Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Mateos M-V, Hernández M-T, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013;369:438-47. DOI: 10.1056/NEJMoa1300439

Supplementary Appendix

Supplement to: Lenalidomide Plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

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Supplementary Appendix Part I – Collaborators

In addition to the authors, the following investigators participated in the study: *Hospital de Santa Maria, Lisbon, Portugal* - G. Esteves; *IPO de Oporto, Oporto, Portugal* - M. Mariz; *IPO de Lisboa, Lisbon, Portugal* - J. Parreira; *Hospital General de Segovia, Segovia, Spain* - J.M. Hernández Martín; *Hospital La Paz, Madrid, Spain* - A. López de la Guía; *Hospital La Princesa, Madrid, Spain* - A. Alegre Amor; *Hospital Universitario Virgen del Rocio, Sevilla, Spain* - M. Luz Martino Galiana; *Hospital Clínico Universitario de Valencia, Valencia, Spain* - A.I. Teruel Casasús; and *Hospital Jerez de la Frontera, Cádiz, Spain* - J.L. Guzmán Zamudio.

Supplementary Appendix Part II – Independent Data Monitoring Committee

The Independent Data Monitoring Committee included two multiple myeloma experts:
Professor Thierry Facon, M.D., Service des Maladies du Sang, Lille, France
Professor Philippe Moreau, M.D., University Hospital Hôtel-Dieu, Nantes, France

Supplementary Appendix Part III – International Uniform Response Criteria for Multiple Myeloma

Response	Criteria for Response[a]
sCR	CR as defined below plus Normal FLC ratio, and Absence of clonal plasma cells in bone marrow by immunohistochemistry or immunofluorescence
CR	Negative immunofixation of serum and urine, and Disappearance of any soft tissue plasmacytoma, and < 5% plasma cells in bone marrow
VGPR	Serum and urine M-component detectable by immunofixation but not on electrophoresis, or ≥ 90% reduction in serum M-component plus urine M-protein level <100 mg per 24 h
PR	≥ 50% reduction of serum M-component and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg/24 h If the serum and urine M-component are not measurable[b], a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-component are not measurable, and serum FLC assay is also not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-component, provided baseline plasma cell percentage was ≥ 30% In addition, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD	Not meeting the criteria for either CR, VGPR, PR or PD

[a]Two consecutive assessments made at any time are required; no known evidence of progressive or new bone lesions if radiographic studies were performed is also required. Radiographic studies are not required to satisfy these response criteria.

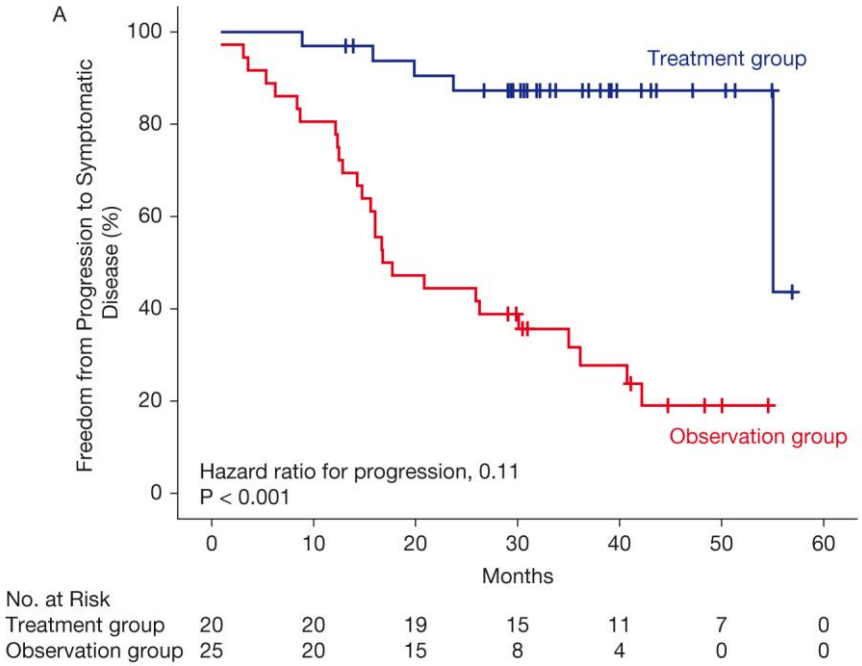
[b]Measurable disease defined as serum M-component ≥ 1 g/dl (≥ 10 gm/l)[10 g/l], urine M-component ≥ 200 mg/24 h, and serum FLC assay: involved FLC level ≥ 10 mg/dl (≥ 100 mg/l) provided serum FLC ratio is abnormal.

CR, complete response; FLC, free light chain; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

Adapted from:
Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006; 20:1467-73.
Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011; 117:4691-5.

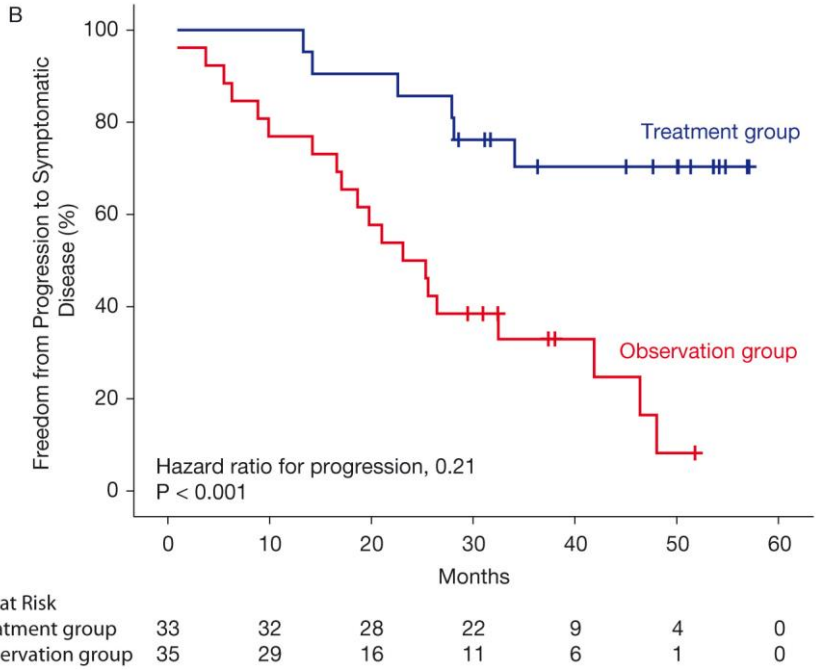
Supplementary Appendix Part II – Supplementary Figures

Figure S1. Time to Progression to Symptomatic Disease According to Time Between Diagnosis and Trial Enrollment (Panel A: ≤6 Months; Panel B: >6 Months).



No. at Risk

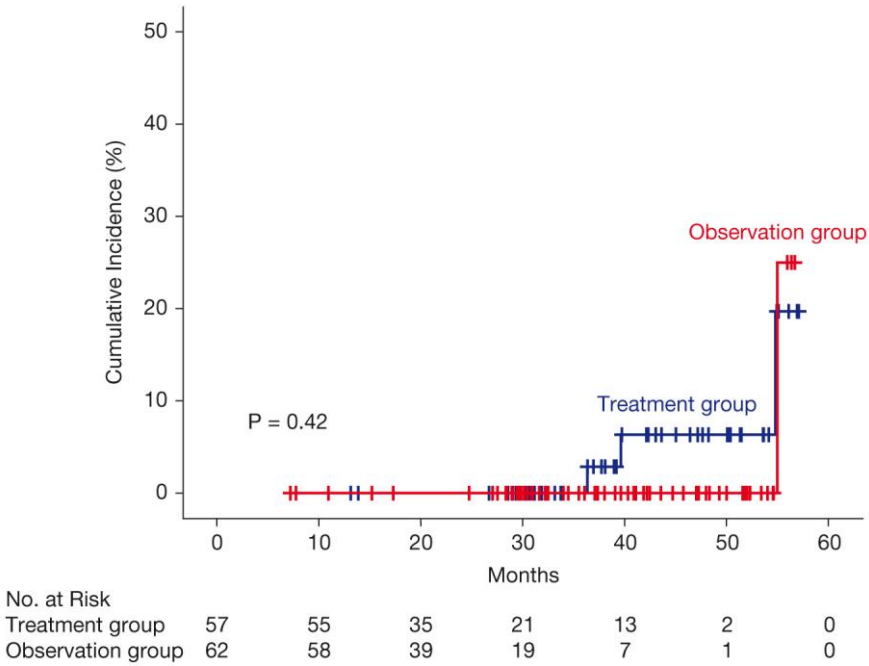
Treatment group	20	20	19	15	11	7	0
Observation group	25	20	15	8	4	0	0



No. at Risk

Treatment group	33	32	28	22	9	4	0
Observation group	35	29	16	11	6	1	0

Figure S2. Cumulative Incidence of Second Primary Tumors in the Treatment and the Observation Groups.



No. at Risk							
Treatment group	57	55	35	21	13	2	0
Observation group	62	58	39	19	7	1	0

Supplementary Appendix Part III – Supplementary Tables

Table S1. List of Patients Who Died in the Observation Group.

Pt	Age	MC	MC at inclusion (g/L or g/24h)	MC at progression (g/L or g/24h)	Myeloma-related symptomatology	TTP to symptomatic disease (m)	OS (m)	Treatment	Cause of death
1	80	IgAK	43,6	55.0	Renal failure+hypercalcemia	5.3	15	VMP	Disease progression
2	60	IgGλ	64,5	72.0	Anemia+renal failure	3.4	7.7	Bortezomib-based regimen	Disease progression
3	81	BJK	3,7	5.2	Anemia+renal failure	26.4	47.03	Bortezomib-based regimen	Disease progression
4	75	IgAK	34.5	63.3	Anemia+bone disease	8.8	10.93	VMP	Sudden death
5	50	IgAK	36.3	46.5	Anemia+bone disease	20.8	37.2	HDT-ASCT	Disease progression
6	67	IgAλ	18.0	35.7	Anemia+bone disease+renal failure+hypercalcemia	19.7	28.4	HDT-ASCT	Transplant-related adverse event*
7	72	IgGK	35.5	41.4	Anemia	12.5	17.3	VMP	Disease progression
8	57	IgGλ	33.0	34.0	Anemia+renal failure	12.1	24.7	Bortezomib-based regimen	Disease progression
9	74	IgAλ	57.3	61.3	Anemia	6.3	28.3	Bortezomib-based regimen	Disease progression
10	82	IgAλ	2.5	3.7	Bone disease	21.3	35.5	VMP	Disease progression
11	75	IgGK	19.3	17.1	Renal failure	25.3	30.1	Bortezomib-based regimen	Treatment-related adverse event**
12	70	IgAK	25.9	33.4	Anemia+bone disease	5.5	36.0	VMP	Disease progression
13	79	IgGK	37.9	39.1	Anemia+hypercalcemia+ Bone disease	3.5	7.2	MP	Treatment -related adverse event**

*Infection at the day +35 post HDT-ASCT

**Respiratory infection

HDT-ASCT, high dose therapy followed by autologous stem cell transplantation, MC, monoclonal component, OS, overall survival, Pt, patient number, TTP, time to progression, VMP, bortezomib, melphalan and prednisone.