that these novel agents are not yet approved in all countries (e.g. bortezomib in Europe [5]); therefore, the choice of induction therapy also depends on the availability of these novel drugs in the individual health care systems [4].

CONSOLIDATION and MAINTENANCE THERAPY

role of consolidation and maintenance therapy still has to be defined

The rationale behind administration of consolidation and maintenance therapy is to improve responses after HDT with ASCT. Whereas consolidation therapy is given for a short period immediately after ASCT aiming at improving responses to HDT, maintenance therapy is given for a longer period and aims to extend the duration of response, progression-free survival (PFS) and overall survival (OS) while maintaining a good quality of life [4].

Though, the treatment paradigm of the introduction of novel agents as consolidation and maintenance therapy is currently investigated in clinical trials, mature results demonstrating the positive impact, of consolidation and maintenance therapy on clinical outcomes are needed before the widespread introduction into clinical practice [4].

Currently, the following regimens are used as consolidation and maintenance therapy:

- thalidomide as single agent or in combination with prednisone,
- lenalidomide would be an alternative to thalidomide because of reduced neurologic toxicity [4].

alloSCT not recommended in standard-risk patients

Allogeneic stem-cell transplantation (alloSCT) is also considered to be an option for the treatment of MM and is currently the only treatment approach achieving complete remission or even cure. Though, alloSCT is not recommended for standard-risk patients due to a transplant-related mortality of 10-15% and the risk of chronic graft-versus-host disease (GVHD). AlloSCT should only be performed in high-risk patients within clinical trials [13].

6 Evidence

search in 4 databases yielding 262 references

A literature search was conducted on the 24th of May 2012 in 4 databases (Ovid Medline, Embase, Cochrane Library, CRD Database) yielding 262 results. Considered were controlled phase III and phase II studies investigating the effect of the novel agent bortezomib in the consolidation or maintenance setting after ASCT in newly diagnosed MM patients.

2 controlled phase III studies included

Overall, 2 references [20, 21] reporting results of 2 phase III studies – one assessing bortezomib as consolidation therapy and one assessing bortezomib as maintenance therapy – were included. In mid of July 2012, during compilation of this report results of the HOVON-65/GMMG-HD4 trial were published by Sonneveld et al [22] and thus included in this report. Though, several phase II studies investigating bortezomib as consolidation or mainte-

nance therapy were identified in the search, these trials were not included herein as they had no control group.

6.1 Efficacy and safety - Phase III studies

6.1.1 Consolidation therapy

Table 1: Summary of efficacy results of the NCT01134484 trial

Study title Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study [20]		
Study identifier	ClinicalTrials.gov: NCT01134484 EudraCT: 2005-003723-39	
Design	open-label, multicentre, randomised phase III trial	
	Duration	Enrolment: May 2006 – April 2008 Median follow-up: 36 months, but study still on-going at time of report publication, but not recruiting patients Cut-off date for the available report: June 30, 2010
Hypothesis	Superiority	
Funding	Seràgnoli Institute of Haematology at the University of Bologna: coordinated study, contributed to study design, data collection, data analysis, data interpretation, writing of the report, and the decision to submit for publication Janssen-Cilag: provided bortezomib free of charge	
Treatment groups	Intervention	1. INDUCTION THERAPY three 21-day cycles of bortezomib, thalidomide and dexamethasone (VTD) ✪ 1.3mg/m² bortezomib on days 1, 4, 8 and 11 ✪ 100mg thalidomide daily for the first 14 days and 200mg daily thereafter ✪ 40mg dexamethasone daily on 8 of the first 12 days but not consecutively; total of 320mg per cycle 2. ASCT ✪ mobilization of peripheral blood stem cells: 4g/m² cyclophosphamide; 10µg/kg G-CSF daily starting on day 2 after cyclophosphamide ✪ double ASCT – 3-6 months apart from each other ✪ both transplantations were supported by 200mg/m² melphalan; 5µg/kg G-CSF daily starting on day 5 after melphalan ✪ between the transplantations 100mg thalidomide daily and 40mg dexamethasone on days 1-4, every 28 days were given

		3. CONSOLIDATION THERAPY (3 months after ASCT) two 35-day cycles of VTD therapy ✪ 1.3mg/m² bortezomib on days 1, 8, 15 and 22 ✪ 100mg thalidomide daily ✪ 40mg dexamethasone on days 1, 2, 8, 9, 15, 16, 22 and 23 **4. MAINTENANCE THERAPY** ✪ 40mg dexamethasone on days 1-4 every 28 days	
	Control	**1. INDUCTION THERAPY** three 21-day cycles of thalidomide and dexamthasone (TD) ✪ 100mg thalidomide daily for the first 14 days and 200mg daily thereafter) ✪ 40mg dexamethasone daily on 8 of the first 12 days but not consecutively; total of 320mg per cycle) **2. ASCT** ✪ mobilization of peripheral blood stem cells: 4g/m² cyclophosphamide; 10µg/kg G-CSF daily starting on day 2 after cyclophosphamide ✪ double ASCT – 3-6 months apart from each other ✪ both transplantations were supported by 200mg/m² melphalan; 5µg/kg G-CSF daily starting on day 5 after melphalan ✪ between the transplantations 100mg thalidomide daily and 40mg dexamethasone on days 1-4, every 28 days were given **3. CONSOLIDATION THERAPY (3 months after ASCT)** two 35-day cycles of TD therapy ✪ 100mg thalidomide daily ✪ 40mg dexamethasone on days 1-4 and 20-23 **4. MAINTENANCE THERAPY** ✪ 40mg dexamethasone on days 1-4 every 28 days	
Endpoints and definitions	Rate of complete or near complete response to induction therapy (primary outcome)	CR / nCR	*complete response [23]:* - negative immunofixation on the serum and urine - disappearance of any soft tissue plasmacytomas - ≤5% plasma cells in bone marrow - no increase in tumour size of lytic bone lesions *near complete response [24]:* - absence of myeloma protein on electrophoresis, independent of the immunofixation-test status - stable bone disease - normal serum calcium concentration
	Time to best CR or nCR		time from start of treatment to complete or near complete response achieved at any time
	Time to progression	TTP	time from start of treatment to progression
	Time to relapse	TTR	time from start of treatment to relapse
	Progression-free survival	PFS	time form start of treatment to progression, or death from any cause
	Overall survival	OS	time from start of treatment to death
	Very good partial response	VGPR	serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein <100mg per 24h [25]

	Partial response	PR	- ≥50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of 6 weeks - reduction in 24h urinary light chain excretion either by ≥90% or to <200mg, maintained for a minimum of 6 weeks - for patients with non-secretory myeloma only, ≥50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks - ≥50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination) - no increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response)
	Minimal response or Stable disease	MR / SD	*minimal response [23]* - 25-49% reduction in the level of serum monoclonal paraprotein - 50-89% reduction in 24h urinary light chain excretion - for patients with non-secretory MM only, 25-49% reduction in plasma cells - 25-49% reduction in the size of soft tissue plasmacytomas - no increase in the size or number of lytic bone lesions *stable disease [23]* - not meeting the criteria of either minimal response or progressive disease
	Progressive disease	PD	- >25% increase of the level of serum monoclonal paraprotein - >25% increase in 24h urinary light chain excretion - >25% increase in plasma cells - definite increase in the size of existing bone lesions or soft tissue plasmacytoma - development of new bone lesions or soft tissue plasmacytoma - development of hypercalcaemia not attributable to any other cause
<u>Results and analysis</u>			
Analysis description	**intention-to-treat analysis** 80% power to detect a significant increase in rate of complete plus near complete response from 15% with TD induction therapy to 27% with VTD induction therapy. All tests were two-sided with p values of less than 0.05 deemed significant		
Analysis population	Inclusion	✲ 18-65 years of age ✲ previously untreated symptomatic and measurable myeloma ✲ Karnofsky performance status of ≥60% ✲ adequate haematological function - absolute neutrophil count of ≥1.0x10^9 per litre - platelet count of ≥70x10^9 per litre ✲ adequate renal function - serum creatinine of ≤176 µmol/litre ✲ adequate cardiac function = absence of - uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrolment	

		- New York Heart Association class II-IV heart failure - uncontrolled angina - clinically significant pericardial disease - cardiac amyloidosis ✪ adequate hepatic function - aspartate aminotransferase ≤2.5 times the upper limit of normal (ULN) - total bilirubin ≤1.5 times the ULN
	Exclusion	✪ peripheral neuropathy of grade ≥2 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0) ✪ history of venous thromboembolism ✪ previous diagnosis of thrombophylic alterations
	Characteristics	*Intervention vs Control, %* Median age, years (range): 58 (52 to 62) vs 57 (51 to 62) Male/female: 58/42 vs 57/43 *Myeloma subtype* IgG/IgA/Light Chain: 65/17/17 vs 62/23/14 ISS stage I/II/III: 45/39/16 vs 45/39/16 *FISH analysis for cytogenetic abnormalities* absence of del(13q), t(4;14), or del(17p): 46 vs 48 presence of del(13q): 47 vs 46 presence of t(4;14) with or without del(17p): 24 vs 26

Descriptive statistics and estimated variability	Treatment group	*Intervention (VDT)*	*Control (TD)*	*P value*
	Number of subjects	n = 236	n = 238	
	After induction therapy, n (%; 95% CI)			
	CR	44 (19; 13.7 to 23.6)	11 (5; 2.0 to 7.3)	<0.0001
	CR or nCR	73 (31; 25.0 to 36.8)	27 (11; 7.3 to 15.4)	<0.0001
	VGPR or better	146 (62; 55.7 to 68.1)	66 (28; 22.0 to 33.4)	<0.0001
	PR or better	220 (93; 90.0 to 96.4)	187 (79; 73.4 to 83.8)	<0.0001
	Minimal response or SD	16 (7; 3.6 to 10.0)	39 (16; 11.7 to 21.1)	0.0011
	PD	0	12 (5; 2.3 to 7.8)	0.0005
	After first ASCT			
	CR	89 (38; 31.5 to 43.9)	54 (23; 17.4 to 28.0)	0.0004
	CR or nCR	123 (52; 45.7 to 58.5)	74 (31; 25.2 to 37.0)	<0.0001
	VGPR or better	186 (79; 73.6 to 84.0)	137 (58; 51.3 to 63.8)	<0.0001
	PR or better	220 (93; 90.0 to 96.4)	201 (84; 79.9 to 89.1)	0.0025
	Minimal response or SD	15 (6; 3.2 to 9.5)	20 (8; 4.9 to 11.9)	0.39
	PD	1 (<1; 0.0 to 1.3)	17 (7; 3.9 to 10.4)	0.0001
	After second ASCT			
	CR	98 (42; 35.2 to 47.8)	72 (30; 24.4 to 36.1)	0.0105
	CR or nCR	130 (55; 48.7 to 61.4)	98 (41; 34.9 to 47.4)	0.0024
	VGPR or better	193 (82; 76.9 to 86.7)	152 (64; 57.8 to 70.0)	<0.0001
	PR or better	220 (93; 90.0 to 96.4)	199 (84; 78.9 to 88.3)	0.0011
	Minimal response or SD	14 (6; 2.9 to 8.9)	19 (8; 4.5 to 11.9)	0.38
	PD	2 (1; 0.0 to 2.0)	20 (8; 4.9 to 11.9)	0.0001

	After consolidation therapy			
	CR CR or nCR VGPR or better PR or better Minimal response or SD PD	116 (49; 42.8 to 55.5) 147 (62; 56.1 to 68.5) 201 (85; 80.6 to 89.7) 218 (92; 89.0 to 95.8) 12 (5; 2.3 to 7.9) 6 (3; 0.5 to 4.6)	82 (34; 28.4 to 40.5) 108 (45; 39.1 to 51.7) 162 (68; 62.1 to 74.0) 201 (84; 79.9 to 89.1) 16 (7; 3.5 to 9.9) 21 (9; 5.2 to 12.4)	0.0012 0.0002 <0.0001 0.0071 0.45 0.0032
	Best response to overall treatment protocol			
	CR CR or nCR VGPR or better PR or better Minimal response, SD or PD	136 (58; 51.3 to 63.9) 168 (71; 65.4 to 77.0) 210 (89; 85.0 to 93.0) 227 (96; 93.7 to 98.6) 9 (4; 1.4 to 6.3)	97 (41; 34.5 to 47.0) 128 (54; 47.4 to 60.1) 175 (74; 67.9 to 79.1) 212 (89; 85.1 to 93.0) 26 (11; 7.0 to 14.9)	0.0001 <0.0001 <0.0001 0.0031 0.0031
	Median time to CR or nCR, months (interquartile range)	9 (3.1 to NR)	14 (8.4 to NR)	<0.0001
	Estimated 3-year probability of progression or relapse	29%	39%	0.0061
	Estimated 3-year PFS	68%	56%	0.0057
	Estimated 3-year OS	86%	84%	0.30
Effect estimate per comparison	*Comparison groups*	*Intervention (VDT) vs Control (TD)*		
	Median time to CR or nCR	HR	0.61	
		95% CI	0.49 to 0.76	
		P value	<0.0001	
	Estimated 3-year probability of progression or relapse	HR	0.61	
		95% CI	0.43 to 0.87	
		P value	0.0073	
	PFS	HR	0.63	
		95% CI	0.45 to 0.88	
		P value	0.0061	

Abbreviations: NR – not reached, CI – confidence interval, HR – hazard ratio

Table 2: Most frequent adverse events according to NCI-CTCAE version 3.0

		NCT01134484		
Outcome, n (%)		**Intervention (VTD)** (n=236)	**Control (TD)** (n=238)	**P value**
Grade 1 – 4 non-haematological AEs reported in at least 10% of patients during induction therapy				
	Constipation	99 (42)	67 (28)	NR
	Neuropathy	80 (34)	34 (14)	NR
	Skin rash	67 (28)	17 (7)	NR
	Fever	28 (12)	24 (10)	NR
	Infections	24 (10)	35 (15)	NR
	Oedema	25 (11)	13 (5)	NR
	Gastrointestinal events (excluding constipation)	46 (19)	19 (8)	NR
Serious AEs and grade 3 or 4 AEs reported in at least 2% of patients during induction therapy				
	Any serious AE	31 (13)	30 (13)	0.86
	Any grade 3 or 4 AE	132 (56)	79 (33)	<0.0001
	Any grade 3 or 4 non-haematological AE	120 (51)	73 (31)	<0.0001
	Skin rash	24 (10)	4 (2)	0.0001
	Peripheral neuropathy	23 (10)	5 (2)	0.0004
	Deep vein thrombosis	8 (3)	12 (5)	0.53
	Constipation	10 (4)	7 (3)	0.45
	Infections excluding herpes zoster	7 (3)	11 (5)	0.35
	Gastrointestinal events (excluding constipation)	5 (2)	1 (<1)	0.0982
	Cardiac toxicity	5 (2)	5 (2)	0.99
	Liver toxicity	4 (2)	7 (3)	0.37
Discontinuation during or after induction therapy				
	Overall	13 (6)	26 (11)	0.0319
	Toxic effects	10 (4)	7 (3)	0.45
	Disease progression	0	12 (5)	<0.0001
	Other reasons	2 (1)	7 (3)	0.21
	Early death	1 (<1)	0	0.31
Discontinuation during or after consolidation therapy				
	Toxic effects	4	1	NR
	Disease progression	4	1	NR
	Other reason	4	3	NR

474 patients (I 236 vs C 238) with previously untreated myeloma received thalidomide and dexamethasone with or without bortezomib as induction therapy and also as consolidation therapy after ASCT. The primary endpoint was CR and nCR to induction therapy. Thus, drawing definite conclusions on bortezomib consolidation therapy is difficult since the study was powered to detect an increase in rate of CR plus nCR after induction therapy with VTD compared to TD. Secondary endpoints were CR or nCR to double transplantation and subsequent consolidation therapy with the induction regimen. The baseline patient and disease characteristics were well balanced. Cytogenetic abnormalities such as del(13q) and t(4;14) were present in 46-47% and 24-26% of patients, respectively.

bortezomib as induction therapy before and consolidation therapy after ASCT

Throughout the study (induction therapy, high-dose therapy + ASCT and consolidation therapy) clinical outcomes (CR, nCR, VGPR, PR) were better in the intervention arm than in the control arm: 58% of patients in the intervention arm achieved CR as a best response compared to 41% in the control arm. To which extent the superior response rate after consolidation therapy is actually attributable to consolidation therapy with bortezomib is unknown due to lack of random allocation to *consolidation* therapy and also the response upgrade (i.e. <CR prior consolidation and then achieving CR during / after consolidation therapy), if any, during consolidation therapy was not reported.

improved response rate with bortezomib throughout the study

I 58% vs C 41%

effect of bortezomib as consolidation therapy still unknown

Median PFS was superior for patients treated with VTD (HR 0.63, p=0.0061) and median time to CR or nCR was 5 months (p<0.0001) shorter in this group. Data on cytogenetic abnormalities associated with poor prognosis were available from 90% of patients. Subgroup analyses according to the cytogenetic abnormalities indicated that VTD as induction and consolidation therapy can overcome the adverse effect of t(4;14) compared to TD alone.

results suggest that bortezomib can overcome the adverse prognosis of t(4;14)

Reported AEs were those observed after induction therapy. Information about AEs during or after bortezomib consolidation is lacking. The two most common grade 3 and 4 AEs were peripheral neuropathy and skin rash, both occurring more frequently in the VTD than in the TD arm. The only AE reported in the publication during consolidation therapy was frequency of peripheral neuropathy which affected 2 patients (1%) in the VTD arm and none in the TD arm.

most common and most severe AEs:

peripheral neuropathy, skin rash

Of the 236 patients in the VTD arm 227 completed induction therapy, 212 and 168 completed one or two transplantations, respectively and 165 completed 2 cycles of VTD consolidation therapy. In the TD arm 238 patients received induction therapy, 196 and 166 completed one or two transplantations, respectively and 165 completed two cycles of TD consolidation therapy.

6.1.2 Maintenance therapy

Table 3: Summary of efficacy results of the HOVON-65/GMMG-HD4 trial

Study title Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: Results of the randomized phase III HOVON-65/GMMG-HD4 trial [22].		
Study identifier	International Standard Randomised Controlled Trial Number Register: IS-RCTN64455289 EudtraCT Number: 2004-000944-26	
Design	Prospective, randomized phase III trial (HOVON-65/GMMG-HD4); 75 centres in the Netherlands, Germany and Belgium.	
	Duration	Enrolment: May 2005 –May 2008 Median follow-up: 40.9 months (95% CI, 39.7 to 42.5) Cut-off date for final analysis: NR
Hypothesis	Superiority	
Funding	Supported by the Dutch Cancer Foundation, the German Federal Ministry of Education and Research, and unrestricted Grant No. MMY3003 from Janssen-Cilag-Ortho Biotech. The German Multicenter Myeloma Group was supported by grants from Novartis, Amgen (No. P2004-0060), Chugai and Roche.	
Treatment groups	Intervention	**1. INDUCTION THERAPY** three 4-week cycles of bortezomib, doxorubicin and dexamethasone (PAD) ✪ bortezomib: 1.3mg/m² i.v. on days 1, 4, 8 and 11 ✪ doxorubicin: 9mg/m² i.v. on days 1-4 ✪ dexamethasone: 40mg orally on days 1-4, 9-12 and 17-20 **2. ASCT** ✪ mobilization of peripheral blood stem cells: 1000mg/m² cyclophosphamide on day 1; 15mg/m² doxorubicin on days 1-4, 40mg dexamethasone orally on days 1-4, and G-CSF (10µg/kg filgrastim or 300µg/m² lenograstim) per day subcutaneously divided into 2 doses per day from day 9 until the last stem cell collection ✪ after stem cell collection patients were treated with 1 or 2 cycles of 200mg/m² high-dose melphalan (HDM) and ASCT followed by maintenance therapy **3. CONSOLIDATION THERAPY -** none **4. MAINTENANCE THERAPY** (Start: 4 weeks after HDM) ✪ 1.3mg/m² bortezomib i.v. once every 2 weeks for 2 years (if neutrophils ≥0.5 x 10^9/l and platelets >20 x 10^9/l)
	Control	**1. INDUCTION THERAPY** three 4-week cycles of vincristine, doxorubicin and dexamethasone (VAD) ✪ vincristine: 0.4mg i.v. on days 1-4 ✪ doxorubicin: 9mg/m² i.v. on days 1-4 ✪ dexamethasone: 40mg orally on days 1-4, 9-12 and 17-20 **2. ASCT** ✪ mobilization of peripheral blood stem cells: 1000mg/m² cyclophosphamide on day 1; 15mg/m² doxorubicin on days 1-4, 40mg dexamethasone orally on days 1-4, and G-CSF (10µg/kg filgrastim or 300µg/m² lenograstim) per day

		subcutaneously divided into 2 doses per day from day 9 until the last stem cell collection ✪ after stem cell collection patients were treated with 1 (HOVON study group) or 2 (GMMG study group) cycles of 200mg/m² HDM and ASCT followed by maintenance therapy 3. **CONSOLIDATION THERAPY -** none 4. **MAINTENANCE THERAPY** (Start: 4 weeks after HDM) ✪ 50mg thalidomide daily for 2 years	
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Defined as the time form random assignment until progression, relapse or death, whichever comes first.
	Complete response	CR	- Absence of the original monoclonal paraprotein (M-protein) in serum and (10 x concentrated) urine by immunofixation, maintained for at least 6 weeks - <5% plasma cells in a representative bone marrow aspirate or otherwise in a bone marrow biopsy. Only in patients with non-secretory myeloma, bone marrow investigation must be repeated after an interval of 6 weeks to confirm CR - No increase in size or number of lytic bone lesions (development of compression fractures does not exclude CR) - Disappearance of any soft tissue plasmacytoma
	Very good partial response	VGPR	- Meeting the criteria for PR but show a 90% reduction of serum M-protein concentration for at least 6 weeks
	Partial response	PR	- 50% reduction of serum M-protein concentration maintained for at least 6 week - Reduction in 24hrs urine M-protein either by ≥90% or to <200mg, maintained for at least 6 weeks - In patients with non-secretory myeloma, ≥50% reduction in plasma cells in a representative bone marrow aspirate, or otherwise bone marrow biopsy, maintained for at least 6 weeks - 50% reduction in size of soft tissue plasmacytoma - No increase in size or number of lytic bone lesions (development of compression fractures does not exclude PR)
	Minimal response	MR	- 25% reduction of serum M-protein concentration maintained for at least 6 weeks - 50% reduction in 24hrs urine M-protein, maintained for at least 6 weeks - In patients with non-secretory myeloma, ≥25% reduction in plasma cells in a representative bone marrow aspirate, or otherwise bone marrow biopsy, maintained for at least 6 weeks - 25% reduction in size of soft tissue plasmacytoma - No increase in size or number of lytic bone lesions (development of compression fractures does not exclude MR)
	No change	NC	- Not meeting the criteria of either minimal response or progressive disease
	Progressive disease	PD	- 25% increase in serum M-protein level, which must also be an absolute increase of at least 5g/l and confirmed at least once - 25% increase in 24h urine M-protein, which must also be an absolute increase of at least 100mg/24hrs and confirmed at

			least once - 25% increase in plasma cells in a representative bone marrow aspirate or bone marrow biopsy - Definite increase in the size of existing bone lesions or soft tissue plasmacytoma - Development of new bone lesions or soft tissue plasmacytoma (development of compression fractures does not exclude continued response and may not indicate progression) - Development of hypercalcaemia (corrected serum calcium >2.80 mmol/l) not attributable to any other cause
	Overall survival	OS	Defined as the time from registration to death from any cause. Patients still alive were censored at the date of last contact.
Results and analysis			
Analysis description	**Intention-to-treat analysis (ITT)** The number of events needed to detect the difference (PFS increase to 50% at three years = relative hazard ratio of 0.74 for the experimental arm) with a power of 80% and α=0.049 (two-sided and adjusted for interim analysis at a significance level of 0.001) is 356 and the required number of randomly assigned patients is 800.		
Analysis population	Inclusion		✪ patients with newly diagnosed and confirmed diagnosis of MM stage II or III according to the Durie-Salmon criteria ✪ age 18 to 65 years inclusive ✪ WHO performance status 0-3 (WHO=3 is allowed only when caused by MM and not by co-morbid conditions)
	Exclusion		✪ systemic amyloid light chain amyloidosis ✪ nonsecretory MM ✪ serum bilirubin ≥30 µmol/l or aminotransferases ≥2.5 times normal level ✪ neuropathy grade ≥ 2 ✪ history of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma ✪ HIV positivity
	Characteristics		*Intervention (PAD) vs Control (VAD), %* Median age, years (range): 57 (31 to 65) vs 57 (25 to 65) Male sex: 61 vs 60 WHO performance status 0/1/2/3/unknown: 47/41/8/4/1 vs 44/42/11/2/1 ISS stage I/II/III/unknown: 35/36/20/9 vs 35/30/26/9 M-protein isotype IgA/IgG/IgD/LCD: 22/61/1/15 vs 23/57/1/19 M-protein light chain kappa/lambda: 67/33 vs 67/33 Creatinine, mg/dL ≤2/>2: 91/9 vs 89/11 No. of skeletal lesions: 0/1-2/≥3/unknown: 25/11/62/3 vs 23/10/64/3 Serum LDH ≤ULN/≥ULN/unknown: 80/17/3 vs 80/17/3 Genetic abnormalities

		del(13q), done/ positive, % of done: 88/41 vs 90/44 t(4;14), done/ positive, % of done: 64/14 vs 63/13 del(17p13), done/ positive, % of done: 70/9 vs 76/13		
Descriptive statistics and estimated variability	Treatment group	*Intervention (PAD)*	*Control (VAD)*	*P value*
	Number of subjects	n=413	n=414	
	Median PFS, months	35	28	NR
	5-year OS, %	61	55	NR
	Response after induction, % CR ≥nCR ≥VGPR ≥PR	 7 11 42 78	 2 5 14 54	 <0.001 <0.001 <0.001 <0.001
	Response after HDM, % CR ≥nCR ≥VGPR ≥PR	 21 31 62 88	 9 15 36 75	 <0.001 <0.001 <0.001 <0.001
	Response overall, % CR ≥nCR ≥VGPR ≥PR	 36 49 76 90	 24 34 56 83	 <0.001 <0.001 <0.001 0.002
	Response upgrade during maintenance, % any response upgrade <CR → CR <nCR → nCR <VGPR → VGPR <PR → PR	 23 12 6 5 0	 24 11 4 7 3	 0.64 0.73 0.25 0.30 0.008
Effect estimate per comparison	*Comparison groups*	*(PAD)vs Control (VAD)*		
	Median PFS adjusted for ISS	HR	0.75	
		95% CI	0.62 to 0.90	
		P value	0.002	
	5-year OS adjusted for ISS	HR	0.81	
		95% CI	0.63 to 1.05	
		P value	0.11	

Abbreviations: NR – not reported; HR – hazard ratio; CI – confidence interval

Table 4: Summary of adverse events from the first interim analysis

Study ID: HOVON-65/GMMG-HD4								
Outcome, n (%)	**Intervention, PAD** (n=413)				**Control, VAD**(n=414)			
	PAD induction (n=410)		Bortezomib maintenance (n=229)		VAD induction (n=411)		Thalidomide maintenance (n=270)	
Any AE	400 (98)		222 (97)		401 (98)		260 (96)	
Grade ≥3	**258 (63)$^{+}$**		110 (48)		220 (54)		123 (46)	
AE classified as SAE	**187 (46)$^{+}$**		**77 (34)$^{+}$**		148 (36)		61 (23)	
AE leading to discontinuation, dose reduction or delay of bortezomib	112 (27)		81 (359		N/A		N/A	
Death from AE	7 (2)		0 (0)		9 (2)		0 (0)	
	All grades	**Grade 3-4**	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**	**All grades**	**Grade 3-4**
Haematologic toxicities, %								
Anaemia	28	8	**27^{+}**	1	24	7	15	1
Neutropenia	4	3	2	0	2	1	4	1
Thrombocytopenia	**39$^{\#}$**	**10^{+}**	**37$^{\#}$**	4	18	5	19	2
Infections	56	26	**75^{+}**	24	49	21	61	18
Herpes zoster	2	0	2	0	0	0	1	0
Non-haematologic toxicities, %								
Wasting, fatigue	27	4	20	1	28	4	20	1
GI symptoms	**67^{++}**	**11^{++}**	48	5	59	7	40	4
Cardiac disorders	27	8	19	3	24	5	13	2
Thrombosis	6	4	1	1	5	3	1	1
Peripheral neuropathy	**37$^{\#}$**	**24$^{\#}$**	33	5	26	10	**53$^{\#}$**	8

NOTE: Bold numbers indicate a statistically significant higher proportion compared with the other arm.
**p<0.01; $^{\#}$p<0.001; **p<0.05*

bortezomib as induction before and maintenance therapy after ASCT

The HOVON-65/GMMG-HD4 trial enrolled 827 patients (PAD arm: 413 vs VAD arm: 414) newly diagnosed with MM to assess efficacy of sustained bortezomib (i.e. as 2-year maintenance therapy after HDT with ASCT) treatment. Baseline patient and disease characteristics were well balanced. Information on genetic abnormalities was not available for all patients, but for those who was no difference between the two arms existed.

VAD vs PAD: 65% vs 55% of patients received maintenance therapy

Of all enrolled patients, 65% in the VAD and 55% in PAD group received maintenance treatment with thalidomide and bortezomib, respectively. In the VAD arm, 347 patients received HDM. Of these, 77 (22%) patients went off protocol after HDM because of alloSCT (n=21; 6%), persisting toxicity (n=11; 3%), or other reasons (n=45; 13%). In the PAD arm 229 received HDM, of whom 123 (35%) patients went off protocol because of alloSCT

(n=28; 8%), persisting toxicity (n=47; 13%, mainly polyneuropathy) or other reasons (n=48; 14%). According to the treatment protocol, maintenance therapy should have been given for 2 years. 47% of patients starting bortezomib maintenance and 27% of patients starting thalidomide maintenance therapy actually completed maintenance therapy according to protocol.

superior overall response rates in the PAD arm

response upgrade during maintenance therapy did not differ between groups

Response rates were superior in the PAD arm compared to the VAD arm after both, induction treatment and high-dose therapy with ASCT. The upgrade of response during maintenance therapy (i.e. from less than CR to CR) was observed to an equal extent in both groups with 23% in the PAD arm compared to 24% in the VAD arm. The median time to any response upgrade after the start of maintenance therapy was 7 (range 1 to 57) months and 6 (range 1 to 35) months in the PAD and VAD group, respectively.

+7 months median PFS in PAD vs VAD

Median PFS was 7 months longer in the PAD arm compared to the VAD arm (HR 0.75; 95% CI 0.62 to 0.90; p=0.002). Median OS was not reached at 66 months; 5-year OS observed was 61% in the PAD arm and 55% in the VAD arm.

bortezomib might overcome the adverse effect of del(17p13), t(4;14) and increased serum creatinine

Neben et al. (2012) presented details about the data of the 35 German sites which included comprehensive FISH cytogenetic analysis [21]. According to this analysis, patients with del(17p13) had improved clinical outcomes when treated with PAD compared to VAD. Since del(17p13) was an independent predictor for worse PFS and OS outcomes in the control arm, but not in the bortezomib arm, this finding suggests, that bortezomib treatment can improve, but not fully overcome adverse outcomes associated with del(17p13) [21]. PAD also yielded better, yet not statistically significant results than VAD in patients with t(4;14). Further, bortezomib induction and maintenance resulted in superior outcomes in patients with increased serum creatinine but not in patients with normal serum creatinine.

6.2 Efficacy and safety - further studies

no controlled phase II studies found

No controlled phase II studies investigating the efficacy and safety of bortezomib as consolidation or maintenance therapy after ASCT were found.

7 Estimated costs

Velcade® (bortezomib) is approved as an i.v. injection at a dose of 1.3mg/m² body surface area [5].

Assuming an average body surface area of 1.79m² [26] 2.33mg of bortezomib would be required for one injection. In Austria, one vial of 3.5mg bortezomib costs EUR 1,242 [27]. Thus one vial of 3.5mg (EUR 1,242) would be required.

maintenance therapy – estimated monthly costs: € 2,484.-

costs for 2-year maintenance: € 59,616

Bortezomib as maintenance therapy was administered at a dose of 1.3mg/m² once every 2 weeks for the duration of 2 years in the HOVON-65/GMMG-HD4 trial [21]. For an average patient one two-week cycle is EUR 1,242 resulting in EUR 2,484 per month. Assuming a two-year period maintenance therapy with bortezomib results in treatment costs of EUR 59,616.

consolidation therapy – estimated monthly costs: € 4,968.-

A phase III trial investigated bortezomib as consolidation therapy after ASCT at a dose of 1.3mg/m² on days 1, 8, 15 and 22 of a five-week cycle (two cycles were given) together with thalidomide and dexamethasone. Treatment costs for bortezomib in a consolidation combination would be EUR 4,968 for one cycle and EUR 9,936 for 2 cycles.

add-on to existing costs

As bortezomib does not replace any other treatment and is not intended to be used as a single-agent in the transplant setting, these cost estimates have to be regarded as add-on costs rather than absolute treatment costs.

8 Ongoing research

5 ongoing phase III studies found

On www.clinicaltrials.gov five ongoing phase III studies investigating the efficacy and safety of bortezomib included in the consolidation or maintenance treatment after ASCT in newly diagnosed MM patients were found:

NCT01208766: a phase III trial comparing the efficacy and safety of bortezomib, melphalan and prednisone (VMP) with high-dose melphalan followed by bortezomib, lenalidomide and dexamethasone (VRD) consolidation and leanlidomide maintenance in newly diagnosed MM patients. The estimated completion date for this study is December 2015.

NCT00416208: this phase III trial investigates the progression free survival of patients with MM aged between 61 to 75 years receiving consolidation therapy with bortezomib to those without receiving bortezomib after HDT with ASCT. Study ends when the last patient will finish the 30-months follow-up; this is estimated to be May 2013.

NCT00416273: this phase III trial investigates the efficacy and safety of consolidation therapy with or without bortezomib after HDT with melphalan and ASCT in patients aged between 18 to 60 years. This study will end when the last patient has had a follow-up phase of 30 months, which is estimated to be May 2013.

NCT01134484: a randomized phase III study to assess the efficacy and safety of bortezomib-thalidomide-dexamethasone (VTD) versus thalidomide-dexamethasone (TD) as induction therapy in preparation for, and as con-

solidation therapy after, melphalan-based double-ASCT in previously untreated symptomatic MM patients aged ≤65 years. This study is estimated to be completed by December 2015.

NCT01109004: a phase III study designed to investigate tandem-ASCT plus maintenance therapy versus single-ASCT plus consolidation therapy with lenalidomide, bortezomib and dexamethasone followed by maintenance therapy or single-ASCT plus maintenance therapy as part of upfront treatment of MM. Lenalidomide will be used as maintenance treatment for three years in all arms. The primary completion date for this study is estimated to be May 2016.

On www.clinicaltrialsregister.eu four ongoing phase III studies investigating bortezomib in the above mentioned indication were found, however, only one further trial was identified in addition to those registered at clinicaltrial.gov:

EudraCT Number 2004-000944-26: this randomized phase III trial aims to assess the efficacy of bortezomib combined with intensive chemotherapy and as maintenance therapy in comparison with intensive therapy with vincristine followed by thalidomide maintenance in patients with previously untreated MM patients.

9 Commentary

since 2003 and 2004 approved by EMA and FDA for the treatment of MM

Bortezomib has been approved by the US FDA and the EMA, as third-line therapy in patients with MM who have undergone or cannot undergo ASCT since 2003 and 2004, respectively [3, 7]. In 2008, the EMA extended the approved indication of bortezomib to first-line therapy of patients ineligible for ASCT and the US FDA amended the licensed indication to the treatment of MM without further specification. Thus, bortezomib is implicitly licensed for consolidation and maintenance therapy in the US but not in Europe. In addition, the US FDA approved bortezomib for the treatment of patients with mantle cell lymphoma in 2006 [8, 9].

current standard of first-line therapy in MM:
HDT supported by ASCT

focus of this report: bortezomib as consolidation or maintenance therapy

Up to now, high-dose therapy (HDT) supported by ASCT is considered standard of care for first-line therapy in patients with symptomatic MM. Within previous years, novel agents such as thalidomide, lenalidomide and bortezomib have been investigated and implemented in several treatment lines of MM. Recently, these drugs have been incorporated in the front-line induction therapy in combination with other agents in clinical treatment guidelines [4, 28]. The focus within this HSO report lies on the treatment effect of bortezomib when used as consolidation or maintenance therapy after HDT with ASCT, which is currently in clinical investigation [29].

improved response rates with bortezomib combination regimens shown in 2 phase III trials

Overall, 2 phase III studies investigating the effect of bortezomib as short-term consolidation [20] or as 2-year maintenance therapy [22] were included. The first study assessed bortezomib with thalidomide and dexamethasone as induction and consolidation therapy after HDT with ASCT compared to thalidomide and dexamethasone as induction and consolidation therapy. Besides improved response rates compared to the control arm, median time to CR or nCR (HR 0.61, 95% CI 0.49 to 0.76; $p<0.0001$) as well as median PFS (HR 0.63, 95% CI 0.45 to 0.88; $p=0.0061$) were superior in

the intervention arm. AEs reported in detail were only those occurring during induction therapy. During or after consolidation therapy 12 (5.1%) patients in the intervention and 5 (2.1%) patients in the control arm discontinued therapy.

response upgrade during maintenance therapy did not differ between treatment groups

The second study, the HOVON-65/GMMG-HD4 trial randomised 833 newly diagnosed MM patients either to PAD induction and maintenance therapy or to VAD induction and maintenance therapy. The objective was to assess whether PAD (bortezomib, doxorubicin, dexamethasone) as induction before HDM with ASCT and as maintenance after HDM with ASCT would achieve better response, quality of response, PFS and OS compared to induction and maintenance with VAD (vincristine, doxorubicin, dexamethasone). Response after induction therapy and also response overall was better in the PAD arm compared to the VAD arm. Though, response upgrade during maintenance therapy did not differ between those two groups and less patients (55%; n=229) in the PAD arm compared to the VAD arm (65%; n=270) received maintenance treatment.

no information on QoL available

Neither of the phase III trials reported quality of life (QoL). The most common and severe adverse events reported were peripheral neuropathy, skin rash and gastrointestinal events overall. During maintenance treatment anaemia, thrombocytopenia and infections were more frequent in the bortezomib-containing arm but peripheral neuropathy of any grade was more frequent in the control arm. AEs specifically reported during bortezomib consolidation therapy are not available.

the effect of bortezomib could not be independently assessed in the post-transplant setting

Even though the studies have used bortezomib as consolidation or as maintenance therapy, their role for the treatment of MM remains unclear. By reasons that patients were randomised already to different induction regimens and due to missing efficacy results specifically for the maintenance and consolidation treatment, the observed effect is mainly attributable to induction therapy. To establish if consolidation and/or maintenance therapy offer an additional benefit, controlled trials randomising patients to bortezomib or to e.g. BSC *after* HDT+ASCT are needed.

while having more effective treatment options available with the novel agents, questions about the most appropriate combination and sequence of the available options arise

With the introduction of novel agents (e.g. thalidomide, lenalidomide and bortezomib) being used in various treatment lines of MM treatment outcomes have improved, but concurrently questions regarding the most appropriate choice of therapy have arisen. For example, it is unclear which combination regimen should be given as induction therapy; what is the clear advantage of consolidation or maintenance therapy after ASCT and which chemotherapeutic agents should be used in which sequence, combination or patients. Another question concerns the optimal timing of HDM with ASCT – should it still be administered as upfront therapy or does ASCT yield better results as salvage therapy. In the absence of randomised studies comparing the different options head-to-head, it is difficult to recommend a specific sequence of regimens.

bortezomib might overcome the adverse effect of del(17p13)

Another challenge will be the identification of certain predictive factors (e.g. del(17p13) or t(4;14), increased serum creatinine) for selecting patients most likely to benefit from bortezomib treatment [20, 22].

not only efficacy but also safety issues and costs have to be considered in the choice of therapy

In addition to the efficacy aspects also safety aspects (e.g. cumulative toxicity with multiple-drug combinations or extended use (e.g. consolidation and/or maintenance therapy) of anti-cancer agents) and costs of the different treatment regimens have to be considered in the treatment management of MM patients.

To sum up, there are currently multiple effective therapeutic options for the treatment of the still incurable disease MM available. In the near future the main task will be to find the most effective sequence and combination of these therapeutic strategies [15, 30] in order to prolong OS and to improve or at least maintain quality of life.

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