Minor clone of del(17p) provides a reservoir for relapse in multiple myeloma

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Supplementary data for

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Supplementary Figure 1

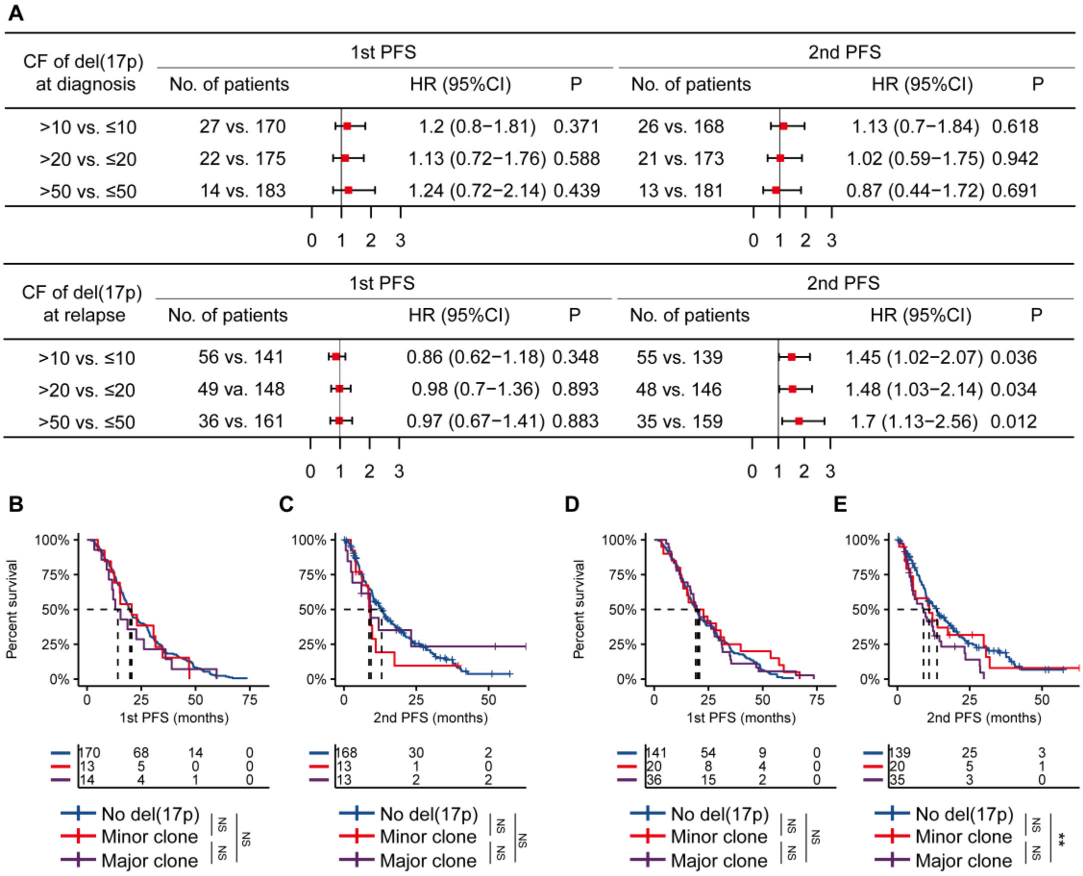

Figure S1.

Related to figure 4.

(A) Forest plots of HR for median survival in patients with different cell fractions of del(17p) at diagnosis (upper) or at relapse (lower). (B, C) Kaplan-Meier curves in patients at diagnosis with no del(17p), a minor clone of del(17p) or a major clone of del(17p). Different landmarks are used: PFS from diagnosis (B) and PFS from relapse (C). NS, not significant, by two-sided log-rank test. (D, E) Kaplan-Meier curves in patients at relapse with no del(17p), a minor clone of del(17p) or a major clone of del(17p). Different landmarks are used: PFS from diagnosis (D) and PFS from relapse (E). NS, not significant, **P < 0.01, by two-sided log-rank test.

Supplementary Figure 2

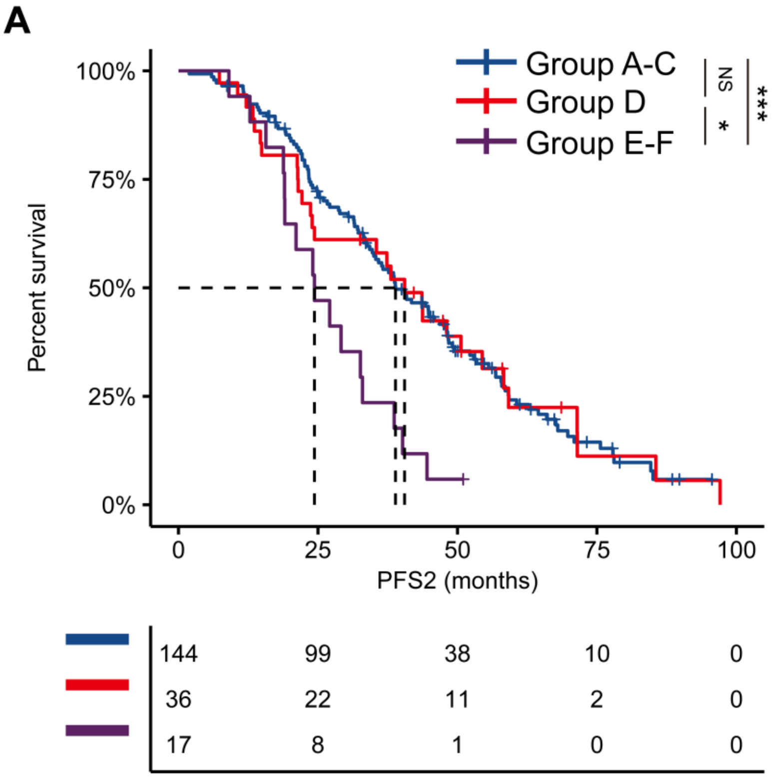

Figure S2.

Six del(17p) evolutionary patterns are merged to 3 groups according to the survival curves in figure 5B. Kaplan-Meier curves for PFS2 are presented. NS, not significant, *P < 0.05, ***P < 0.001, by 2-sided log-rank test.

Table S1. Baseline characteristics of 995 patients in the diagnosis dataset and 293 patients in the relapse dataset.

	NDMM dataset (N = 995)	RRMM (N = 293)
Median age (years), median (range)	60 (29-83)	58 (32-78)
Male, n/N (%)	580/995 (58)	162/293 (55)
Hemoglobin (g/dL), median (range)	9.9 (4.5-19.0)	12.2 (5.6-17.2)
Platelets ($\times 10^9$/L), median (interquartile range)	189 (130-245)	198 (134-248)
Creatinine (umol/L), median (range)	81.0 (28.3-667.5)	81.8 (32.9-726.5)
LDH (U/L), median (range)	169.1 (46.5-654.2)	189.1 (67.9-687.444)
B2M (μg/mL), median (interquartile range)	4.56 (2.98-8.37)	4.30 (2.91-6.88)
BMPCs (%), median (interquartile range)	22 (10-43)	24 (10-43)
ISS stage, n/N (%)		
I or II	659/995 (76)	164/293 (56)
III	236/995 (24)	129/293 (44)
Serum M-component, n/N (%)		
IgG	440/995 (44)	120/293 (41)
IgA	262/995 (26)	767/293 (26)
Light chain	230/995 (23)	59/293 (20)
CAs by iFISH, n/N (%)		
[a]High-risk	252/995 (25)	97/293 (33)
Induction treatment regimens, n/N (%)		
PI-based induction	760/995 (76)	196/293 (67)
IMID-based induction	109/995 (11)	32/293 (11)
PI+IMID-based induction	125/995 (13)	65/293 (22)
First-line ASCT, n/N (%)	328/995 (33)	105/293 (36)
Post induction response, n/N (%)		
sCR or CR	189/995 (19)	41/293 (14)
VGPR or PR	706/995 (71)	199/293 (68)
Less than PR	100/995 (10)	53/293 (18)

[a]High risk CA: presence of t (4;14), t(14;16) and/or del(17p).

Abbreviations: *NDMM* newly diagnosed multiple myeloma, *RRMM* relapsed or refractory multiple myeloma, *PI* proteasome inhibitor, *IMiD* immunomodulatory drug, *LDH* lactate dehydrogenase, *B2M* beta 2 microglobulin, *BMPCs* bone marrow plasma cells, *ISS* international staging system, *CAs* cytogenetic abnormalities, *iFISH* interphase fluorescence in situ hybridization, *ASCT* autologous stem cell transplantation, *PR* partial response, *VGPR* very good partial response, *CR* complete response, *sCR* stringent complete response.

Table S2. Baseline clinical characteristics of the 197 MM patients with paired iFISH results.

Characteristics	**At diagnosis**
Male, n (%)	124/197 (63)
Age (years), median (range)	60 (29-83)
ISS stage III, n./N (%)	89/197 (45)
Extramedullary invasion, n/N (%)	24/197 (12)
Abnormal karyotype, n/N (%)	47/197 (22)
Hemoglobin (g/dL), median (range)	9.9 (4.5-19.0)
Platelets (×10^9/L), median (interquartile range)	188 (129-244)
Cytogenetics, n/N (%)	
Del(13q)	112/197 (57)
Gain/amp(1q)	99/197 (50)
Del(17p)	14/197 (7)
IgH rearrangement	118/197 (60)
t(4;14)	44/189 (23)
t(11;14)	34/189 (18)
t(14;16)	9/189 (5)
[a]t(14;undefined)	24/190 (13)
At least one CA by iFISH	174/197 (88)
[b]High-risk CAs	65/197 (33)
Induction treatment regimens, n/N (%)	
PI-based induction	132/197 (67)
IMID-based induction	18/197 (9)
PI+IMiD-based induction	47/197 (24)
First-line ASCT, n/N (%)	41/197 (21)
[c]**Post-induction negative flow-MRD, n/N (%)**	43/183 (23)

[a]t(14; undefined): patients with an undefined abnormality of the 14q32 loci not corresponding to one of the above three described common translocations.

[b] High risk CA: presence of t (4;14), t(14;16) and/or del(17p).

[c] MRD sensitivity threshold: 10^{-4}.

Table S3. The number of cytogenetic aberrations in patients who maintain at standard-risk, maintain at high-risk and evolve to high-risk at diagnosis and at relapse.

	Maintain at standard-risk (N = 112)		Maintain at high-risk (N = 62)		Evolve to high-risk (N = 20)	
Cytogenetics, n/N	**At diagnosis**	**At relapse**	**At diagnosis**	**At relapse**	**At diagnosis**	**At relapse**
Del(13q)	49/112	50/112	47/62	47/62	13/20	13/20
Gain/amp(1q)	51/112	67/112	38/62	51/62	8/20	11/20
Del(17p)	0/112	0/112	11/62	16/62	0/20	20/20
IgH rearrangement	55/112	55/112	59/62	59/62	4/20	4/20
t(4;14)	0/108	0/108	44/59	44/60	0/19	0/19
t(11;14)	31/108	31/108	1/59	1/58	2/19	2/19
t(14;16)	0/108	0/108	9/59	9/59	0/19	0/19
t(14;undefined)[a]	21/109	21/109	2/59	2/59	1/19	1/19

[a] t(14; undefined): patients with an undefined abnormality of the 14q32 loci not corresponding to one of the above three described common translocations.

Table S4. Effect of characteristics on 1st PFS and 1st OS in patients with paired iFISH results at diagnosis and at relapse (N = 197).

	1st PFS			1st OS		
Independent variable	P for univariable analysis	HR (95% CI) for multivariable analysis	P for multivariable analysis	P for univariable analysis	HR (95% CI) for multivariable analysis	P for multivariable analysis
Age ≥65 vs. <65	0.012	1.75 (1.20-2.74)	0.014	0.004	1.64 (1.08-2.51)	0.021
Post-induction response						
Less than PR vs. CR or sCR	0.001	2.86 (1.52-5.36)	0.001	0.505	NI	/
PR vs. CR or sCR	0.082	1.41 (0.89-2.21)	0.140	0.184	NI	/
VGPR vs. CR or sCR	0.046	1.65 (0.98-2.78)	0.058	0.466	NI	/
ISS stage						
II vs. I	0.597	NI	/	0.809	1.05 (0.61-1.80)	0.860
III vs. I	0.256	NI	/	0.072	1.50 (0.91-2.45)	0.110
Post-induction MRD status						
MRD+ vs. MRD-	0.009	1.44 (0.96-2.15)	0.076	0.239	NI	/
Transplantation, yes vs. No	0.032	0.93 (0.63-1.37)	0.715	0.586	NI	/
Del(17p) at relapse						
Minor clone vs. No del(17p)	0.754	1.11 (0.58-1.40)	0.507	0.044	1.31 (0.75-2.28)	0.350
Major clone vs. No del(17p)	0.932	1.22 (0.45-1.48)	0.640	0.002	1.91 (1.23-2.98)	0.004

All variables with a $P < 0.1$ in univariable analysis were included in the multivariable model.

HR, hazard ratio; *CI* confidence intervals, *NI*, not included in analysis.

Table S5. Effect of characteristics on 2nd PFS and 2nd OS in patients with paired iFISH results at diagnosis and at relapse (N = 197).

	2nd PFS			2nd OS		
Independent variable	P for univariable analysis	HR (95% CI) for multivariable analysis	P for multivariable analysis	P for univariable analysis	HR (95% CI) for multivariable analysis	P for multivariable analysis
Age ≥65 vs. <65	0.356	NI	/	0.040	1.40 (0.91-2.13)	0.122
Post-induction response						
Less than PR vs. CR or sCR	0.772	NI	/	0.659	NI	/
PR vs. CR or sCR	0.177	NI	/	0.306	NI	/
VGPR vs. CR or sCR	0.155	NI	/	0.757	NI	/
ISS stage						
II vs. I	0.495	NI	/	0.787	NI	/
III vs. I	0.599	NI	/	0.126	NI	/
Post-induction MRD status						
MRD+ vs. MRD-	0.198	NI	/	0.672	NI	/
Transplantation, yes vs. No	0.769	NI	/	0.693	NI	/
Del(17p) at relapse						
Minor clone vs. No del(17p)	0.624	NA	/	0.008	1.90 (1.10-3.29)	0.021
Major clone vs. No del(17p)	0.010	NA	/	0.001	2.35 (1.449-3.70)	0.001

All variables with a $P < 0.1$ in univariable analysis were included in the multivariable model.

HR, hazard ratio; *CI* confidence intervals, *NI*, not included in analysis, *NA* not applicable.

Table S6. The distribution clonal sizes of del(17p) for 197 patients at diagnosis and relapse.

		At diagnosis			
		No del(17p)	Del(17p) ≤ 10%	Del(17p) 10%-50%	Del(17p) > 50%
At relapse	No del(17p)	134	0	4	3
	Del(17p) ≤ 10%	0	0	0	0
	Del(17p) 10%-50%	13	0	4	3
	Del(17p) > 50%	21	2	5	8