Horizon Scanning in Oncology

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1 Drug description

Generic/Brand name/ATC code: Lenalidomide/Revlimid®/ L04AX04

Developer/Company: Celgene Europe Limited

Description: Lenalidomide is a second generation immune-modulatory agent with several modes of action, inducing anti-neoplastic, anti-angiogenic, pro-erythropoietic and immune-modulatory effects. These effects are exerted by inhibition of TNF-α production, activation of T-cells and by reduction of serum levels of the cytokines vascular endothelial growth factor and basic fibroblast growth factor [1, 2].

lenalidomide is an immune-modulatory agent with anti-neoplastic, anti-angiogenic, pro-erythropoietic effects

Revlimid® capsules are available at different dosages: 2.5 mg, 5 mg, 10 mg, 15 mg and 25 mg. The currently licensed dosage for previously treated multiple myeloma (MM) patients is 25mg lenalidomide in addition to 40mg dexamethasone.

25 mg daily orally

Dose adjustments are indicated for patients with impaired renal function [3]. Side-effects associated with this drug are venous thromboembolism and special caution is required in femalepatients of childbearing age, because lenalidomide causes foetal harm at all doses [4]. Furthermore, a higher incidence of second primary cancers (e.g. myelodysplastic syndrome) was observed under lenalidomide therapy.

adverse events: thrombocytopenia, deep venous thrombosis, pulmonary embolism

2 Indication

Lenalidomide is indicated for the first-line therapy of patients with MM who are not eligible for high-dose chemotherapy with bone marrow transplant.

3 Current regulatory status

In Europe, lenalidomide is not yet licensed for first-line therapy, but has market authorisation

licensed for previously treated patients with MM in Europe

- in combination with dexamethasone for the treatment of MM patients who have received at least one prior therapy in 2007.

Orphan drug designation was assigned in 2003 [5].

In the U.S., lenalidomide is an orphan drug and only available within the RevAssist® Programme, a risk evaluation and mitigation strategy. The Food and Drug Administration (FDA) granted market authorisation for Revlimid® for [4]:

.. and in the US

- patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndrome associated with a del(5q) ab-

normality with or without additional cytogenetic abnormalities in December 2005.

- MM, in combination with dexamethasone, in patients who have received at least one prior therapy in June 2006.

4 Burden of disease

MM accounts for ~10% of hematologic malignancies

MM is an incurable malignant plasma cell disorder characterised by osteolytic bone lesions, renal disease and immunodeficiency and 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 [6, 7].

incidence: 4-6 per 100,000 habitants

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

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 with men being more often affected than women. About 20% of patients are symptom-free at time of diagnosis [8, 9]. MM is often referred to as a disease of the elderly with only about 35% of MM patients being younger than 65 years [10, 11]. Raised erythrocyte sedimentation rate, 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 [12].

tests to confirm diagnosis, estimate tumour burden and prognosis

If a diagnosis of MM is suspected, a range of investigations and tests are indicated to confirm diagnosis, to 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 myeloma or solitary plasmocytoma, all of which not requiring systemic therapy in the first instance [6, 8, 12].

heterogeneous natural history

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

The natural history of MM is very heterogeneous. Initially, the Durie and Salmon system [13] was the staging system of choice until it was superseded by the International Staging System (ISS) for MM [14]. 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 [8, 12]. Though, the ISS is valid for prognostic purposes, its use to determine choice of therapy for individual patients is still unproven [12].

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 demonstrated by fluorescence in situ hybridisation (FISH) [12]. Patients presenting these prognostic factors are generally referred to as "high-risk" MM patients. Preliminary data suggest that the adverse effects (AEs) of these factors may be abrogated by newer agents, but to confirm this observation further prospective evaluation is required [12].

200 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 [8, 9], there are about 360 patients newly diagnosed with MM in Austria per year. Applying the above mentioned estimates, nearly 200 patients older than 65 years are newly diagnosed with symptomatic disease each year. In

Europe, there are about 21,000 new MM cases and approximately 16,000 deaths per year [15].

5 Current treatment

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 [8].

symptomatic MM:

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

For patients with advanced stage (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 and autologous stem-cell transplantation (ASCT). However, the age limit of 65 years is rather arbitrary since 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) [16, 17].

for ASCT ineligible patients: commonly used regimen: melphalan, prednisolone, thalidomide

For patients ineligible for transplant several agents are available and can be used either alone or in combination. These agents are:

- Steroids (e.g. dexamethasone and prednisone).
- Thalidomide.
- Lenalidomide.
- Bortezomib.
- Alkylating agents (e.g., melphalan and cyclophosphamide).
- Other cytotoxic drugs (e.g., vincristine, doxorubicin, and liposomal doxorubicin).

No standard of care has been defined yet and enrolment onto clinical trials is therefore highly recommended. However, commonly used regimens in the first-line setting are:

- MPT: melphalan, prednisolone, thalidomide
- VMP: bortezomib, melphalan, and prednisone [9, 18-22].

6 Evidence

1 phase III, 1 phase I/II trial, 1 retrospective analysis

A literature search was conducted in four databases (Ovid Medline, Embase, Cochrane Library, CRD Database) on 3rd of September 2012. Overall 626 references were identified. Of these, one phase III trial [23] (including supplementary material [24, 25]), one phase I/II study [26] and one retrospective analysis [27] were included in this report.

6.1 Efficacy and safety - Phase III studies

Table 1: Summary of efficacy

Study title Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma [23, 28]			
Study identifier	ClinicalTrials.gov number: NCT00405756, Protocol Number: CC-5013-MM-015		
Design	Randomised (1:1:1 ratio), double-blind, multicentre (82 centres in Europe, Australia, Israel), placebo controlled, 3-arm parallel group study, phase III		
	Duration	Enrolment: February 2007 – September 2008 Median follow-up: 30 months Cut-off date for final analysis: On-going (estimated study completion date: September 2013)	
Hypothesis	Superiority		
Funding	Celgene		
Treatment groups	Overall	459 patients	
	Control (MP) (n=154)	Induction: 28-day cycles of melphalan (0.18 mg/kg days 1 - 4), prednisone (2 mg/kg days 1 - 4) and placebo Maintenance: placebo	
	Intervention 1 (MPR-R) (n=152)	Induction: 28-day cycles of melphalan (0.18 mg/kg days 1 - 4), prednisone (2 mg/kg days 1 - 4), and lenalidomide (10 mg days 1 - 21) Maintenance: lenalidomide (10 mg days 1 - 21 of each 28-day cycle) until disease progression or the development of unacceptable rates of adverse effects.	
	Intervention 2 (MPR) (n= 153)	Induction: 28-day cycles of melphalan (0.18 mg/kg days 1 - 4), prednisone (2 mg/kg days 1 - 4), and lenalidomide (10 mg days 1 - 21) Maintenance: placebo	
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	time of randomization until the date of progression (based on the myeloma response criteria [29]) or death from any cause during treatment or until data censoring at the last date at which the patient was known to be progression-free.
	Overall survival	OS	time of randomization until the date of death from any cause or until data censoring at the last date at which the patient was known to be alive.
	Response rate	RR	based on the myeloma response criteria [29]: categories of response will include complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) [24]

	Time to response	TTR	calculated as the time from randomisation to the first documented objective response including CR and PR [24]		
	Duration of response	DOR	time from the initial response to the first documentation of confirmed progressive disease [24]		
Results and analysis					
Analysis description	Intention-to-treat: to detect a 50% improvement in median progression-free survival, from 15 months (MP) to 22.5 months (MPR-R).				
Analysis population	*Characteristics*		*Control*	*Intervention 1*	*Intervention 2*
	Age, median (range) in yrs		72 (65 - 91)	71 (65 – 87)	71 (65 – 86)
	65 – 75/>75 in yrs (%)		75.3/24.7	76.3/23.7	75.8/24.2
	Sex: male/female (%)		48.7/51.3	46.7/53.3	53.6/ 46.4
	Karnofsky PS score, median (range)		90 (60 – 100)	80 (60 – 100)	80 (60 – 100)
	ISS: I/II/III (%)		18.2/31.2/50.6	18.4/32.9/48.7	18.2/31.2/50.6
	Inclusion		symptomatic, measurable, newly diagnosed multiple myeloma who were not candidates for transplantation (≥65 years of age) were eligible for this trial		
	Exclusion		absolute neutrophil count of less than 1500 per cubic millimetre, a platelet count of less than 75,000 per cubic millimetre, a haemoglobin level of less than 8.0 g per decilitre, renal insufficiency (a serum creatinine level of >2.5 mg per decilitre [>221 µmol per litre]), and peripheral neuropathy of grade 2 or higher		
Descriptive statistics and estimated			*Control (MP)*	*Intervention 1 (MPR-R)*	*Intervention 2 (MPR)*
	Treatment group overall		*N = 154*	*N = 152*	*N = 153*
	PFS, median (months)		13.0	31.0	14.0
	3-year OS, %		66	70	62
	RR (%)		50.0	77.0[1]	68.0[2]
		CR	3.2	9.9	3.3
		PR	46.8	67.1	64.7
		Very good PR	9.1	23.0[1]	29.4
		SD	45.5	18.4	26.1
		PD	0	0	1.3
		Not evaluable	4.5	4.6	4.6
	TTR, median (months)		3	2[1]	2[1]
		Range	1 -15	1-9	1-6

[1] P<0.001 for the comparison with the MP group

[2] P=0.002 for the comparison with the MP group

	DOR (months) CR + PR, median (95%CI) CR, median (95%CI) PR, median (95%CI)	 13 (10 – 18) 22 (10 -24) 10 (9 – 15)	 29 (22 – NR)[3] NR (36 – NR)[3] 19 (11 –NR)	 13 (12 – 15) 31 (23 -33) 11 (9 – 13)
	QoL	NA	NA	NA
	Subgroup analyses			
	Maintenance group	*N = 102*	*N = 88*	*N = 94*
	PFS, median (months)	NR	26	7
	Patients 65 – 75 yrs	*N = 116*	*N = 116*	*N = 116*
	PFS, median (months)	12	31	15
	Patients >75 yrs	*N = 38*	*N = 36*	*N = 37*
	PFS, median (months)	15	19	12
Effect estimate per comparison	*Comparison groups (overall study population)*		*Intervention 1 (MPR-R) vs Intervention 2 (MPR)*	
	PFS	HR	0.49	
		95%CI	NA	
		P value	<0.001	
			Intervention 1 (MPR-R) vs Control (MP)	
		HR	0.40	
		95%CI	NA	
		P value	<0.001	
	OS		*Intervention 1 (MPR-R) vs Control (MP)*	
		HR	0.95	
		95%CI	NA	
		P value	0.81	
			Intervention 1 (MPR - R) vs Intervention 2 (MPR)	
		HR	0.79	
		95%CI	NA	
		P value	0.25	
	Comparison groups (subgroup analyses)		*Intervention 1 (MPR-R) vs Intervention 2 (MPR)*	
	PFS (maintenance)	HR	0.34	
		95%CI	NA	
		P value	<0.001	

[3] P<0.001 for the comparison with th MPR group and the comparison with the MP group

	PFS (age 65 – 70 yrs) Outcome		*Intervention 1 (MPR-R) vs Intervention 2 (MPR)*
		HR	0.48
		Variability	NA
		P value	<0.001
			Intervention 1 (MPR-R) vs Control (MP)
		HR	0.30
		Variability	NA
		P value	<0.001
Notes	Patients in whom progressive disease developed during induction therapy discontinued the double-blind treatment phase and could enrol in an open-label extension phase to receive lenalidomide (25 mg on days 1 through 21 of each 28-day cycle) alone or with dexamethasone (40 mg on days 1 through 4, 9 through 12, and 17 through 20). All patients received aspirin thromboprophylaxis (75 to 100 mg daily) during induction. Three analyses were specified by the protocol, when 148 progression-free survival events (50%), 207 events (70%), and 296 events (100%) had occurred. On the basis of the first analysis (data cut-off, April 2009), the data and safety monitoring committee recommended unblinding of the study because the prespecified O'Brien–Fleming superiority boundary (two-sided alpha level of 0.003 at 50% information [148 progression-free survival events]) for the primary end point had been crossed (hazard ratio, 0.50; P<0.001).		

Abbreviations: CR = complete response, CI = confidence interval, HR = hazard ratio, NA = not available; NR = not reached, PD = progressive disease, PR = partial response, SD =stable disease, QoL = quality of life, yrs = years,

Table 2: most frequent adverse events of grade 3 and 4 (occurring in at least 5% of the safety population and adverse events of clinical interest occurring in at least 2% of the safety population)

Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma [23, 28]							
Grade (according to CTC version 3.0)	**Outcome, n (%)**	**Control (MP)** (n=153)	**Intervention 1 (MPR-R)** (n=150)	**Intervention 2 (MPR)** (n=152)	**Control (MP)** (n=102)	**Intervention 1 (MPR-R)** (n=88)	**Intervention 2 (MPR)** (n=94)
		Induction			**Maintenance**		
Grade 3	Haematologic						
	Neutropenia	45 (29)	100 (67)	97 (64)	1 (1)	4 (5)	0
	Thrombocytopenia	18 (12)	53 (35)	58 (38)	2 (2)	0	0
	Anaemia	21 (14)	36 (24)	40 (26)	5 (5)	2 (2)	2 (2)
	Leukopenia	21 (14)	35 (23)	39 (26)	-	-	-
	Febrile neutropenia	0	7 (5)	2 (1)	-	-	-
	Non-haematologic						
	Infection	11 (7)	14 (9)	20 (13)	1 (1)	3 (3)	2 (2)
	Fatigue	5 (3)	8 (5)	2 (1)	1 (1)	2 (2)	0
	Deep-vein thrombosis	1 (1)	2 (1)	6 (4)	0	2 (2)	1 (1)
	Cardiac disorder	5 (3)	5 (3)	4 (3)	-	-	-
	Diarrhoea	0	3 (2)	2 (1)	0	3 (3)	0
	Rash	2 (1)	7 (5)	7 (5)	-	-	-
	Bone pain	-	-	-	4(4)	4(5)	1 (1)
	Diabetes mellitus	-	-	-	0	2 (2)	0

Grade 4	Haematologic						
	Neutropenia	12 (8)	52 (35)	49 (32)	0	2 (2)	0
	Thrombocytopenia	6 (4)	17 (11)	19 (12)	0	5 (6)	2 (2)
	Anaemia	2 (1)	4 (3)	4 (3)	0	2 (2)	1 (1)
	Leukopenia	2 (1)	6 (4)	8 (5)	-	-	-
	Febrile neutropenia	0	3 (2)	2 (1)	-	-	-
	Non-haematologic						
	Infection	0	1 (1)	3 (2)	2 (2)	2 (2)	0
	Fatigue	0	0	1 (1)	0	1 (1)	0
	Deep-vein thrombosis	0	0	1 (1)	0	0	0
	Cardiac disorder	0	3 (2)	4 (3)	-	-	-
	Diarrhoea	0	1 (1)	0	0	1 (1)	0
	Rash	0	0	0	-	-	-
	Bone pain	-	-	-	1 (1)	0	0
	Diabetes mellitus	-	-	-	0	0	0
Others	Treatment-related deaths	-	3 (2)	1 (1)	-	-	-
	Discontinuation due to AE [28]	8 (5)	24 (16)	22 (14)	-	8 (9)	-

phase III trial included 459 patients randomised to three treatment arms

lenalidomide induction therapy and lenalidomide maintenance therapy were compared to placebo

This phase III trial evaluated lenalidomide induction and maintenance therapy in patients aged ≥65 years who were considered ineligible for high-dose chemotherapy and ASCT. 459 patients were randomised in a 1:1:1 ratio to either of three groups: 1. melphalan + prednisone + placebo induction therapy followed by placebo maintenance (MP), 2. melphalan + prednisone + lenalidomide induction followed by lenalidomide maintenance therapy (MPR–R) or to 3. melphalan + prednisone + lenalidomide induction followed by placebo maintenance therapy (MPR). Patients who completed all 9 cycles of induction therapy could enter maintenance therapy as well could patients who had to stop induction therapy due to intolerance. Patients with disease progression during induction therapy were unblinded and could enter an open-label extension phase with either lenalidomide alone or in combination with dexamethasone. Patients' baseline characteristics were comparable, with the exception of a better Karnofsky performance status score in the MP group than in the two other groups. Median age was 71 years.

PFS + 18 months in patients receiving lenalidomide induction and maintenance therapy vs placebo therapy

this gain mainly due to maintenance therapy

The primary outcome was progression-free survival (PFS) in the MPR-R group compared to the MP group. Overall, median PFS was 31 months in the MPR-R group, 14 months in the MPR and 13 months in the MP group. Risk of progression or death was reduced by 60% in the MPR-R group in comparison to the MP group and by 51% in comparison to the MPR group. Between the two groups *without* lenalidomide maintenance therapy (i.e. MPR and MP) no difference in PFS existed. An additional analysis compared PFS from the start of maintenance therapy between the two groups which had been treated with lenalidomide induction therapy yielding a hazard ratio of 0.34 ($p<0.001$). Furthermore, complete or partial responses, were superior for the two groups which had received lenalidomide and duration of response was significantly longer for the maintenance lenalidomide group (MPR-R) than for those with placebo maintenance (MPR + MP).

Thus the main effect on PFS was triggered by maintenance therapy with lenalidomide. However, patients entering the maintenance phase (overall 284 patients that is 62%) had a higher proportion of patients ≤75 years, scored better on the ISS and had a better renal function than those initially randomised [28].

patients entering maintenance therapy had better baseline characteristics than those initially enrolled

PFS subgroup analyses (according to gender, ISS, renal function or β_2-microglobulin and albumin levels, Karnofsky PS) comparing MPR-R and MP always favoured the lenalidomide group. Only in the rather small group of patients aged >75 years no significant difference existed [28]. 3-year OS rates were comparable between the three groups but these outcomes might be confounded due to crossing-over to lenalidomide and 46% received second-line therapy in the MPR-R group, 69% in the MPR and 76% in the MP group respectively [28].

no significant difference for patients >75 years but all other subgroup analyses favoured lenalidomide therapy

OS showed no difference

Higher grade haematologic AEs during induction therapy occurred more often in the lenalidomide groups than in the placebo group (see table 2) and more patients in these groups received granulocyte colony-stimulating factor and platelet transfusion. Also, a higher proportion of patients in the MPR-R and in the MPR group discontinued therapy due to AEs. 2% of deaths in the MPR-R group and 1% in the MPR group, respectively, were considered as treatment-related; no results were provided for the MP group. Second primary tumours developed in 7% of patients in the two lenalidomide groups in contrast to 3% in the MP group. Only haematologic second primary tumours were mentioned in the publication and included acute myeloid leukaemia (4 patients in the MPR-R, 2 in the MPR group), myelodysplastic syndromes (1 patient in the MPR-R group, 3 in the MPR group), T-cell acute lymphoblastic leukaemia (1 patient in the MPR-R group) and chronic myelomonocytic leukaemia (1 in the MPR-R group). Tumours other than hematologic ones were observed in 5 patients in the MPR-R group, in 4 in the MPR and in 3 in the MP group.

AEs also more common in lenalidomide groups

secondary primary tumours in 7% in lenalidomide treated patients and in 3% in placebo group

In the maintenance phase side-effects were less frequent (see table 2).

6.2 Efficacy and safety - further studies

Prior to the phase III trial, the maximum tolerated MPR-R dose was elicited in a phase I/II dose-escalation study [30]. Results for patients who had been treated with this maximum dose (the regimen used in the phase III study) were presented in a separate publication [26]. 21 transplant ineligible patients with a median age of 69 years were enrolled. 19% discontinued therapy due to AEs, 33% initially reduced therapy of which 19% stopped therapy eventually. Grade 3 and 4 neutropenia was seen in 38% and in 14% of patients, and thrombocytopenia in 14% and 10%. Non-haematologic AEs of grade 3/4 occurred in 29%, with the most frequent ones being febrile neutropenia (10%) and vasculitis (10%). Thromboembolic events were seen in 5%. For efficacy outcomes, a median PFS of 28.5 months, complete responses in 24% and partial responses in 33% were reported. OS at 2 years was 91%.

1 phase I/II trial

grade 3 neutropenia in 38%, thromboembolic events in 5%

PFS 28.5 months

retrospective analysis including 17 patients with single-agent lenalidomide

A retrospective analysis of 17 previously untreated patients treated with single-agent lenalidomide was performed [27]. Patients received 25mg daily instead of 10mg like in the phase III trial. The overall response rate was 47% and median time to first response was 50 days. Six patients needed dexamethasone due to disease progression. No grade 4 AEs were noted but thrombocytopenia, the most frequent AE of grade 3, was observed in 19%. No thromboembolic occurred.

7 Estimated costs

monthly treatment costs of € 5,400

In Austria, the estimated costs for one package Revlimid® containing 21 capsules of 10mg is 5,475.-€ [31], corresponding to the monthly costs of lenalidomide therapy. Overall treatment costs cannot be calculated, because the mean treatment duration is unknown.

Besides costs for lenalidomide itself, expenditures for melphalan and prednisone, as well as supportive treatment (e.g. granulocyte colony stimulating factor, platelet transfusion) have to be taken into account.

8 Ongoing research

on-going trials

On www.clinicaltrials.gov 5phase III trials for the first-line therapy of MM patients were found.

- NCT01093196: to compare three all-oral combinations: lenalidomide with dexamethasone in comparison with lenalidomide in association with MP (MPR) and lenalidomide in association with cyclophosphamide - prednisone (in newly diagnosed symptomatic MM patients. Estimated study completion date: November 2014.
- NCT00689936: to compare lenalidomide plus low-dose dexamethasone until progressive disease or for 18 four-week cycles versus the combination of melphalan, prednisone, and thalidomide given for 12 six-week cycles in patients with previously untreated MM who are either 65 Years of age or older or not candidates for stem cell transplantation. Estimated study completion date: March 2016.
- NCT01554852: compares a standard chemotherapy regimen of cyclophosphamide, dexamethasone plus thalidomide with a newer regimen of cyclophosphamide, dexamethasone plus lenalidomide. Estimated primary completion date: September 2017.
- NCT00551928: compares the combination of lenalidomide with low-dose melphalan versus high-dose melphalan in newly diagnosed, symptomatic MM patients. The stated study completion date was August 2011, but the protocol has not been updated recently.

- NCT01335399: compares the addition of elotuzumab to lenalidomide/low-dose dexamethasone. Estimated primary completion date: May 2016.

On www.clinicaltrialsregister.eu 6 phase III trials were found:

- 2008-003486-58: A pharmacogenomic study to predict survival, best response and toxicity in newly diagnosed MM patients who are either 65 years of age or older treated with either a combination of melphalan-prednisone-thalidomide or lenalidomide-dexamethasone. Estimated study completion date: not available.
- 2007-004007-34: Randomized phase III trial in elderly patients with previously untreated symptomatic MM comparing MP-Thalidomide followed by thalidomide maintenance versus MP-Lenalidomide followed by maintenance with lenalidomide. Estimated study completion date: not available.
- 2010-019173-16: to evaluate two regimens of bortezomib based induction therapy and lenalidomide consolidation followed by lenalidomide maintenance treatment. Estimated study completion date: not available.
- 2006-001865-41: Determine the efficacy and safety of lenalidomide (Revlimid) in combination with melphalan and prednisone versus placebo plus melphalan and prednisone in subjects with newly diagnosed multiple myeloma who are 65 years of age or older. Estimated study completion date: not available.
- 2008-004083-39: lenalidomide and dexamethasone with or without intensification by high-dose melphalan in the treatment of multiple myeloma. Estimated study completion date: not available.
- 2007-004823-39: to compare the efficacy of lenalidomide plus low-dose dexamethasone given until progressive disease to that of the combination of melphalan, prednisone, and thalidomide given for 12 six-week cycles. Estimated study completion date: not available.

In addition, lenalidomide is under investigation for ASCT eligible MM patients and is in phase III for other cancers such as myelodysplastic syndrome, large B-cell lymphoma, chronic lymphocytic leukaemia and mantle cell lymphomas.

9 Commentary

lenalidomide currently not licensed in Europe for first-line MM therapy

For many decades, MP was considered standard therapy for transplant-ineligible MM patients. With the advent of novel agents, this treatment paradigm has changed and combinations of bortezomib or thalidomide with MP are commonly used regimens for the first-line therapy of these patients.

increase in PFS mainly due to maintenance therapy

Lenalidomide, a drug currently licensed in Europe only for previously treated MM patients, was also evaluated in the first-line setting for transplant ineligible patients. A phase III trial compared MP and MPR followed by placebo maintenance to MPR followed by lenalidomide maintenance therapy [23]. Enrolled were 459 patients aged over 65 years who were considered in-

eligible for transplant. PFS was prolonged by 17 months in the MPR-R in comparison to MPR and by 18 months in comparison to MP. Between the two groups with placebo maintenance no difference in PFS existed. Response rates also yielded improved results for patients treated with lenalidomide. Data on 3-year OS, on the other hand, were comparable between the treatment groups but these findings might have been compromised due to crossing over to lenalidomide. AEs were also more frequent in the lenalidomide groups than in the MP only group. The most common higher-grade AEs (i.e.≥grade 3) during induction therapy were haematologic side-effects (MPR-R vs MPR vs MP) such as neutropenia (67% vs 64% vs 29%), thrombocytopenia (35% vs 38% vs 12%) and anaemia (24% vs 26% vs 14%) and more patients consequently discontinued lenalidomide therapy due to AEs than in the placebo group.

no difference in 3 year OS - due to cross-over?

common AEs during induction – foremost haematologic in up to 67%

The increase in PFS in the MPR-R group is mainly attributable to lenalidomide *maintenance* therapy but only 88 patients (=58%) in the MPR-R and 94 patients (=61%) in the MPR group entered the maintenance phase. Also, side-effects were less frequently observed than during induction therapy. Despite the fact that no commonly accepted criteria for determination of transplant eligibility exist - besides age, co-morbidities and the biological age are being considered - the primary inclusion criteria (i.e. ≥65 years, Karnofsky performance score ≥60%, no serious medical condition) did not necessarily result in identification of transplant-*ineligible* patients in the first place. Moreover, subjects entering the maintenance phase showed even better characteristics [25]. Hence, it remains questionable if these patients are actually comparable to those who would be deemed ASCT ineligible in clinical practice. A subgroup analysis comprising patients older than 75 years and thus potentially ineligible for ASCT indicated no statistically significant difference in PFS for patients treated with MPR-R in comparison to MP. The incidence of AEs in this age group would have been of interest, but was not reported. Hence, if elderly patients with potentially more comorbidities can actually benefit from lendalidomide therapy needs to be explored further.

main improvement in PFS due to maintenance comprising fewer patients with better baseline characteristics than those initially enrolled

potentially eligible for ASCT?

unclear if elderly patients with comorbidities will benefit from lenalidomide

of interest: AEs in this age group

Another issue is the lack of convincing data for OS, since the validity of PFS and response rates as surrogates has not been established unequivocally [32, 33]. Furthermore, since transplant ineligible patients are usually elderly patients with co-morbidities, it is of utmost importance if improvements in response and PFS will actually translate into improved quality-of-life [34]. Even though assessment of health-related quality-of-life was planned according to the study protocol [24], no results for this outcome were reported but would be, in light of high rates of AE, helpful in determining the utility of lenalidomide.

if PFS gain will translate into OS gain unclear

no QoL data

Another point concerns the comparator used in the phase III study, because MP only, without agents such as bortezomib or thalidomide, cannot be considered standard of care anymore [21]. The comparison of MP + thalidomide to MP + lenalidomide is being assessed in an on-going phase III study (end of recruitment is planned for 2013) [34]. In the absence of direct comparative data, different side-effect profiles might offer a means for selecting therapy. For example, peripheral neuropathies, an AE associated with thalidomide, are less common with lenalidomide [35, 36] which might thus be preferred for patients with existing neurologic disorders [35]. On the other hand, thromboembolic events during lenalidomide therapy are of concern. In the phase III study 3% of patients experienced deep vein thrombosis despite thromboprophylaxis. A pooled analysis of three trials reported that 8%

comparator used not standard therapy anymore but ongoing phase III trial

AE profile for choosing treatment – lenalidomide for patients with peripheral neuropathies

of all patients experienced deep vein thrombosis despite the fact that the majority of patients (i.e. 88%) had received anticoagulants [37]. However, this analysis was based on only 125 patients.

but: thromboprophylaxis required and higher incidence of second primary tumours

Also the risk of second primary cancers is increased with lenalidomide therapy. The FDA released a safety announcement in May 2012, notifying the public that patients with newly diagnosed multiple myeloma who had been treated with lenalidomide after ASCT had almost a three-fold increased risk of developing new types of cancer, especially acute myeloid leukaemia, myelodysplastic syndromes and B-cell lymphoma malignancies [38]. EMA's Committee for Medicinal Products for Human Use also addressed this question, but concluded that the benefits still outweighed the risk associated with lenalidomide – at least for the currently licensed indication (i.e. previously treated patients) [39].

dosage, combination and sequence still needs to be evaluated

Due to the development of new treatment strategies for the first-line therapy of MM patients, the importance of frontline therapy with ASCT is being challenged [40]. Even though the phase III trial included patients who were considered transplant ineligible, the main effect of MPR-R was due to maintenance therapy in relatively young patients. If similar effects without increased toxicity can be observed in elderly and frail patients too, needs to be investigated further. The optimal dosage, the best combination – if at all – as well as the best sequence of therapies still needs to be determined [1, 41]. Selection of the optimal treatment strategy might also be improved by further characteristics such as cytogenetics [33, 35, 42].

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