Optimizing current therapeutic options for relapsed/refractory multiple myeloma

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Expert panel: purpose

- An expert panel convened to reach a consensus regarding the optimal use of Lenalidomide + Dex in the management of patients with multiple myeloma, including the following topics
  - selecting appropriate patients for lenalidomide treatment
  - optimal dosing for lenalidomide and drug combination partners (e.g. Dex), as well as duration of therapy
  - prevention and management of adverse events
  - integration of lenalidomide into a continuous treatment approach

Unmet clinical needs for patients with multiple myeloma

- Multiple myeloma is characterized by regrowth of residual tumours and immune suppression
  - the majority of patients with multiple myeloma will eventually relapse within 3 years regardless of therapy
  - continued therapy beyond best response may help prolong PFS
- An ideal therapy should target both tumour growth and concomitant immunosuppression while being orally administered and well tolerated during long-term use

Attal M, et al. Blood. 2006;108:3289-94.

Bortezomib in relapsed/refractory MM

Bortezomib was approved for use as monotherapy for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

APEX trial: Bortezomib versus Dexamethasone in patients with relapsed/ refractory myeloma

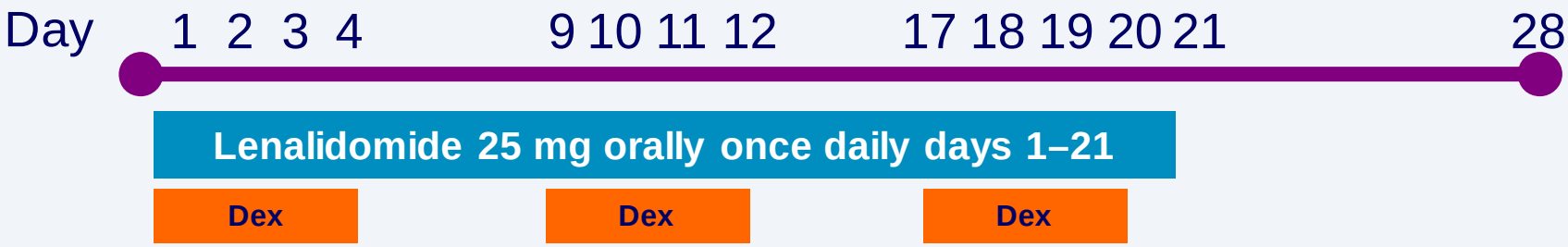
	ORR	TTP	OS
Bortezomib (n = 327)	43%	6.2 months	29.8 months
Dexamethasone (n= 330)	18%	3.5 months	23.7 months
p-value	p < 0.001	p < 0.001	p = 0.027

Efficacy results: longer ORR, TTP and OS with Bortezomib vs. Dex

Niesvizky R, et al. Br J Haematol. 2008;143:46-53.

Lenalidomide + Dex licensed in the EU in June 2007

In June 2007 Lenalidomide was approved for use in combination with dexamethasone for the treatment of MM in patients who have received at least one previous therapy



Dex: 40 mg orally once daily on days 1–4, 9–12, and 17–20 cycles 1–4*

Dex

Dex: 40 mg orally once daily on days 1–4 after cycle 4*

* Prescribing physicians should carefully evaluate which dose of dexamethasone to use, taking into account the condition and disease status of the patient.

Revlimid® SmPC. Celgene Europe Limited (Windsor, UK). Last updated 31/01/2011.

MM-009 and MM-010: phase 3 trials of Lenalidomide + Dex in relapsed/refractory MM

Lenalidomide 25 mg days 1–21
Placebo days 22–28
Dex 40 mg days 1–4, 9–12, 17–20

4 courses

→ **Continue until progression**

Placebo days 1–28
Dex 40 mg days 1–4, 9–12, 17–20

→ Same, except Dex days 1–4

Primary end-point: time to progression (TTP) (by Bladé criteria)
Secondary end-points: overall survival (OS), overall response rate (ORR), safety, first skeletal-related event, performance status

- **Efficacy results with Lenalidomide + Dex vs Dex alone**
  - higher response rates (60.6% 21.9%; $p < 0.001$)
  - longer TTP (median 13.4 vs 4.6 months; $p < 0.001$)
  - longer OS (median 38 vs 31.6months; $p = 0.048$)

Dimopoulos MA, et al. Leukemia. 2009;23:2147-52.
Dimopoulos M, et al. N Engl J Med. 2007;357:2123-32. Weber DM, et al. N Engl J Med. 2007;357:2133-42.

Response to second-line therapy in relapsed/refractory MM

The results on subsequent treatments from the VISTA trial suggest that retreatment with bortezomib or an IMiD-containing regimens following frontline VMP & MP, provided a favorable response.

Complete Response to second-line therapy

Subsequent therapy	VMP	MP
Bortezomib	41%	59%
Lenalidomide	73%	67%
Thalidomide	37%	47%

Mateos MV, et al. J Clin Oncol. 2010;28:2259-2266.

Optimal time to initiate treatment with Lenalidomide + Dex: consensus panel opinion

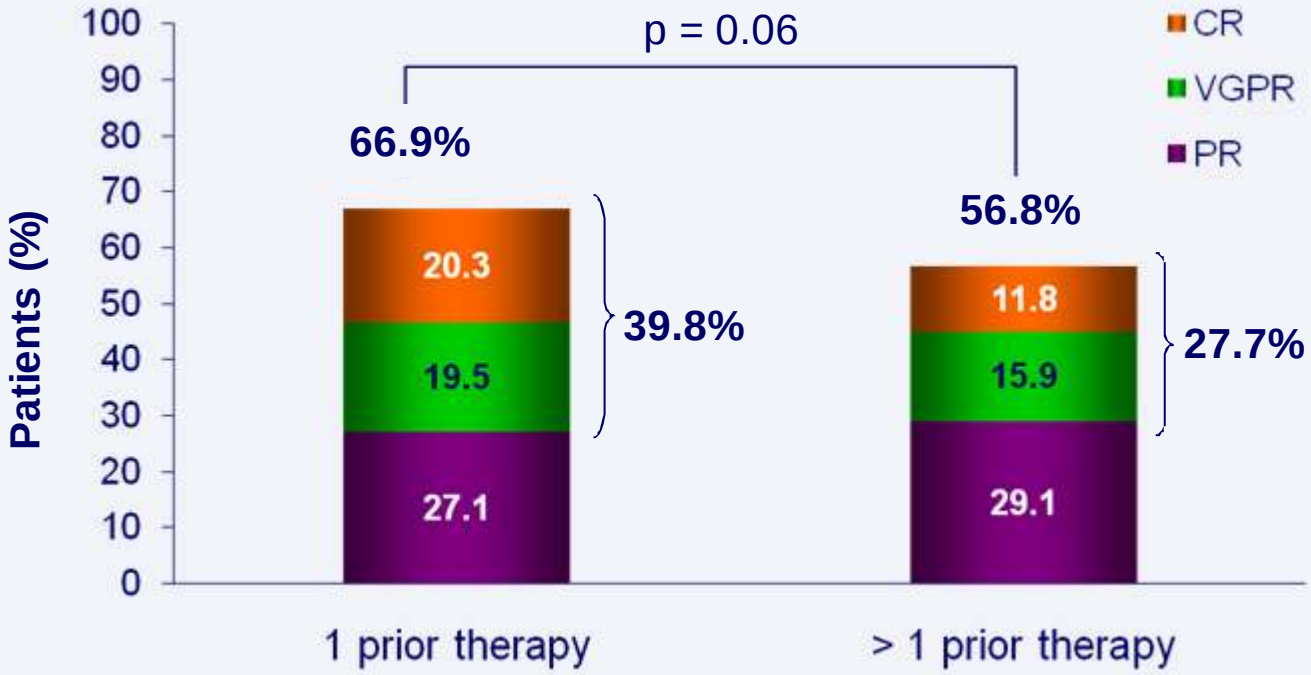
- **Lenalidomide + Dex is most effective when used at first relapse**
  - CR + VGPR is higher when Lenalidomide + Dex is given at first relapse (39.8% vs 27.7%, p = 0.025)

- **Lenalidomide + Dex can be administered regardless of the type of prior therapy**
  - efficacy is independent of prior treatment with ASCT, bortezomib, or thalidomide
    - Thalidomide-refractory patients may have lower efficacy

Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4]. Mateos MV, et al. J Clin Oncol. 2010;28:2259-2266. Stadtmauer EA, et al. Eur J Haematol. 2009;82:426-32. Wang M, et al. Blood. 2008;112:4445-51.

Treatment with Lenalidomide + Dex at first relapse achieved VGPR or better in 40% of patients

MM-009 and MM-010: pooled analysis

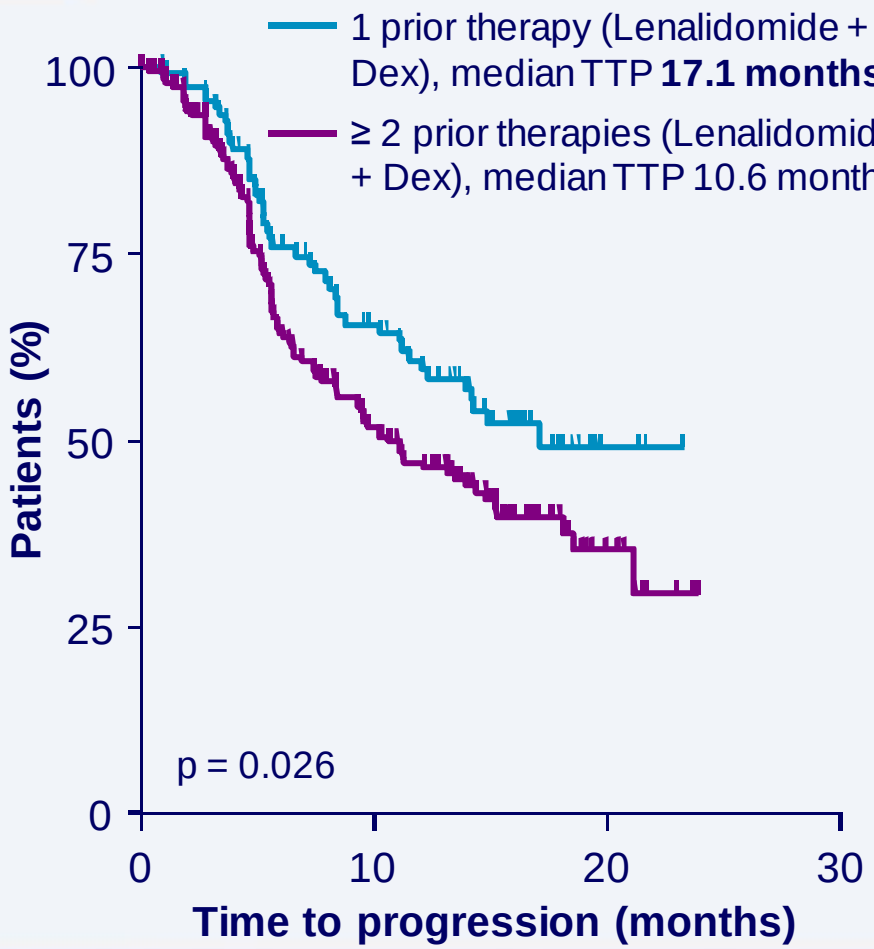


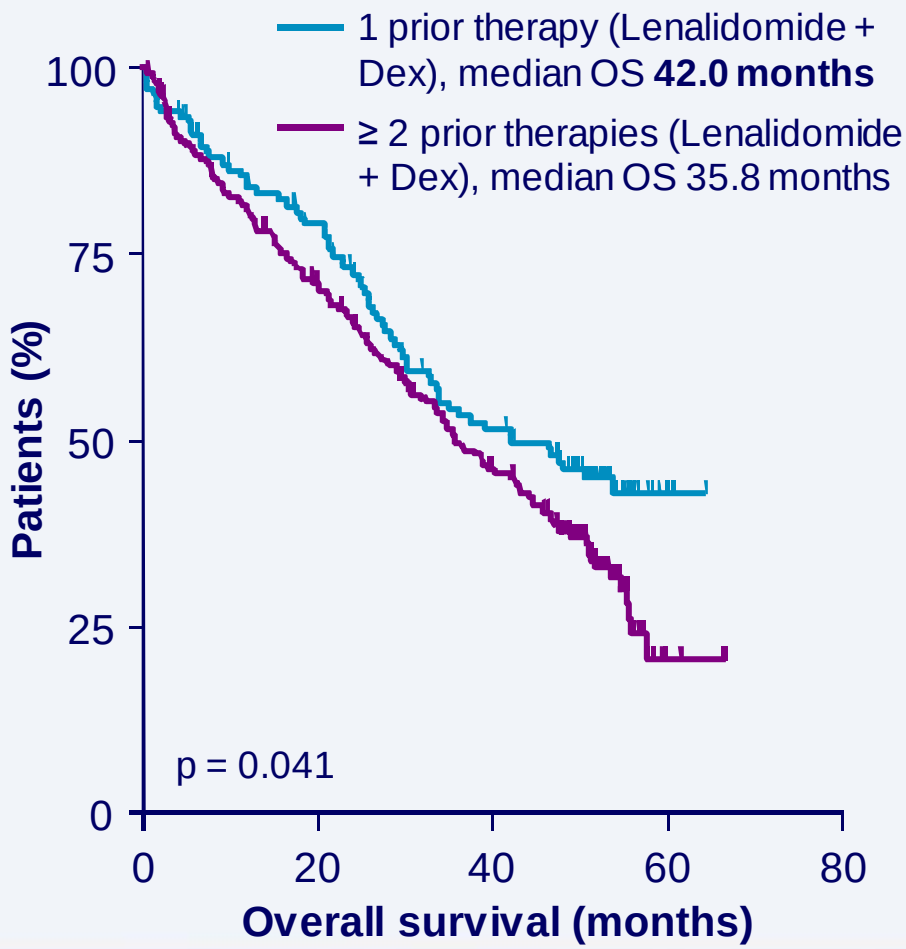
CR or VGPR rate significantly higher with second-line than with later therapy (39.8% vs 27.7%; p = 0.025)

Stadtmauer EA, et al. Eur J Haematol. 2009;82:426-32.

Longer TTP and OS when Lenalidomide + Dex was used at first relapse rather than as salvage therapy

MM-009 and MM-010: pooled analysis





Stadtmauer EA, et al. Eur J Haematol. 2009;82:426-32.

Full-dose Lenalidomide followed by a lower maintenance dose improved PFS in RRMM

Dose reduction	Median PFS (range), months	Complete Response (%)
Before 12 months (n = 39)	28 (18–37)	31
At or after 12 months (n = 25)	NR (36–NR)	52
No dose reduction (n = 52)	37 (22–NR)	40

- To achieve maximum PFS benefit patients with RRMM should be treated for at least 12 months with full-dose Lenalidomide + Dex
- Thereafter patients may benefit from continued therapy, with Lenalidomide dose adjustments for adverse events if needed, without compromising efficacy

NR = not reached.

Dimopoulos MA, et al. Leukemia 2011 in press.

Patient monitoring schedule: consensus panel opinion

- Patients without cytopenias at baseline may be monitored every 2 weeks for the first 2–3 treatment cycles
- Patients with neutropenia or thrombocytopenia at baseline may require more intensive monitoring as clinically indicated
- For responding patients receiving continuous Lenalidomide + Dex therapy, monitoring at the start of each new treatment cycle (i.e. every 4 weeks) is sufficient
- Patients with renal insufficiency (RI) may require more intensive monitoring

Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Optimal starting dose of Lenalidomide + Dex: consensus panel opinion

- For patients with RI, the starting dose of Lenalidomide should be adjusted depending on the degree of impairment
- For patients with neutropenia or thrombocytopenia at baseline, the starting dose of Lenalidomide should be adjusted
- Before initiating Lenalidomide + Dex, creatinine clearance and complete blood count should be assessed in all patients

Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Recommended starting dose for Lenalidomide according to RI and neutropenia or thrombocytopenia

	Renal function[1,2]			
	Normal $CL_{Cr} \geq 50$ mL/min	**Moderate RI 30 mL/min $\leq CL_{Cr}$ < 50mL/min**	**Severe RI CL_{Cr} < 30 mL/min**	**End-stage renal disease CL_{Cr} < 30 mL/min (requiring dialysis)**
If baseline ANC[1,2] > 1,000/µL and platelets > 50,000/µL*	25 mg once daily	10 mg once daily	15 mg every other day	5 mg once daily
If baseline ANC[2] < 1,000/µL or platelets < 50,000/µL*	15 mg once daily**	15 mg every other day**	5 mg once daily**	5 mg every other day**
	G-CSF support / platelet transfusion as needed; monitor frequently			

* SmPC recommends not starting lenalidomide at ANC < 1,000/µL and/or platelets < 30,000–75,000/µL (depending upon bone marrow infiltration by plasma cells).
** Recommendations not according to SmPC; opinion of consensus panel.

Adjust the dose at subsequent cycles if changes in CL_{Cr} or blood cell count occur

1. Revlimid® SmPC. Celgene Europe Limited (Windsor, UK). Last updated 31/01/2011.
2. Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Optimal starting dose of dexamethasone: consensus panel opinion

Low-dose dexamethasone in combination with Lenalidomide can be considered, particularly in elderly patients

Age (years)	Dexamethasone dose
≤ 65	40 mg/day, days 1–4 and 15–18 of each 28-day cycle for first 4 cycles
65–75	40 mg/day weekly
≥ 75	20 mg/day weekly

Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Dex dose reductions improved efficacy of Lenalidomide + Dex

MM-009 and MM-010: subgroup analysis

	Dexamethasone unchanged (n = 224)	Dexamethasone reduced (n = 56)	p value
Response, n (%)			
Overall response	124 (55.3)	44 (78.5)	0.001
Complete response	32 (14.3)	13 (23.2)	
Near-complete response	33 (14.7)	13 (23.2)	
Partial response	59 (26.3)	18 (32.1)	
Stable disease	75 (33.5)	10 (17.9)	
Progressive disease	4 (1.8)	1 (1.8)	
Response not evaluable	21 (9.4)	1 (1.8)	
Efficacy (months)*			
Median TTP	10.3	NR	0.005
Median OS	33.5	NR	0.019

*Most conservative median estimate obtained assumes all censored patients died immediately after censor date.

NR = not reached.

San Miguel JF, et al. Blood. 2007;110:[abstract and poster 2712].

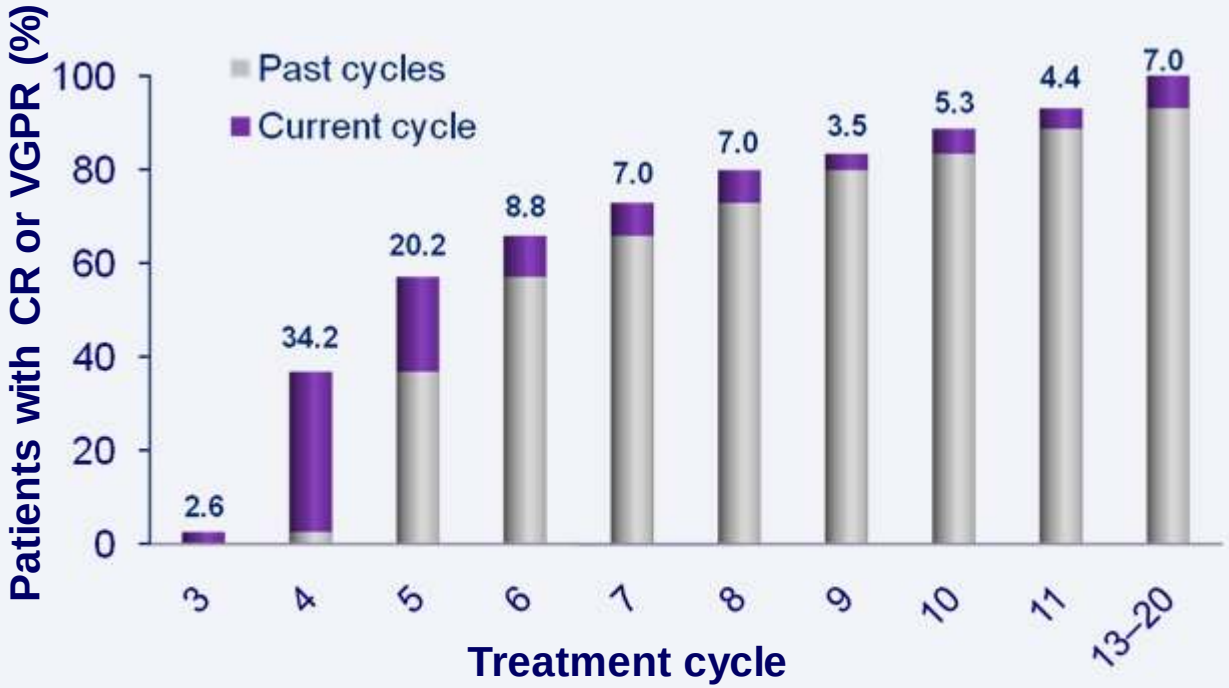
Optimal duration of treatment with Lenalidomide + Dex: consensus panel opinion

- In responding patients, treatment with Lenalidomide + Dex should continue until disease progression; same approach may apply for patients with stable disease when no other treatment options are available
- Treatment should continue at the best-tolerated dose of each agent
- Caution with long-term Dex is required

Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Long-term treatment with Lenalidomide + Dex improved the quality of the response

MM-009 and MM-010: CR or VGPR achieved in 114 of 353 patients treated with Lenalidomide + Dex



Patients achieving CR/VGPR
- 82% had PR at first evaluation

Patients achieving PR as initial response
- 50.5% achieved CR/VGPR

Patients achieving PR by cycle 4
- 43% achieved CR/VGPR

Patients achieving PR by cycle 6
- 38% achieved CR/VGPR

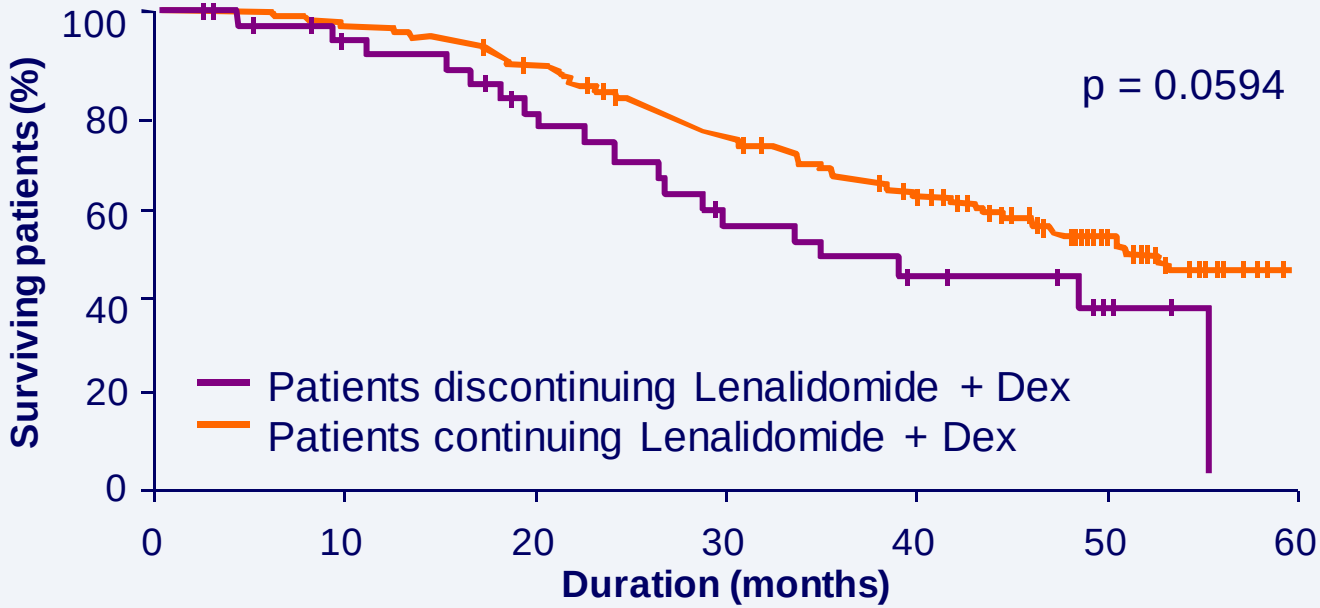
Continuing Lenalidomide + Dex treatment results in additional late CR or VGPR

Harousseau JL, et al. Haematologica. 2010;95:1738-44.

Longer treatment with Lenalidomide + Dex resulted in longer OS

MM-009 and MM-010: subgroup analysis

OS of patients treated with Lenalidomide + Dex who had a PR or better: continued treatment vs early discontinuation



	Patients n	Events, n (%)	Censored, n (%)	Median survival, months (95% CI)
Patients discontinuing Lenalidomide + Dex	38	19 (50)	19 (50)	35.0 (26.4–55.7)
Patients continuing Lenalidomide + Dex	174	82 (47)	92 (53)	50.9 (43.0–NR)

San Miguel JF, et al. Clin Lymphoma Myeloma Leuk. 2011;11:38-43.

Lenalidomide + Dex in the treatment of relapsed/refractory MM: safety

MM-009 and MM-010: pooled analysis

Grade ≥ 3 adverse events (AEs) in > 5% of patients

Adverse event, n (%)	Lenalidomide + Dex	Placebo + Dex
Neutropenia	125 (35.4)**	12 (3.4)
Thrombocytopenia	46 (13.0)**	22 (6.3)
Anaemia	38 (10.8)*	21 (6.0)
Pneumonia	32 (9.1)	19 (5.4)
All thromboembolic events	56 (15.9)**	19 (5.4)
Hyperglycaemia	27 (7.6)	27 (7.7)
Fatigue	23 (6.5)	17 (4.9)
Muscle weakness	20 (5.7)	11 (3.1)
Hypokalaemia	20 (5.7)	5 (1.4)
Asthenia	17 (4.8)	18 (5.1)

* $p < 0.001$; ** $p < 0.05$.

Dimopoulos MA, et al. Leukemia. 2009;23:2147-52.

Management and prevention of myelosuppression: consensus panel opinion

- Neutropenia and thrombocytopenia in patients treated with Lenalidomide + Dex are predictable and manageable
- Neutropenia can be managed with a combination of growth factor support or Lenalidomide dose modifications
- Thrombocytopenia can be managed with a combination of platelet transfusions or Lenalidomide dose modifications

Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Neutropenia was predictable in patients receiving Lenalidomide + Dex

- In the MM-009 and MM-010 trials, grade 3 or 4 neutropenia occurred in 35.4% of the 353 patients who received Lenalidomide + Dex[1]
- Febrile neutropenia occurred in 3.4%[2,3]
- Neutropenia occurred early on in treatment and declined over time[4,5]
- The majority of events occurred during the first 3 months of treatment[5]

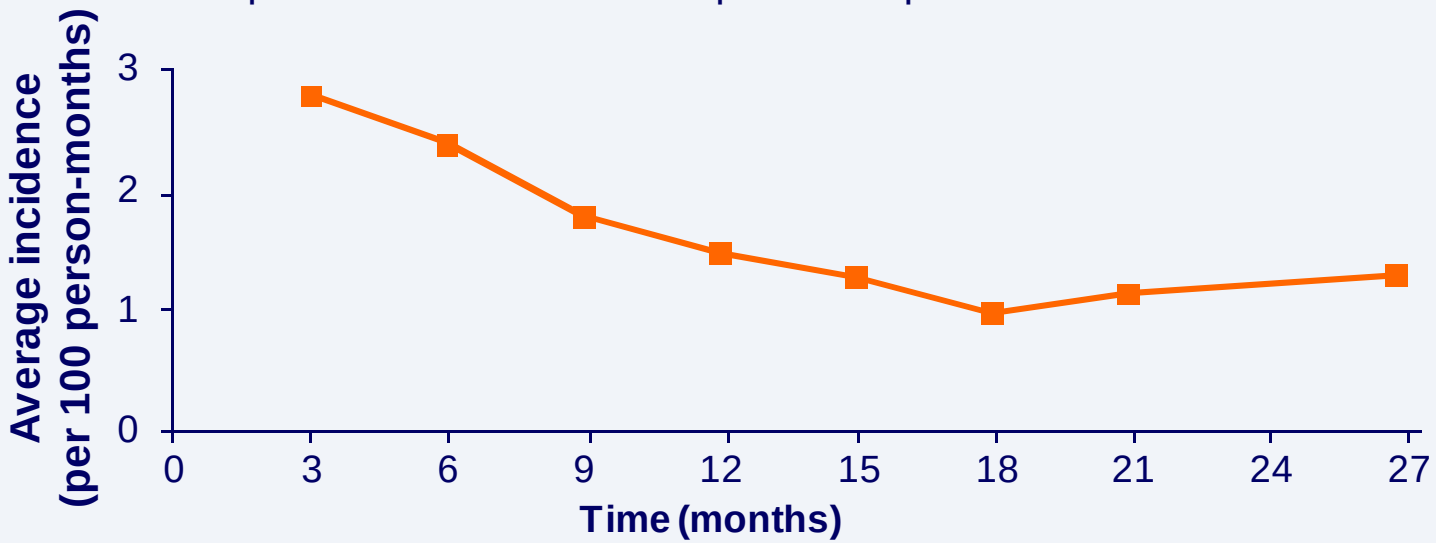
1. Dimopoulos MA, et al. Leukemia. 2009;23:2147-52. 2. Weber DM, et al. N Engl J Med. 2007;357:2133-42.
3. Dimopoulos M, et al. N Engl J Med. 2007;357:2123-324. 4. Ishak J, et al. Blood. 2008; 112:[abstract 3708]. Updated data presented at ASH 2010.
5. San Miguel JF, et al. Clin Lymphoma Myeloma Leuk. 2011;11:38-43.

Hazard rates of neutropenia declined over time in patients continuing Lenalidomide + Dex

MM-009 and MM-010 subgroup analysis

Neutropenia

This subanalysis looked at 212 (out of 353) patients who achieved ≥ partial response



N	174	173	160	149	127	97	47	18	3
Events	14	24	25	26	24	17	11	–	1

San Miguel JF, et al. Clin Lymphoma Myeloma Leuk. 2011;11:38-43.

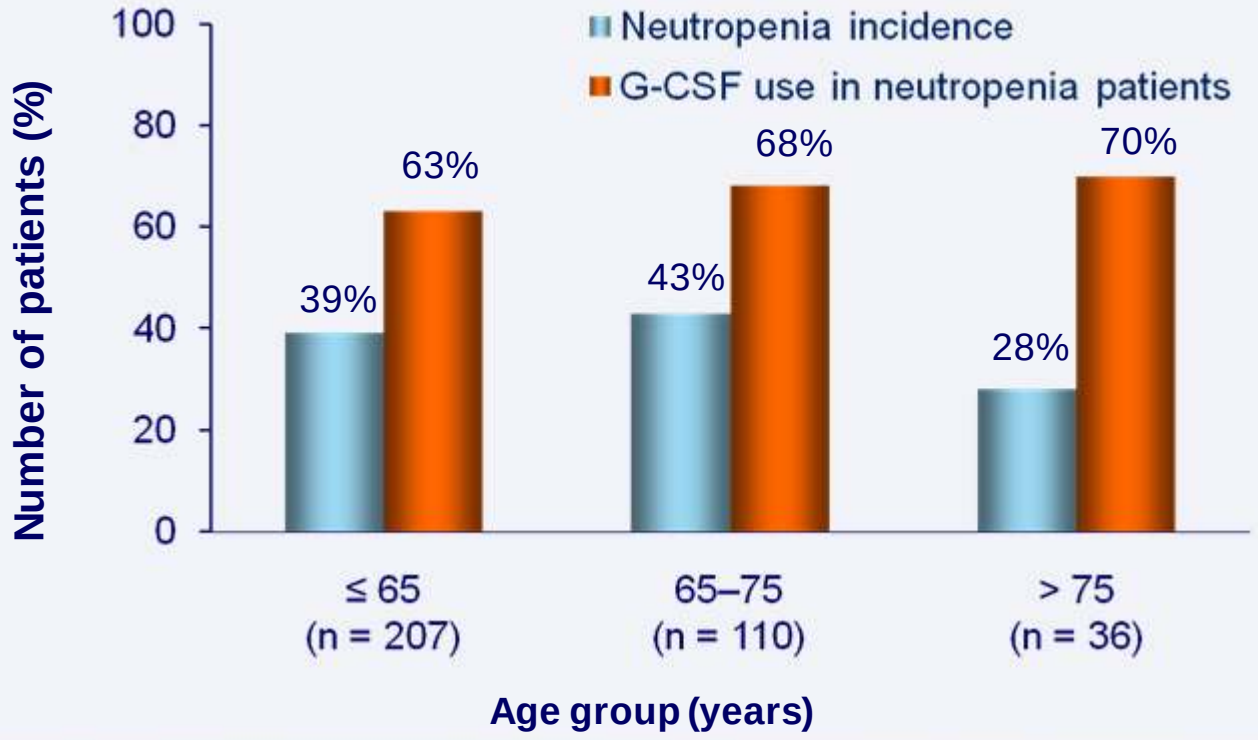
Risk factors for neutropenia

- MM-009/010 subanalysis pooled data: baseline ANC was the only factor significantly predicting grade 3 or 4 neutropenia during Lenalidomide + Dex treatment in patients with relapsed/refractory multiple myeloma[1]
- Moderate RI, as measured by creatinine clearance in mL/min, did significantly correlate ($p < 0.05$) with higher risk of grade 3 or 4 neutropenia as compared with mild or no RI[2]
- In contrast, severe RI did not significantly correlate with higher risk of grade 3 or 4 neutropenia when compared with mild or no RI[2]
  - 32% in patients with mild or no RI ($Cl_{Cr} \geq 60$)
  - 48% in patients with moderate RI ($30 \leq Cl_{Cr} < 60$)
  - 38% in patients with severe RI ($Cl_{Cr} < 30$)

1. Lonial S, et al. Blood. 2009;114:[abstract 2879].
2. Dimopoulos M, et al. Cancer. 2010;116:3807-14.

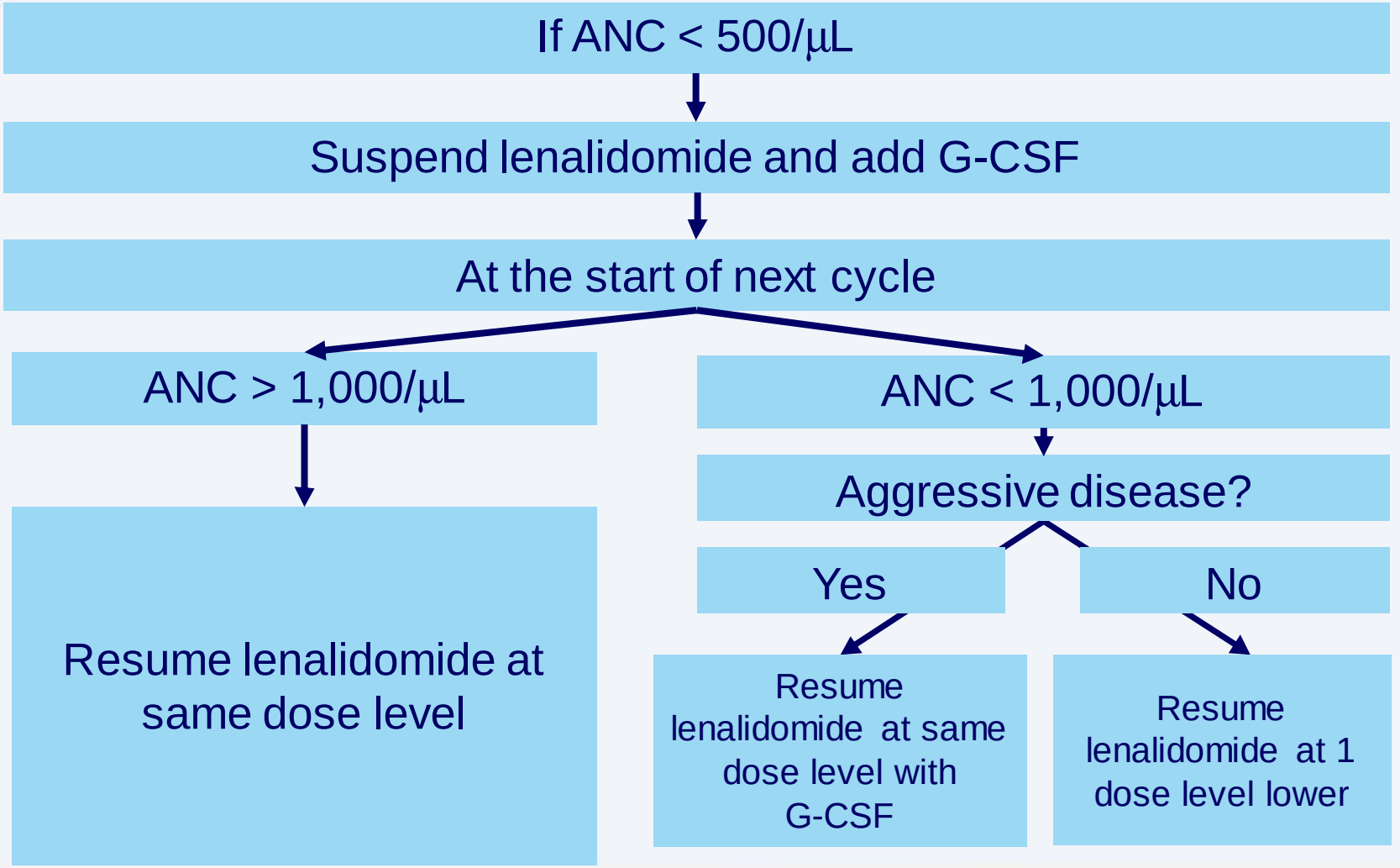
Increased age was not a risk factor for neutropenia with Lenalidomide + Dex

Proportion of all patients in MM-009 and MM-010 experiencing grade 3 or 4 neutropenia in each age group during the Lenalidomide + Dex treatment period vs proportion of patients with neutropenia receiving G-CSF (G-CSF use was similar in all age groups)



Lonial S, et al. Blood. 2009;114:[abstract 2879].

Management of neutropenia: consensus panel opinion



Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Recommended starting dose for Lenalidomide according to RI and neutropenia or thrombocytopenia

	Renal function[1,2]			
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If baseline ANC[1,2] > 1,000/µL and platelets > 50,000/µL*	25 mg once daily	10 mg once daily	15 mg every other day	5 mg once daily
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	G-CSF support / platelet transfusion as needed; monitor frequently			

* SmPC recommends not starting lenalidomide at ANC < 1,000/µL and/or platelets < 30,000–75,000/µL (depending upon bone marrow infiltration by plasma cells).
** Recommendations not according to SmPC; opinion of consensus panel.

Adjust the dose at subsequent cycles if changes in CL_{Cr} or blood cell count occur

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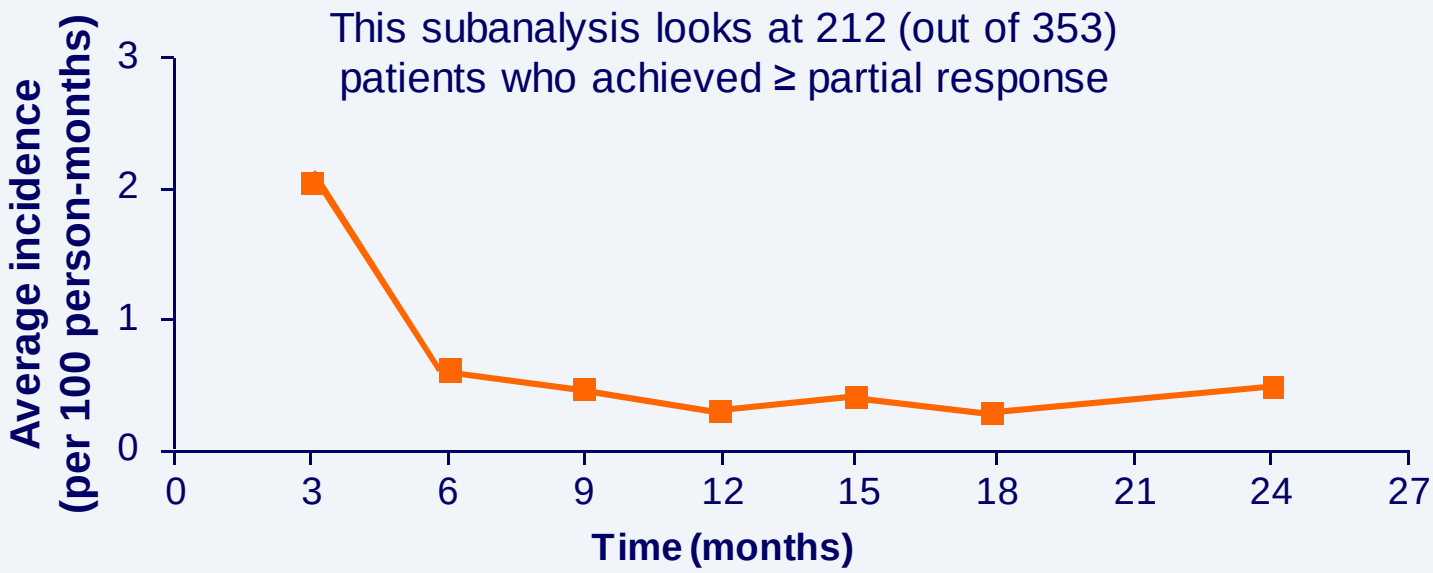
2. Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Hazard rates of thrombocytopenia declined over time in patients continuing Lenalidomide + Dex

MM-009 and MM-010 subgroup analysis

Thrombocytopenia



N	174	173	160	149	127	97	47	18	3
Events	10	5	3	1	2	1	–	1	–

San Miguel JF, et al. Clin Lymphoma Myeloma Leuk. 2011;11:38-43.

Management of thrombocytopenia

- When platelet level first falls to < 30×10^9/L
  - interrupt lenalidomide treatment
- When platelet level returns to ≥ 30×10^9/L
  - resume lenalidomide at dose level 1
- For each subsequent drop to < 30×10^9/L
  - interrupt lenalidomide treatment
- Upon return to ≥ 30×10^9/L
  - resume lenalidomide at next lower dose level
- Do not dose below 5 mg once daily

Starting dose	25 mg
Dose level 1	15 mg
Dose level 2	10 mg
Dose level 3	5 mg

Revlimid® SmPC. Celgene Europe Limited (Windsor, UK). Last updated 31/01/2011.
Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Management and prevention of peripheral neuropathy

- Lenalidomide can be given to patients with existing neuropathy or a history of peripheral neuropathy (PN)[1]
- Lenalidomide rarely exacerbates pre-existing PN[1,2]
- For agents that are associated with PN, assessment before every dose is recommended[3]
- If PN occurs, prompt intervention is crucial to enable the improvement /reversal of symptoms[3]
- In patients with pre-existing PN, the use of drugs without neurotoxic potential such as Lenalidomide is preferred[3]

1. Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4]. 2. Delforge M, et al. Poster presented at ASH. Blood. 2009;114:[abstract 3873]. 3. Ludwig H, et al. The Oncologist. 2011;16:388-403.

Management and prevention of VTE: consensus panel opinion

- Thromboprophylaxis should be considered for patients treated with Lenalidomide + Dex and should continue for the entire duration of treatment*
- Lenalidomide + Dex should be resumed in patients considered stable on anticoagulation therapy
- Aspirin prophylaxis is appropriate for patients with standard VTE risk; LMWH is recommended for patients with higher risk of VTE*
- LMWH prophylaxis should continue for at least the first 4 cycles of therapy; thereafter, patients may be switched to aspirin prophylaxis*

* Not in line with SmPC; opinion of consensus panel.

Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

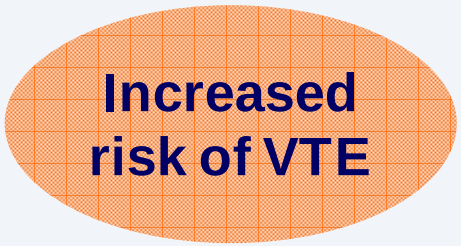
Management and prevention of VTE: lenalidomide prescribing information

- Patients with risk factors for VTE should be closely monitored
- Erythropoietic agents or other agents that increase risk of thrombosis should be used with caution in patients receiving Lenalidomide + Dex
- Thromboprophylaxis such as LMWH or low-dose aspirin should be recommended
  - especially in patients with additional thrombotic risk factors
  - decision to take antithrombotic prophylactic measures should be made after assessment of patient's risk factors
- If patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started
  - once the patient is stabilized on anticoagulation, lenalidomide treatment may be restarted at the original dose
  - patient should continue anticoagulation therapy during the course of lenalidomide treatment

Revlimid® SmPC. Celgene Europe Limited (Windsor, UK). Last updated 31/01/2011.
Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Individual and treatment-related risk factors for VTE in MM patients

1. High-dose Dex
2. Use of erythropoietin
3. Immobilization
4. Previous history of VTE



Rajkumar SV, et al. Lancet Oncol. 2010;11:29-37. Rizzo JD, et al. J Clin Oncol. 2008;26:132-49. Klein U, et al. Ann Hematol. 2009; 88: 67-71. Palumbo A, et al. Leukemia. 2008;22:414-23. Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Hazard rates of thrombotic events declined over time in patients continuing Lenalidomide + Dex

MM-009 and MM-010 subgroup analysis

Thrombotic events

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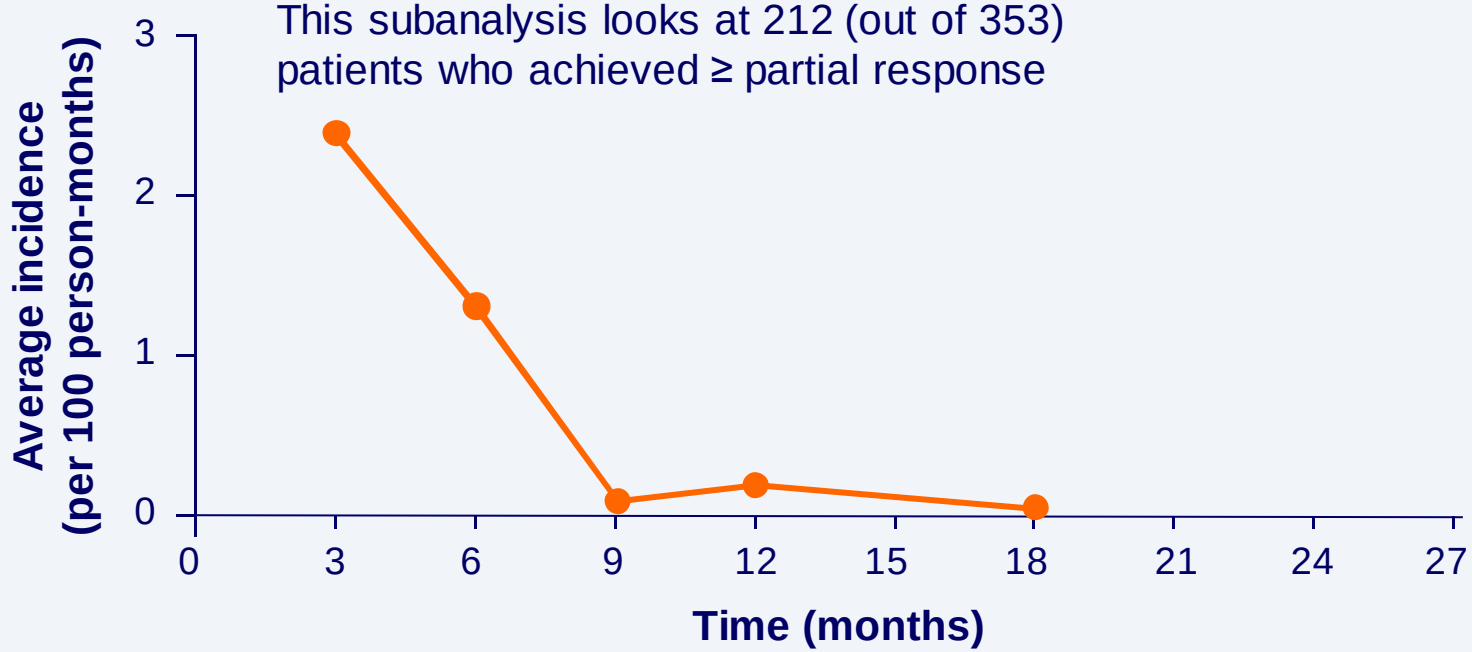

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Events	12	13	1	3	–	1	–	–	–

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Low VTE risk associated with bortezomib

	Rates of VTE events (%)	
	MPV (n = 340)	MP (n = 337)
Phase III: VISTA[1]	2	3
	Bortezomib (n = 331)	High-dose Dex (n = 332)
Phase III: APEX[2]	0.6	2.7
	Bortezomib (n = 256)	Bortezomib + Dex (n = 106)
Phase II: SUMMIT/CREST[3,4]	1.6	0.9

1. San Miguel JF, et al. New Engl J Med. 2008;359:906-17. 2. Jagannath S, et al. Brit J Haematol. 2009;146:619-26.
3. Richardson PG, et al. New Engl J Med. 2003;348: 2609-17. 4. Jagannath S, et al. Brit J Haematol. 2004;127:165-72.

Management and prevention of other AEs during Lenalidomide + Dex: consensus panel opinion

- Limited, localized rash
  - antihistamines and topical steroids
- Diffuse, desquamating, exfoliative, bullous rash
  - discontinue lenalidomide
- Infection
  - routine antibiotic prophylaxis for first 3 cycles of therapy
- Muscle cramps
  - magnesium supplementation
- Dex-related symptoms (myopathy, non-neutropenic infection, psychological changes, hyperglycaemia)
  - consider reduction in Dex dose

Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Expert panel opinion: consensus summary

- Lenalidomide + Dex has demonstrated an overall survival benefit vs. Dex alone in relapsed/refractory MM patients
- Lenalidomide + Dex is a well-tolerated treatment option for relapsed/refractory MM
- Lenalidomide + Dex should be given as early line of MM treatment and may continue until disease progression in responding patients
- Lenalidomide + Dex can be used in patients with renal impairment provided that the dose is adjusted appropriately
- Most adverse events with Lenalidomide + Dex occur during the first few cycles of therapy and can be managed and/or minimized with dose adjustments, supportive care, and/or appropriate prophylaxis

Panel Opinion is based on clinical data and observations by the expert panel, which may not be representative for all clinical situations and further research is currently ongoing. Please refer to the SmPC for full prescribing information for Lenalidomide In RRMM.

Dimopoulos MA, et al. Leukemia. [Epub ahead of print 2011 Feb 4].

Expert panel

- M.A. Dimopoulos
- A. Palumbo
- M. Attal
- M. Beksaç
- F. Davies
- M. Delforge
- H. Einsele
- R. Hajek
- J-L. Harousseau
- F. Leal da Costa
- H. Ludwig
- U-H. Mellqvist
- G. Morgan
- J.F. San Miguel
- S. Zweegman
- P. Sonneveld

The Continuum of Care for the Multiple Myeloma Patient

Wednesday 4 May 2011
10:30–12:30
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