Horizon Scanning in Oncology

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1 Drug description

Generic/Brand name/ATC code:

Pomalidomide, CC-4047/ Imnovid® (Europe), Pomalyst® (U.S.)/L04AX06

Developer/Company:

Celgene Corporation

Description

pomalidomide is a new immunomodulatory drug

Pomalidomide, an analogue of thalidomide, is a new immunomodulatory antineoplastic agent. The mechanism of action of pomalidomide is not fully understood but three broad modes of action have been identified: an anti-tumour effect (antiproliferative, pro-apoptotic), modulation of the bone marrow micro-environment (anti-angiogenic, anti-inflammatory) and modulation of the immune system (natural killer-cells and T-cell activation/stimulation) [1]. Thus, this agent induces apoptosis and inhibits proliferation of multiple myeloma (MM) cells by modulating expression of cytokines that stimulate T-cells and natural killer cells or down-regulate angiogenesis [2, 3]. Pomalidomide has also shown activity in lenalidomide and/or bortezomib-resistant MM cell lines [3-5].

activity in lenalidomide and/or bortezomib resistant MM cell lines

4 mg capsules orally on 21 days of a 28 days cycle

Pomalidomide is available in 1 mg, 2 mg, 3 mg and 4 mg capsules for oral administration. The dosage is 4 mg per day taken orally on days 1–21 of repeated 28-day cycles until disease progression [6]. Because of the risk of venous thromboembolism (deep venous thrombosis and pulmonary embolism) with pomalidomide therapy, prophylactic anti-thrombotic therapy is indicated.

2 Indication

for patients with relapsed and refractory MM who have received at least two prior treatment regimens

Pomalidomide is indicated for patients with relapsed and refractory MM who have received at least two prior treatment regimens, including both lenalidomide and bortezomib and who have demonstrated disease progression on the last therapy.

3 Current regulatory status

orphan designation in Europe and licensed in August 2013

Orphan designation was assigned to pomalidomide for the treatment of MM by the EMA in October 2009 [7]. On the 30th of May 2013, EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending marketing authorisation for pomalidomide and on the 5th of August 2013 marketing authorisation was issued for pomalidomide

- in combination with dexamethasone for the treatment of adult patients with relapsed and refractory MM who have received at least two prior treatment regimens, including both lenalidomide and

bortezomib, and have demonstrated disease progression on the last therapy [8].

licensed in the U.S. in February 2013

In the U.S., pomalidomide also has orphan drug status for MM and the FDA granted market authorization on February 2013 for

- patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy [9].

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 B-cell type of lymphoma. MM accounts for about 10% of all haematological malignancies and is, after non-Hodgkin's lymphoma (NHL), the second most common haematologic malignancy, with men being affected more often than women [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 [12]. MM is therefore often referred to as a disease of the elderly, with only about 35% of MM patients being younger than 65 years [13, 14].

incidence: 4–6 per 100,000 habitants

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

About 20% of patients are symptom-free at time of diagnosis [15, 16]. 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 [17].

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 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, none of which require systemic therapy in the first instance [10, 15, 17].

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 [18] was the staging system of choice until it was superseded by the International Staging System (ISS) for MM [19]. 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. Biological parameters in particular (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 stage [15, 17]. The ISS is valid for prognostic purposes, but its use to determine choice of therapy for individual patients is still unproven [17]. Factors associated with poor prognosis include genetic abnormalities such as t(4;14), t(14;16) and deletion 17p demonstrated by fluorescence in situ hybridisation [17]. Patients presenting these prognostic factors are generally referred to as "high-risk" MM patients.

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

Despite advances in treatment options for MM, nearly all patients eventually relapse. Relapse is defined as development of progressive disease after maximal response has been achieved, whereas refractory refers to patients that are either unresponsive to current therapy or progress within 60 days of last treatment [20]. These patients usually have a poor prognosis with a median overall survival (OS) less than a year [20, 21].

5 Current treatment

available treatment options

Patients with newly diagnosed MM are initially assessed for stem cell transplant eligibility. Regardless of eligibility for transplantation, systemic treatment options include:

- Immunomodulatory drugs: lenalidomide, thalidomide
- Proteasome inhibitors: bortezomib, carfilzomib (not licensed in Europe)
- Corticosteroids: dexamethasone, prednisone
- Alkylators: e.g melphalan, cyclophosphamide
- Anthracycline: e.g. doxorubicin

therapeutic options after disease progression

However, all patients eventually progress. When patients relapse, duration of response, prior lines of therapy, presence of high-risk disease and toxicities and co-morbidities determine choice of further therapy [22]. Thus, either re-challenge with previous therapies or alternative treatment options are indicated, e.g.

- bortezomib ± pegylated liposomal doxorubicin or dexamethasone
- lenalidomide ± dexamethasone
- thalidomide + dexamethasone
- lenalidomide or bortezomib + cyclophosphamide + dexamethasone
- bortezomib + thalidomide + dexamethasone
- carfilzomib (not licensed in Europe) [23-25].

heavily pre-treated patients with relapsed and refractory MM have limited treatment options

However, for heavily pre-treated patients who have relapsed and refractory disease (that is, progression within 60 days of their last therapy in patients who have previously experienced a minimal response or non-responsive disease to salvage therapy) during or after treatment with bortezomib and/or lenalidomide, therapeutic options are limited and enrolment into a clinical trial is highly encouraged [23, 26].

6 Evidence

literature search in 4 databases yielded 159 hits

A literature search was conducted on the 14th of May in 4 databases (Ovid Medline, Embase, Cochrane Library, CRD Database). Search terms were “pomalidomide”, “pomalyst”, “actimid”, “cc4047”, “cc 4047”, “refractory multiple myelomas” and “multiple myeloma”. Overall 159 references were identified. In addition, the manufacturer was contacted for further evidence and submitted 6 references (2 full texts, 4 abstracts). Of these, one reference [27] had already been identified by the systematic literature

manufacturer submitted 6 further references

search and one was a review [1]. Thus 4 abstracts, all relating to a phase III study, were included.

results of 3 phase II studies and 1 phase III study included

Overall, results of 4 studies were included in this report. For the pivotal CC-4047-MM-002 trial, a phase II study, FDA licensing documents [28] and several abstracts [29-37] were used. Results of the phase III trial have been published as conference abstracts [38-44], but shortly prior to publication of this report the full text was published and was therefore also included [45]. Two further phase II studies [27, 28, 46] were included.

Excluded were studies where patients had not been treated previously with both lenalidomide and bortezomib [47, 48] and results of phase I and phase II studies available as conference abstracts only.

6.1 Efficacy and safety

6.1.1 Phase III study

Table 1: Summary of efficacy

Study title Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial		
Source of information	Full text [45], EMA licensing documents [49], abstracts, presentation, other [38-44]	
Study identifier	NCT01311687, CC-4047-MM-003, 2010-019820-30, NIMBUS trial	
Design	Multi-centre, randomised, open-label, phase III, 2:1 randomization	
	Duration	*Enrolment:* March 2011 – August 2012 *Median follow-up:* 4.2 months as of September 2012, 10.0 months as of March 2013 *Cut-off dates for analyses:* Final PFS analysis and interim OS: September 2012 Updated PFS and final OS analysis: March 2013
Hypothesis	Superiority: with 85% power to detect a 50% improvement in median PFS (HR 1.5 for pomalidomide plus low-dose dexamethasone vs. high-dose dexamethasone) at a two-sided significance level of 0.05	
Funding	Celgene Corporation	
Treatment groups	Overall study population	N = 455
	POM + DEX (n=302)	Oral pomalidomide 4 mg/day for 21 days and dexamethasone 40 mg (for patients ≤ 75 years) or 20 mg (for patients >75 years) on days 1, 8, 15 and 22 of each 28-day cycle until disease progression or unacceptable toxicity
	HiDEX (n=153)	Oral high-dose dexamethasone 40 mg (for patients ≤ 75 years) or 20 mg (for patients >75 years) on days 1–4, 9– 12, and 17–20 of a 28-day cycle until disease progression or unacceptable toxicity

Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Number of months between randomization and disease progression in accordance with International Myeloma Working Group criteria (IMWG)) or death
	Overall survival	OS	NA
	Overall response rate	ORR	Proportion of patients achieving at least partial response according to IMWG criteria or EBMT criteria for minor response only based on investigator assessment
	Duration of response	DOR	In patients with at least partial response
	Time to progression	TTP	Time from randomization to the first documented progression confirmed by the Independent Response Adjudication Committee
	Quality of life	QoL	Change scores and minimal important differences were calculated as meaningful change from baseline through C5 (1 standard error of measurement) for 5 clinically relevant EORTC QLQ-C30 domains (Global Health Status, Physical Functioning, Fatigue, Emotional Functioning, and Pain)
Results and analysis			
Analysis description	Intention-to-treat PFS was estimated with the Kaplan- Meier product-limit method and a log-rank test (stratified by the three randomisation stratification variables) was used as the primary analytic method to compare survivorship functions between treatment groups.		
Analysis population	Inclusion	✠ Documented diagnosis of multiple myeloma and have measurable disease ✠ Prior treatment with ≥ 2 treatment lines of anti-myeloma therapy ✠ Either refractory or relapsed and refractory disease defined as documented disease progression during or within 60 days of completing their last myeloma therapy ✠ At least 2 consecutive cycles of prior treatment that included lenalidomide and bortezomib ✠ Failed treatment with both lenalidomide and bortezomib in one of the following ways: 1) Documented progressive disease on or within 60 days of completing treatment with lenalidomide and/or bortezomib, or 2) In case of prior response (≥ PR) to lenalidomide or bortezomib, subjects must have relapsed within 6 months after stopping treatment with lenalidomide and/or bortezomib-containing regimens, or 3) Subjects who have not had a ≥ minimal response (MR) and have developed intolerance/toxicity after a minimum of two cycles of lenalidomide- and/or bortezomib-containing regimen ✠ Adequate prior alkylator therapy ✠ ECOG PS score of 0 - 2	
Analysis population	Exclusion	✠ Previous therapy with pomalidomide ✠ Hypersensitivity to thalidomide, lenalidomide, or dexamethasone ✠ Resistance to high-dose dexamethasone used in the last line of therapy ✠ Peripheral neuropathy ≥ Grade 2 ✠ Subjects who received an allogeneic bone marrow or allo-geneic peripheral blood stem cell transplant ✠ Subjects who are planning for or are eligible for stem cell transplant	

Analysis population	Characteristics		POM + DEX	HiDEX
		Median age, yrs (range)	64 (35 – 84)	65 (35 – 87)
		>65, %	45	47
		>75, %	8	8
		ECOG PS, %		
		0 –1	82	80
		2 – 3	17	18
		Median number of prior therapies, n (range)	5 (2 – 14)	5 (2 – 17)
		More than 2, %	94	95
		Previous treatments, %		
		Thalidomide	57	61
		Lenalidomide	100	100
		Bortezomib	100	100
		Refractory to, %		
		lenalidomide	95	92
		bortezomib	79	79
		lenalidomide and bortezomib	75	74
		Median time from diagnosis, yrs	5.3	6.1
		Baseline MM Stage, %		
		I–II	65	61
		III	31	35
Descriptive statistics and estimated variability	Treatment group		POM + DEX	HiDEX
	Number of subjects		N = 302	N = 153
	Median PFS, months (95%CI) September 2012			
	Independent Review Adjudication Committee		3.6 (3.0 – 4.6)[1]	1.8 (1.6 – 2.1) [1]
	Investigator assessed		3.8 (3.4 – 4.6)	1.9 (1.9 – 2.1)
	March 2013			
	Investigator assessed		4.0 (3.6 – 4.7)	1.9 (1.9 – 2.2)
	Median OS, months (95%CI) September 2012		11.9 (10.4 – 15.5)	7.8 (6.4 - 9.2)
	March 2013		12.7 (10.4 – 15-5)	8.1 (6.9 – 10.8)
	ORR, n (%)[2] - March 2013		95 (31)	15 (10)
	≥VGPR		14 (5)	1 (<1)
	sCR/CR		3 (1)	0 (0)
	PR		78 (26)	14 (9)

[1] Data were presented in weeks and were converted to months by multiplication by 7 and division by 30.5.

[2] Response based investigator assessment and IMWG criteria, except for MR (based on EBMT criteria)

Descriptive statistics and estimated variability	**Median DOR**, months (95%CI) September 2012 March 2013	 2.8 (NA) 7.0 (6.0 – 9.0)	 1.8 (NA) 6.1 (1.4 – 8.5)
	TTP, months (95%CI)	4.7 (4.0 – 6.0)	2.1 (1.9 – 2.5)
	Median times to first worsening of QoL domains, days (95%CI)		
	Global Health Status	114 (71 – 143)	85 (37 – 140)
	Physical Functioning	174 (123 – 288)	60 (57 – 113)
	Fatigue	113 (71 – 169)	124 (64 – 235)
	Emotional Functioning	190 (145 – 361)	124 (64 – 235)
	Pain	147 (89 –NE)	113 (58 – NE)
Effect estimate per comparison	Comparison groups		POM + DEX vs. HiDEX
	PFS – September 2012 (IRAC)	HR	0.45
		95%CI	0.35 – 0.59
		P value	<0.0001
	PFS – March 2013	HR	0.48
		95%CI	0.39 – 0.60
		P value	<0.0001
	OS – September 2012	HR	0.53
		95%CI	0.37 – 0.74
		P value	0.0002
	OS – March 2013	HR	0.74
		95%CI	0.56 – 0.97
		P value	0.028
	ORR – March 2013	Odds ratio	4.22
		95%CI	2.35 – 7.58
		P value	<0.0001
	DOR	HR	0.52
		95%CI	0.25 – 1.05
		P value	0.0631
	TTP	HR	0.46
		95%CI	0.36 – 0.59
		P value	<0.0001
	Time to QoL worsening:		
	Global Health Status	P value	0.058
	Physical functioning	P value	0.088
	Fatigue	P value	0.038
	Emotional functioning	P value	0.023
	Pain	P value	0.203

Abbreviations: CI = confidence interval, EBMT = European Group for Blood and Bone Marrow Transplant, ECOG PS = Eastern Cooperative Oncology Group Performance Status, EORTC = European Organisation for Research and Treatment of Cancer, HiDEX = high dose dexamethasone, HR = hazard ratio, IMWG = International Myeloma Working Group Uniform Response criteria, IRAC = Independent Review Adjudication Committee, MR = minor response, n = Number, NA = not available, NE = not evaluable, NR = not reached, PR = partial response, QoL = quality of life, sCR = stringent complete response, VGPR = very good partial response, SD = stable disease, yrs = years

Table 2: Adverse events (Total AEs ≥20%, grade 3 ≥ 5%, grade 4 ≥ 1% and all grade 5 events are displayed)

MM-003 (March 2013 [45])			
Grade (according to CTC version 4.0)	**Outcome**, n (%)	**POM + DEX** (n=300)	**HiDEX** (n=150)
Total	Infections and infestations	203 (68)	79 (53)
	Anaemia	157 (52)	76 (51)
	Neutropenia	152 (51)	31 (21)
	Fatigue	103 (34)	41 (27)
	Thrombocytopenia	90 (30)	44 (29)
	Pyrexia	80 (27)	34 (23)
	Diarrhoea	66 (22)	28 (19)
	Constipation	65 (22)	22 (15)
	Cough	61 (20)	15 (10)
	Back pain	59 (20)	24 (16)
	Dyspnoea	59 (20)	21 (14)
Grade 3	Infections and infestations	72 (24)	28 (19)
	Anaemia	93 (31)	48 (32)
	Neutropenia	77 (26)	13 (9)
	Fatigue	16 (5)	9 (6)
	Thrombocytopenia	27 (9)	13 (9)
	Dyspnoea	13 (4)	7 (5)
	Bone pain	20 (7)	7 (5)
	Pneumonia	30 (10)	10 (7)
	Leukopenia	20 (7)	2 (1)
Grade 4	Infections and infestations	19 (6)	8 (5)
	Anaemia	6 (2)	7 (5)
	Neutropenia	66 (22)	11 (7)
	Thrombocytopenia	40 (13)	26 (17)
	Pneumonia	8 (3)	2 (1)
	Leukopenia	6 (2)	3 (2)
	Febrile neutropenia	5 (2)	-
	Hypercalcaemia	7 (2)	2 (1)
Grade 5	Infections and infestations	11 (4)	13 (9)
	Pneumonia	4 (1)	3 (2)
Others	Venous thromboembolism grade 3 - 4	3 (1)	0
	Treatment-related deaths	11 (4)	7 (5)
	Discontinuation due to AEs	9	10

Abbreviations: CTC = Common Terminology Criteria, n = number

The MM-003 trial, a phase III study, compared pomalidomide + low dose dexamethasone (POM+DEX) to high-dose dexamethasone (HiDEX) in overall 455 patients (302 in the POM-DEX and 153 in the HiDEX arm) with either refractory or relapsed and refractory disease [45]. All patients had received at least 2 lines of prior anti-myeloma therapy, at least 2 consecutive cycles of bortezomib and lenalidomide therapy, alone or in combination and had failed treatment with bortezomib or lenalidomide. Median age was 64 years and the majority of patients had ECOG PS ≤1. More than 90% in each group were refractory to lenalidomide, 79% in each group to bortezomib and >70% to both lenalidomide and bortezomib, respectively.

MM-003 trial: pomalidomide + low dose dexamethasone to high-dose dexamethasone in majority of patients refractory to lenalidomide, bortezomib

The final analysis for PFS, the primary outcome, was conducted in September 2012, followed by an updated analysis for PFS and the final analysis for OS in March 2013. In the publication, PFS was assessed by the investigators but EMA's summary of product characteristics also provides results assessed by an Independent Review Adjudication Committee [49]. PFS consistently favoured the POM+DEX group (e.g. March 2013, investigator assessed PFS: POM + DEX 4.0 months vs. HiDEX 1.9 months, HR 0.48, p<0.0001). Improved OS outcomes were also found in an interim analysis with a median follow-up of 4.2 months (HR=0.54; p<0.001) and were repeated in March 2013 although to a lesser extent (HR 0.74, p= 0.028). This result is influenced by the fact that, based on the interim analysis, the independent data monitoring committee recommended allowing patients from the HiDEX arm to cross-over to the pomalidomide arm. Consequently, 50% of patients in the HiDEX arm (76 individuals) received POM. ORR was observed in 31% of patients in the POM +DEX arm in comparison to 10% in the HiDEX arm, yielding a statistically significant difference. Preliminary results for QoL, measured as time to worsening of QoL symptoms, were presented in one abstract [43] indicating improvements in most domains for the pomalidomide group.

median PFS + 1.8 months for pomalidomide group also improved results for OS, therefore cross-over allowed

ORR: 31% in pomalidomide group vs. 10% in high-dose dexamethasone

indications of improvements in QoL

Concerning any grade adverse events (AEs), the most common were infections (POM+DEX 68% vs. HiDEX 53%), anaemia (POM+DEX 52% vs. HiDEX 51%) and neutropenia (POM+DEX 51% vs. HiDEX 21%). These AEs were also the most frequently observed higher grade AEs. For thromboprophylaxis, thromboembolism of any grade was noted in 2% in the pomalidomide group and 1% in the comparator group. Supportive therapies such as granulocyte colony-stimulating factor were administered to 43% in the pomalidomide arm and 13% in the dexamethasone arm. Red blood cell transfusions were indicated in 20% and 21%, respectively, and platelet transfusion in 20% and 21%. Therapy was discontinued due to AEs in 9% in the POM+DEX arm and 10% in the HiDEX arm [42]. Four patients (2 solid cancers, 2 skin cancers) in the pomalidomide and 1 (skin cancer) in the dexamethasone group developed a second primary malignancy.

most frequent infections, anaemia, neutropenia

4 second primary malignancies in pomalidomide group and 1 in comparator group

In several PFS subgroup analyses, including patients refractory to lenalidomide only (HR 0.50; 95%CI 0.40 – 0.62) or also to bortezomib (HR 0.52; 95%CI 0.41 – 0.68), and for patients with either of these agents as last line therapy, the pomalidomide arm yielded better results. Furthermore, patients with high-risk cytogenetics del(17p13) and t(4p16/14q32) were analysed and improved outcomes for the pomalidomide group were found too (HR 0.46; 95%CI 0.30 – 0.72). Concerning subgroup analyses for OS, improved results were found for patients refractory to lenalidomide (HR 0.73; 9%CI 0.55 – 0.96) and for patients with lenalidomide as their last therapy. However, OS results may have been influenced by cross-over.

several subgroup analyses for PFS favoured the pomalidomide group

6.1.2 Pivotal study (FDA) - MM-002

Table 3: Summary of efficacy

Study title Randomized, open label phase 1/2 study of pomalidomide (POM) alone or in combination with low-dose dexamethasone (LoDex) in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide (LEN) and bortezomib (BORT): phase 2 results [29]			
Source of information	FDA medical review [28], abstracts [29-37]		
Study identifier	NCT00833833, CC-4047-MM-002		
Design	Multi-centre, randomized (1:1 ratio), open-label, dose escalation trial (phase I), cross-over design (phase II) Stratification by age (≤75 years, >75 years; prior number of treatments (2 vs. >2); prior thalidomide exposure (yes vs. no)		
	Duration	*Enrolment:* NA *Median follow-up:* NA *Cut-off date for interim analysis:* 1 April 2011	
Hypothesis	Superiority The boundary for declaring the superiority of Arm A over Arm B was based on an alpha-spending function of the O'Brien-Fleming type with overall α = 0.025, one-tailed.		
Funding	NA		
Treatment groups	Overall study population	N= 221	
	Intervention (n=113)	Oral pomalidomide 4 mg once per day, days 1–21 of each 28-day treatment cycle + Dexamethasone 40 mg once per day on days 1, 8, 15 and 22 of each 28-day cycle for patients ≤ 75 years, and 20 mg for patients >75 years	
	Control (n=108)	Oral pomalidomide 4 mg/d, days 1–21 of each 28-day treatment cycle	
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Time from randomization to the first documentation of disease progression or death from any cause during the study, whichever occurs earlier (response assessed by Independent Response Adjudication Committee (IRAC) according to EBMT criteria)
	Overall response rate	ORR	Partial response (PR) or better which is maintained for at least 6 weeks according to EBMT response criteria
	Duration of response	DOR	Time from the first PR or CR to the first documentation of progressive disease
	Overall survival	OS	Time from randomization to death from any cause
	Time to response	TTR	Time to response was defined as the time from randomization to the first documentation of response (either PR or CR)

Results and analysis				
Analysis description	Intention-to-treat analysis For time to event analyses, the Kaplan-Meier method was used to estimate the distribution functions for each treatment arm. For comparison of treatment arms, the log rank test was used (two-sided, alpha =0.05). The trial had an 85% power to detect a 40% reduction in PFS or OS (median PFS of 6 and 10 months in the pomalidomide (monotherapy) arm vs. the pomalidomide + dexamethasone (combination) arm). Planned accrual was 192 and the actual accrual was 221 patients (113 to the combination arm and 108 to the monotherapy arm). The planned final analysis was at 129 events, and the final analysis was conducted at 167 events.			
Analysis population	Inclusion	✠ Diagnosis of MM and relapsed (=after having achieved at least stable disease for at least 1 cycle of treatment to at least one prior regimen and then developed progressive disease) and refractory disease ✠ ≥2 prior regimens, including ≥2 cycles of lenalidomide and ≥2 bortezomib separately or in combination ✠ Disease progression during or within 60 days (measured from the end of the last cycle) of completing treatment with the last treatment prior to study entry ✠ ECOG PS 0-2		
	Exclusion	✠ Any of the following laboratory abnormalities: • ANC <1,000/µL • Platelet count <75,000/µL for subjects in whom <50% of BM nucleated cells were plasma cells; or a platelet count <30,000/µL for subjects in whom ≥50% of BM nucleated cells were plasma cells • Serum creatinine >3.0 mg/dL • Serum asparate transaminase or alanine aminotransaminase >3.0 x upper limit of normal • Serum total bilirubin >2.0 mg/dL. ✠ Prior malignancies, other than MM, unless the subject had been free of disease for ≥3 years ✠ Peripheral neuropathy ≥grade 2		
Analysis population	Characteristics		POM + DEX	POM
		Age, mean (SD)	64.4 (9.24)	62.9 (10.35)
		≤75 years, %	87.6	88.0
		>75 years, %	12.4	12.0
		Sex, %		
		Male	54.9	52.8
		Female	45.1	47.2
		Baseline MM Stage, %		
		I	7.1	7.4
		II	25.7	26.9
		III	67.3	65.7
		ECOG, %		
		0	28.3	22.2
		1	60.2	65.7
		2	11.5	10.2

		3	0	1.9
		Number of prior MM therapy, median (min, max)	5.0 (2.0 – 13.0)	5.0 (2.0 – 12.0)
		Prior IMiD, %		
		Lenalidomide	100	100
		Thalidomide	68.1	66.7
		Prior bortezomib, %	100	100
		Prior autologous stem cell transplant, %	74.3	75.9
		Prior corticosteroids, %	100	100
		Prior alkylators, %	92.9	95.4
		Prior anthracycline, %	48.7	50.0
		Refractory to, %		
		lenalidomide	77.0	78.7
		bortezomib	72.6	69.4
		lenalidomide and bortezomib	61.1	59.3
Descriptive statistics and estimated variability	Treatment group		POM + DEX	POM
	Number of subjects		N = 113	N = 108
	Median PFS, months (95%CI)		3.8 (3.2 – 4.9)	2.5 (1.9 – 3.7)
	ORR - overall response rate (CR + PR), n (%)		33 (29.2)	8 (7.4)
		CR	1 (0.9)	0 (0)
		PR	32 (28.3)	8 (7.4)
	ORR – subgroup results			
	Refractory to lenalidomide			
		Yes	25.3	7.1
		No	42.3	10.0
	Refractory to bortezomib			
		Yes	28.0	8.0
		No	32.3	6.7
	Refractory to both lenalidomide and bortezomib			
		Yes	27.5	6.3
		No	31.8	10.0
	Median DOR, months (95%CI)		7.4 (5.1 – 9.2)	NE (NE – NE)
	Median OS, months (95%CI)		14.4 (12.3 – NE)	13.6 (9.6 – NE)
	Median time to response, months (range)		1.9 (0.9 – 10.4)	2.0 (1.0 – 11.4)

Effect estimate per comparison	Comparison groups	NA

Abbreviations: ANC = absolute neutrophil count, CI = confidence interval, CR = complete response, d = day, dL = decilitre, DOR = duration of response, EBMT = European Group for Blood and Bone Marrow Transplant, ECOG PS = Eastern Cooperative Oncology Group Performance Status, IMiD = immunomodulatory drug, IRAC = Independent Response Adjudication Committee, µL = microlitre, mg = milligramme, NA = not available, NE = not evaluable, n = number, ORR = overall response rate, OS = overall survival, PFS = progression free survival, PR = partial response, SD = standard deviation, TTR = time to response

Table 4: Treatment-emergent adverse events (Grade 3 or 4: occurring in ≥10% of patients; serious TEAEs: occurring in ≥5% of patients)

CC-4047-MM-002			
Grade (according to NCI CTCAE version 3.0)	**Outcome**, n (%)	**POM + DEX** (n=112)	**POM** (n=107)
Grade 3 or 4	Any	99 (88)	96 (90)
	Neutropenia	43 (38)	50 (47)
	Anaemia	23 (21)	24 (22)
	Thrombocytopenia	21 (19)	24 (22)
	Leukopenia	11 (10)	6 (6)
	Asthenia and fatigue	14 (13)	12 (11)
	Pneumonia	24 (21)	16 (15)
	Back pain	10 (9)	11 (10)
	Dyspnoea	14 (13)	7 (7)
Serious	Any SAE	69 (62)	72 (67)
	Febrile neutropenia	1 (1)	5 (5)
	Pyrexia	5 (5)	3 (3)
	Pneumonia	24 (21)	17 (16)
	Sepsis	3 (3)	6 (6)
	Urinary tract infections	6 (5)	0 (0)
	Dehydration	3 (3)	5 (5)
	Hypercalcaemia	3 (3)	5 (5)
	Back pain and bone pain	3 (3)	5 (5)
	Renal failure	7 (6)	10 (9)
	Dyspnoea & Hypoxia	7 (6)	5 (5)

Abbreviations: CTCEA = Common Terminology Criteria for Adverse Event, NCI = National Cancer Institute, n = number, SAE = serious adverse event, TEAE = treatment-emergent adverse events,

MM-002 trial phase I/II pivotal study

The CC-4047-MM-002 was a phase I/II trial. Phase I of the trial comprised 38 patients (results are not displayed) [50] and phase II comprised overall 221 patients with relapsed and refractory MM. Inclusion criteria were ≥2 prior therapies and ≥2 cycles of therapy including lendalidomide and bortezomib (either separately or in combination) for MM. In addition, patients had to have refractory disease, defined as documented progressive disease ≤60 days after completing their last myeloma therapy.

221 patients with relapsed and refractory MM treated with pomalidomide + low dose dexamethasone or with pomalidomide only

In Phase II, 113 patients were randomised to receive pomalidomide + dexamethasone (POM + DEX) and 108 individuals to pomalidomide only (POM). The majority of patients enrolled were ≤75 years, had an ECOG status of 0 or 1 and stage III MM. Median number of prior therapies was 5 in both groups. All patients had received prior corticosteroids, lenalidomide, and bortezomib. Concerning the latter, 78% were refractory to lenalidomide, 71% to bortezomib and 60% to both agents. Patients with confirmed progressive disease were allowed to cross-over from the POM arm to the combination arm and 61 patients did.

The median treatment duration was 21.6 weeks. In the combination arm, median exposure was 21.8 weeks compared to 20.6 weeks in the POM only arm. Overall, the median number of cycles received was similar between the two groups (5.0 cycles) but, prior to cross-over of patients in the POM only arm, the median number of cycles was only 2.0. Dose-reductions were necessary in 39% of patients in the POM+DEX arm and in 17% in the POM only arm, and dose interruptions occurred in 64% in the combination arm and in 59% in the POM only arm.

median PFS: 3.8 months in combination arm and 2.5 months in pomalidomide only arm; difference in OS 0.8 months

Median PFS, assessed by an Independent Response Adjudication Committee, was the primary outcome and was 3.8 months in the POM-DEX arm and 2.5 in the POM only arm. Overall response rates were 29% in the combination arm and 7% in the single-agent arm. Since only 1 complete response was observed in the POM+DEX arm, the majority were partial responses. The median duration of response was only evaluable in the POM+DEX arm, where it was 7.4 months. The difference in median overall survival was 0.8 months, favouring the combination arm.

several subgroup analyses

ORR 25% – 28%

Several subgroup analyses were planed prior to the study start including subgroups based on gender, age group, number of prior anti-myeloma therapies and prior thalidomide exposure. In addition, several post-hoc analyses were conducted [30-35], including patients previously treated with carfilzomib and refractory status to lenalidomide, bortezomib or both. Objective response rates for patients refractory to lenalidomide, bortezomib or both were 25%, 28% and 28%, respectively, in the POM + DEX arm and 7%, 8% and 6% in the POM only arm. In comparison, the rates for non-refractory patients were 42%, 32% and 32% in the POM+DEX arm and 10%, 7% and 10% in the POM-only arm, respectively.

grade 3 or 4 AE in about 90%
most common: anaemia, neutropenia

Concerning adverse events (AEs), treatment-emergent AEs of grade 3 or 4 were very frequently observed in both groups (88% in the POM+DEX arm, 90% in the POM only arm). The most common were disorders associated with the blood and lymphatic system, i.e. anaemia and neutropenia. Infections, foremost among them pneumonia of grade 3 or 4 were seen in 21% (POM+DEX) and 15% (POM) of patients. More than 60% in each group experienced serious AEs (e.g. life-threatening AEs requiring hospitalisation). The most common serious AEs were infections, mainly pneumonia.

5% – 6% died due to treatment

Overall, 41 patients died of which the majority, i.e. 23 patients, were due to disease progression. Deaths due to treatment-related adverse events were the second most common cause of death. In the POM+DEX group 6 deaths (5.3%) were attributable to treatment, mainly because of infections (4 patients) and cerebral or subarachnoid haemorrhage (2 patients). Seven deaths (6.5%) occurred in patients in the single-agent group (6 infection-related, 1 caused by cerebral or subarachnoid haemorrhage).

6.1.3 Further studies

The IFM 2009-02 trial, a supportive study, was a randomised phase II study testing two different pomalidomide regimens [27, 28]. Forty-three patients received 4 mg pomalidomide on days 1–21 of a 28-day cycle in addition to 40 mg dexamethasone (21/28 group), whereas 41 patients received 4 mg pomalidomide on days 1–28 of a 28-day cycle in addition to 40 mg dexamethasone (28/28 group). Patients had to have relapsed and refractory MM after at least one prior MM therapy and progressive disease after bortezomib and/or lenalidomide treatment. Furthermore, patients had to have received at least two cycles of lenalidomide and bortezomib.

randomised phase II trial comparing 2 different pomalidomide regimens + dexamethasone patients were previously treated with bortezomib/lenalidomide

The study population had a median age of 60 years, 31% were ≥65 years and the vast majority had an ECOG performance status of 0 or 1. The median number of prior MM therapies was 5 and, as stated in the inclusion criteria, all had received prior lenalidomide, bortezomib and glucocorticoids. Overall, 89% were refractory to lenalidomide, 81% to bortezomib and 76% to both agents. ORR 34% – 35%, median PFS 3.7 – 5.4 months.

majority refractory to lenalidomide, bortezomib or both

At median follow-up of 22.8 months, ORR, the primary outcome, was 35% in the 21/28 group and 34% in the 28/28 group. Of these, the main response was PR (27% overall). The median time to first response was 2.7 months and 1.1 months in the 21/28 group and the 28/28 group, respectively. Corresponding numbers for median duration of response were 6.4 months and 8.3 months. Patients receiving pomalidomide on 21 days of a 28-day cycle had a median PFS of 5.4 months, and those receiving pomalidomide on all 28 days of the cycle had a PFS of 3.7 months. OS was the same in both groups (14.9 and 14.8 months, respectively).

Results for ORR, PFS and OS were also presented for subgroups of the whole study population. ORR, PFS and OS were 31%, 3.8 months and 13.8 months, respectively, for patients refractory to lendalidomide and bortezomib. Less favourable outcomes were observed for individuals who had received more than 6 lines of therapy prior to enrolment in the IFM-2009-02 trial (ORR: 21%, PFS: 3.2 months, OS: 9.2 months) and in patients with poor cytogenetic abnormalities that is del(17p) and t(4;14) (ORR: 27%, PFS: 2.6 months, OS: 5.4 months).

subgroup results including patients refractory to lenalidomide and bortezomib, with poor cytogenetic abnormalities

Grade 3 or 4 AEs occurred in 91% (21/28 group) and 83% (28/28 group). The majority of AEs concerned those arising due to myelosuppression such as anaemia, neutropenia and thrombocytopenia. About 74% in each group experienced serious treatment-emergent AEs. The most common was pneumonia (30% in the 21/28 group and 24% in the 28/28 group). The median number of cycles received was 8 in the 21/28 group and 6 in the 28/28 group. Discontinuation due to AEs occurred overall in 2% (2 patients), both of which were in the 28-day cycle group. Three patients (7%) died in each group due to treatment-emergent AEs. Causes of death were pneumonia (2 patients each), and 1 patient each died due to cerebrovascular haemorrhage and renal failure.

grade 3 or 4 AEs in 83%-91%, mainly due to myelosuppression

serious-treatment emergent AEs: pneumonia
7% died in each group due

another phase II study compared 2 mg and 4 mg pomalidomide + dexamethasone in overall 70 patients

AEs comparable to those reported in previous studies

Lacy *et al.* [46] investigated pomalidomide in a sequential phase II study at doses of 2 mg and 4 mg pomalidomide every day of a 28-day cycle in addition to 40 mg dexamethasone weekly. Enrolled patients had to have been treated previously and be refractory to lenalidomide and bortezomib. Overall, 70 patients were included in the study, 35 in each group. The study population consisted mainly of men (≥60%) with a good performance status and a median age ranging between 61 and 62 years. In the 2 mg group all patients had received ≥3 prior chemotherapies and in the 4 mg group ≥94% of patients. ORR, the primary outcome, was 26% in the 2 mg group and 28% in the 4 mg group, while PFS was 6.5 months and 3.2 months, respectively. At 6 months, the OS rate was 78% and 67%, respectively. AEs were comparable to those already described in chapter 6.1, since myelosuppression was the most frequent occurrence. Grade 3 or 4 neutropenia was the most common (2 mg: 51%; 4 mg: 65%) followed by leukopenia (2 mg: 40%; 4 mg: 62%). Despite the fact that 31% of patients experienced pneumonia in the 2 mg cohort, only 9% were considered to be treatment related. In the 2 mg group, 80% experienced neuropathy in comparison to 89% in the 4 mg group, but nearly all cases were of grade 1 or 2.

7 Estimated costs

no cost estimates available

No costs estimates are available yet for Austria.

8 Ongoing research

3 further ongoing phase III trials

Besides the still ongoing MM-003 trial, 3 further phase III studies were identified on clinicaltrials.gov and on clinicaltrialsregister.eu:

NCT01734928 (OPTIMISMM, MM-007): compares the efficacy of the combination of pomalidomide, bortezomib and dexamethasone to the combination of bortezomib and dexamethasone in patients with relapsed/refractory multiple myeloma. This study will also assess how safe the combination of pomalidomide, bortezomib and dexamethasone is compared to the combination of bortezomib and dexamethasone. The estimated study completion date is January 2015.

NCT01324947 (NIMBUS, MM-003/C): evaluates the efficacy and safety of pomalidomide monotherapy in subjects with refractory or relapsed and refractory multiple myeloma who were enrolled in study CC-4047-MM-003 and discontinued treatment with high-dose dexamethasone due to disease progression. The estimated study completion date is September 2013.

NCT01712789 (STRATUS, MM-010): the primary purpose of the study is to evaluate the safety and efficacy of and generate pharmacokinetic and biomarker data for the combination of pomalidomide and low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma. The estimated study completion date is November 2019.

Furthermore, the drug is in phase III for the treatment of myelofibrosis. Moreover, its use for the treatment of several other diseases such as prostate cancer, Waldenstrom's macroglobulinaemia and primary systemic amyloidosis is currently being investigated.

also under investigation for other diseases such as prostate cancer, myelofibrosis, amyloidosis

9 Commentary

Pomalidomide was approved by the FDA in February 2013 and by the EMA in August 2013. The licensed indication is for the treatment of adult patients who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

approved in the U.S. in February 2013 and by EMA in August 2013

The FDA's decision was based on the efficacy outcomes of two phase II studies, the pivotal MM-002 trial (221 patients) and one supportive study, the IFM-2009-02 trial (84 patients). The MM-002 trial compared pomalidomide with and without 40 mg dexamethasone weekly and the IFM 2009-02 trial compared pomalidomide either continuously or for 21 days within a 28 days cycle in addition to 40 mg dexamethasone weekly. Patients were heavily pretreated (a median of 5 prior therapies) and included patients refractory to lenalidomide, bortezomib or both. In the MM-002 trial >70% of patients were refractory to either of the drugs and about 60% to both. These numbers were considerably lower in the IFM-2009-02 trial. ORR in these trials ranged between 29% and 35%, PFS from 3.8 to 5.4 months, OS from 14.4 to 14.9 months and DOR was 6.4 and 7.4 months, respectively.

2 phase II trials (MM-002, IFM-2009-02) served as the basis for the FDA's decision

The FDA acknowledged that, based on the available evidence, isolation of the treatment effect of pomalidomide is not possible since pomalidomide was part of the therapy in both arms. Further the safety population was with overall 303 patients small [28]. However, the drug was approved under the accelerated approval regulations in the U.S., highlighting the need for therapeutic options for heavily pre-treated patients who have relapsed and refractory MM despite established therapies such as bortezomib and lenalidomide [51]. In order to support the results of the phase II studies and ultimately to gain regular approval, the applicant mentioned two confirmatory randomised controlled trials [52]: the MM-003 and the MM-007 trial (NCT01734928). The latter will evaluate the addition of pomalidomide to bortezomib and dexamethasone but study results will not be available prior to January 2015, the final data collection date for the primary outcome measure [41].

even though these trials do not allow isolation of treatment effect, approval in the U.S under accelerated approval regulation

high unmet medical need in heavily pre-treated patients with relapsed and refractory disease

The EMA has recently granted market authorisation based on the results of the MM-003 trial, which had enrolled patients with similar characteristics as the two phase II trials, i.e. heavily pre-treated patients and refractory disease [45]. Pomalidomide + low dose dexamethasone was compared with high-dose dexamethasone in overall 455 patients, yielding statistically significant improved outcomes for patients in the combination arm. The difference in median PFS was 2.1 months and in OS 4.6 months after 10 months of follow-up, favouring the pomalidomide arm. Preliminary outcomes concerning quality-of-life were also presented, indicating improved results for pomalidomide [43]. Nonetheless, the open-label design of the study may influence these results.

phase III study (MM-003) trial available, indicating gains in PFS, OS, QoL for patients treated with pomalidomide + low-dose dexamethasone in comparison to high-dose dexamethasone

AEs of grade 3 or 4 very common, serious AEs in 62%-74%, mainly due to myelosuppression

high embryo-fetal risk, thrombo-prophylaxis indicated

In terms of safety, at least one grade 3 or 4 AE was experienced by about 90% of patients in the phase II studies, the majority being due to myelosuppression, e.g. neutropenia (38%–63%) and anaemia (21%–33%). Serious AEs occurred in 62%–74%. In the phase III trial, grade ≥3 neutropenia was observed in 48% of the pomalidomide group and 16% of the high-dose dexamethasone group, and infections occurred in 30% and 24%, respectively. Comparable rates were found in the two groups for thrombocytopenia (22% vs. 26%). Due to the high embryo-foetal risk of pomalidomide, it is only available under a risk evaluation and mitigation strategy programme in the US. Thrombo-embolic AEs, a side-effect associated with pomalidomide, were rare with thrombo-prophylaxis (1%–2%). Secondary primary malignancies occurred in the MM-003 trial in 4 patients (1.3%) in the pomalidomide arm in comparison to 1 patient (0.7%) in the dexamethasone arm.

substantial changes in MM therapy several new drugs available

direct comparisons and determination of sequences needed

Therapy for MM is currently undergoing substantial changes, raising questions as to the optimal sequences and combination of regimens. For example, pomalidomide is being tested in combination with a proteasome inhibitor. i.e. bortezomib, and several other drugs are in development, including monoclonal antibodies (e.g elotuzumab, lucatumumab, dacetuzumab, daratumumab) and deubiquitylating agents (ixazomib)) [53]. Further, since the first remission [51] usually has the longest duration and yields the best clinical outcomes for patients, the most effective therapies should be used in the front-line setting [51]. Besides direct comparisons of agents available, the efficacies of new agents in earlier stages of treatment are therefore of interest.

further characterisation of patients with highest potential to benefit needed

no information on patients previously treated with thalidomide

In addition, further characterisation of patients with the highest potential to benefit from pomalidomide may be helpful in determining the best treatment strategy. The MM-003 trial conducted subgroup analyses including patients refractory to bortezomib and lenalidomide, efficacy with regards to the last line of therapy and patients with high-risk cytogenetics. Despite conflicting evidence as to the impact of prior therapies on the efficacy of further lines of treatment, there are some indications that patients with thalidomide-refractory disease may be associated with poorer outcomes than those refractory to bortezomib or lenalidomide [51], but no information for patients refractory to thalidomide is available.

predictive biomarkers can help in identifying suitable patients

In the future, development of predictive biomarkers for selecting the optimal therapy and predicting responses to immune-modulatory drugs could also help guide treatment decisions [5, 21]. Safety data for larger patient groups and with a longer follow-up are also important to better describe the risks associated with pomalidomide.

prognosis for pre-treated patients, refractory to established therapy is poor; no standard therapy exists, new treatment options are needed

Heavily pre-treated MM patients remain a difficult to treat group. Especially for patients who are refractory to established therapies such as lenalidomide or bortezomib [51], prognosis is poor with a median OS of about 9 months and a PFS of 5 months [21]. Since no standard therapy for this setting exists [21], agents such as pomalidomide would therefore clearly address an unmet medical need. The first positive results of studies on pomalidomide suggest that relapsed and refractory patients benefit from this therapy. In addition, the oral application also provides a benefit for patients, for example in comparison to carfilzomib, a drug for injection currently licensed only the U.S.

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