Supplementary material

for

Impact of Acquired del(17p) in Multiple Myeloma

Supplementary Table 1.Initial treatment in patients with acquired del(17p) and controls			
Therapeutic regimen	*Acquired del(17p) (n=76)*	*Controls (n=152)*	*P**
• PI-containing induction	21 (27.6)	37 (24.3)	0.751
○ PI+IMiD-based	5 (6.6)	17 (11.1)	0.345
○ PI-based	16 (21.1)	20 (13.2)	
• IMiD-based induction	47 (61.8)	95 (62.5)	
• Other induction	8 (10.5)	20 (13.2)	
• Alkylating agent as part of induction	17 (22.4)	34 (22.4)	1.000
SCT within 1 year of diagnosis	34 (44.7)	82 (53.9)	0.208
SCT within 1 year of diagnosis (and before detection of del(17p) for cases)	33 (43.4)	82 (53.9)	0.160
*P for Fisher's exact test. IMiD indicates Immunomodulatory drug; PI, Proteasome inhibitor; and SCT, stem cell transplantation.			

Supplementary Table 2. Best response to induction therapy in patients with acquired del(17p) and controls			
Best response to therapy	Acquired (17p) (n=69)	Controls (n=151)	*P**
sCR+CR+VGPR	24 (34.8)	40 (26.4)	0.263
sCR+CR+VGPR+PR (ORR)	57 (82.6)	126 (83.4)	0.849
sCR+CR+VGPR+PR+MR (CBR)	62 (89.9)	143 (94.7)	0.247
sCR	2 (2.9)	4 (2.6)	
CR	3 (4.4)	7 (4.6)	
VGPR	19 (27.5)	29 (19.2)	
PR	33 (47.8)	86 (57.0)	
MR	5 (7.3)	17 (11.3)	
SD	7 (10.1)	6 (4.0)	
PD	0 (0)	2 (1.3)	
Sixty nine patients with acquired del(17p) and 151 controls were evaluable for response; *P for Fisher's exact test. CBR indicates clinical benefit rate; CR, complete response; MR, minimal response; ORR, overall response rate; PD: progressive disease; PR, partial response; sCR: stringent CR; SD: stable disease; and VGPR, very good partial response.			

Supplementary Table 3. Sub-group analysis for overall survival landmarked from detection of del(17p) in patients based on prognostic factors at diagnosis and therapy.

Subgroups for analysis	*Acquired del(17p) (n=76)*	*Control patients (n=152)*	*P**
Age <65 (48 vs. 101)	22.3 (13.4-37.2)	56.2 (42.3-80.1)	<0.001
Age ≥65 (28 vs. 51)	11.8 (4.2-18.2)	51.2 (40.8-88.4)	<0.001
No high-risk translocation (62 vs. 138)	18.8 (11.9-25.0)	69.1 (44.8-86.5)	<0.001
High-risk translocation (14 vs. 14)	15.8 (3.8-65.8)	44.4 (25.0-50.0)	0.259
ISS I/II (42 vs. 110)	16.5 (11.2-37.2)	69.1 (45.7-80.1)	<0.001
ISS III (14 vs. 26)	9.7 (1.7-43.7)	40.7 (26.0-NR)	0.026
Low LDH (44 vs. 116)	17.7 (8.6-43.7)	56.2 (44.4-78.8)	<0.001
High LDH (7 vs. 5)	11.2 (2.2-29.8)	37.8 (0-NR)	0.090
Low PC proliferative rate (32 vs. 84)	22.7 (11.7-48.0)	54.0 (44.4-88.4)	0.003
High PC proliferative rate (14 vs. 22)	8.9 (4.2-43.7)	72.8 (38.4-NR)	0.001
PI-containing induction (21 vs. 37)	10.9 (5.8-20.0)	53.8 (40.0-78.8)	<0.001
Others (55 vs. 115)	22.3 (13.4-41.0)	54.0 (42.3-80.1)	<0.001
Early SCT (and before detection of del(17p) for cases) (33 vs. 82)	17.1 (12.7-29.8)	59.7 (44.8-NR)	<0.001
Delayed or no SCT (or after detection of del(17p) for cases)(43 vs. 70)	18.2 (8.3- 35.6)	45.7 (38.3-80.1)	<0.001

*P for log-rank test for Kaplan Meier analysis; ISS indicates international staging system; LDH, Lactate dehydrogenase; PC, Plasma cell; and PI, Proteasome inhibitor.

Supplementary Table 4. Details of subsequent line of therapy in patients with acquired del(17p) (n=76)			
Serial number	*Year of detection of del(17p)*	*Prior line(s) of therapy*	*Subsequent therapy*
1	2005	1	Clarithromycin, lenalidomide and dexamethasone followed by lenalidomide maintenance
2	2006	3	Lenalidomide and dexamethasone
3	2007	9	Samarium and bortezomib clinical trial
4	2007	3	Lenalidomide and dexamethasone
5	2008	2	Lenalidomide and dexamethasone
6	2008	1	Pomalidomide and dexamethasone
7	2008	3	High-dose therapy with autologous stem cell transplant
8	2008	4	High-dose therapy with autologous stem cell transplant
9	2008	2	Cyclophosphamide and prednisone
10	2009	6	High-dose therapy with second autologous stem cell transplant
11	2009	5	Melphalan with high-dose steroid
12	2009	10	High-dose therapy with second autologous stem cell transplant
13	2009	2	Cyclophosphamide prednisone
14	2009	3	Pomalidomide and dexamethasone
15	2009	6	Carfilzomib with dexamethasone
16	2009	1	High-dose therapy with autologous stem cell transplant
17	2009	6	Bortezomib, cyclophosphamide and dexamethasone
18	2009	2	Lenalidomide and dexamethasone
19	2010	4	Measles virus-NIS trial
20	2010	3	Pomalidomide and dexamethasone
21	2010	1	Pomalidomide and dexamethasone
22	2010	3	Pomalidomide and dexamethasone
23	2010	1	High-dose therapy with autologous stem cell transplant followed by bortezomib maintenance
24	2010	4	VDT-PACE
25	2010	5	Pomalidomide and dexamethasone
26	2010	1	Bortezomib and dexamethasone followed by lenalidomide maintenance
27	2010	2	Bortezomib, cyclophosphamide and dexamethasone
28	2010	3	Bortezomib and dexamethasone
29	2010	1	Bortezomib dexmethasone
30	2011	4	High-dose therapy with second autologous stem cell transplant followed by lenalidomide maintenance.

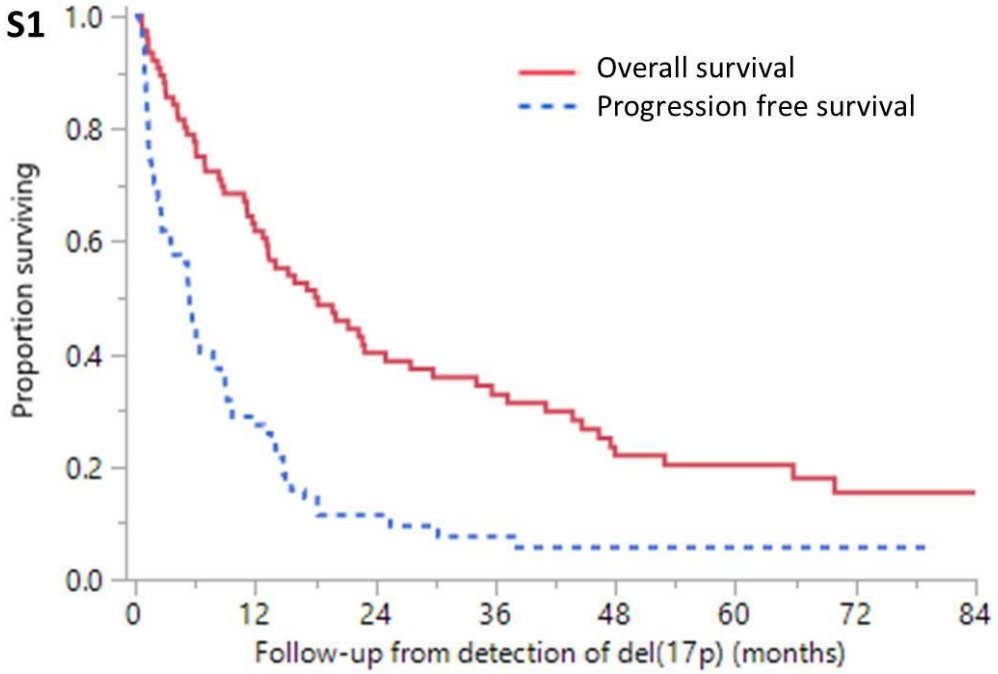
31	2011	2	High-dose therapy with autologous stem cell transplant
32	2011	2	Bortezomib, cyclophosphamide and dexamethasone
33	2011	1	Lenalidomide and dexamethasone
34	2011	4	Pomalidomide and dexamethasone
35	2011	3	Pomalidomide and dexamethasone
36	2011	2	Bortezomib, lenalidomide and dexamethasone
37	2011	4	High-dose therapy with autologous stem cell transplant and bortezomib and lenalidomide maintenance
38	2011	1	Bortezomib, lenalidomide and dexamethasone
39	2011	3	Pomalidomide and dexamethasone
40	2012	2	Lenalidomide and dexamethasone
41	2012	1	Panabinostat with everolimus
42	2012	3	Pomalidomide, bortezomib and dexamethasone
43	2012	2	Bortezomib, cyclophosphamide and dexamethasone
44	2012	1	CHOP with lenalidomide
45	2012	2	Ixazomib and dexamethasone
46	2013	2	High-dose therapy with autologous stem cell transplant followed by pomalidomide maintenance.
47	2013	5	Measles virus-NIS trial
48	2013	9	VDT-PACE followed by second autologous stem cell transplant
49	2013	2	Ixazomib and dexamethasone
50	2013	1	Pomalidomide, bortezomib and dexamethasone
51	2013	1	Bortezomib, cyclophosphamide and dexamethasone followed by high-dose therapy with autologous stem cell transpalnt and bortezomib maintenance
52	2013	1	Bortezomib, cyclophosphamide and dexamethasone
53	2013	3	VDT-PACE
54	2013	3	Pomalidomide dexamethasone
55	2013	5	Pomalidomide and dexamethasone
56	2013	6	Allogeneic stem cell transplant
57	2014	4	Carfilzomib, pomalidomide and dexamethasone.
58	2014	3	VDT-PACE followed by autologous stem cell transplant and lenalidomide maintenance
59	2014	1	Bortezomib, melphalan and prednisone
60	2014	1	Ixazomib and dexamethasone
61	2014	1	Carfilzomib and dexamethasone
62	2014	1	Ixazomib and dexamethasone
63	2014	3	Oprozomib trial
64	2014	2	Pomalidomide, bortezomib and dexamethasone

65	2015	2	Ixazomib,pomalidomide and dexamethasone
66	2015	4	Oprozomib trial
67	2015	3	Bortezomib and dexamethasone
68	2015	1	Pomalidomide and dexamethasone
69	2015	1	Ixazomib,pomalidomide and dexamethasone
70	2016	1	Ixazomib, cyclophosphamide and dexamethasone
71	2016	1	Carfilzomib, pomalidomide and dexamethasone
72	2016	1	Bortezomib, cyclophosphamide and dexamethasone
73	2016	1	Daratumumab, pomalidomide and dexamethasone
74	2016	3	Daratumumab, bortezomib, cyclophosphamide and dexamethasone
75	2016	4	Daratumumab and CHOP
76	2016	2	Daratumumab, pomalidomide and dexamethasone

CHOP indicates cyclophosphamide, doxorubicin, vincristine and prednisone; and VDT-PACE, Total Therapy protocol with bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide and etoposide.

Supplementary Table 5. Comparative analysis between patients with acquired del(17p) and controls for putative risk factors at diagnosis for acquiring del(17p).	
Presumed risk factor for acquiring del (17p)	*Odds ratio (95% CI)*
Age ≥65 years (28/76 vs. 51/152)	0.1.16 (0.65-2.05)
ISS III stage (14/56 vs. 26/136)	1.41 (0.67-2.96)
Elevated LDH (7/51 vs. 5/121)	**3.69 (1.11-12.24)**
Bone marrow plasma cell % ≥50% (21/70 vs. 62/150)	0.61 (0.33-1.11)
High plasma cell proliferative rate (14/45 vs. 22/106)	0.72 (0.78-3.79)
High-risk translocations (14/76 vs. 14/152)	**2.23 (1.00-4.95)**
t(4;14) (12/76 vs. 10/152)	**2.66 (1.09-6.48)**
t(11;14) (15/76 vs. 37/152)	0.76 (0.39-1.50)
Monosomy 13 (27/76 vs. 59/152)	0.86 (0.49-1.54)
Any trisomy/tetrasomy (38/76 vs. 90/152)	0.69 (0.40-1.20)
Hyperdiploidy (trisomy/tetrasomy of ≥2 odd-numbered chromosomes) (32/76 vs. 69/152)	0.87 (0.50-1.53)
PI-containing induction (21/76 vs. 37/152)	1.19 (0.64-2.22)
Alkylating agent in induction (17/76 vs. 36/160)	1.00 (0.52-1.94)
Autologous SCT with high dose melphalan within 1 year of diagnosis (and before detection of del(17p) for cases) (33/76 vs. 82/152)	0.65 (0.38-1.14)
ISS indicates international staging system; LDH, Lactate dehydrogenase; PI, Proteasome inhibitor; and SCT, stem cell transplantation.	

Supplementary figure 1. Survival outcomes in patients with acquired del(17p)- (a) Progression free survival and overall survival in patients with acquired del(17p) from detection of del(17p). The median PFS and OS were 5.4 months (95% CI, 2.7-7.7) and 18.1 months (95% CI, 11.9-25.0) respectively.



Supplementary figure 2. Landmark analysis for overall survival (OS) in patients with acquired del(17p) and controls- OS was calculated from the date of detection of del(17p) for patients with acquired del(17p). For controls, OS was landmarked from a date corresponding to the time duration between diagnosis and detection of del(17p) for respective controls. The respective OS for patients with acquired del(17p) and controls were 18.1 months (95% CI, 11.1-25.0) and 56.2 months (95% CI, 44.4-79.7) (P<0.001).