

# Large registry analysis to accurately define second malignancy rates and risks in a well-characterized cohort of 744 consecutive multiple myeloma patients followed-up for 25 years

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**Suppl. Table 1. Patients with 2 or more additional malignancies (AM), apart from MM (n=13)**

(m/f), age (ys) at MM diagno- sis	Time-line of AM (p/s vs. SPM)	1. tumor; initial diagnosis (ID), last outcome (CR/PR vs. SD/PD)	2. tumor; ID, outcome	3. tumor; ID, outcome	4. tumor; ID, outcome	Cytogenetics	Survival (alive=1, dead=2; cancer-related death: A=yes, B=no)
1. m, 67	p/s	Prostate-ca, ID 1/1998, CR	Urothelial (Bladder)- ca, ID 1/1999, CR	<b>MM, ID 11/2005, SD</b>		nd	2, B <sup>#</sup>
2. m, 66	p/s	Prostate-ca, ID 10/2005, CR	MCL, ID 11/2005, PD	<b>MM, ID 9/2007, SD</b>		nd	2, A
3. m, 79	p/s	Urothelial (Bladder)- ca, ID 7/2004, CR	RCC, ID 7/2006, CR	<b>MM, ID 7/2007, PD</b>		MMPC: t(11;14),+11	2, A
4. m, 81	p/s	Basal-cell-carcinoma, ID 6/1989, CR	Prostate-ca, ID 7/2004, CR	<b>MM, ID 7/2010, SD</b>		MMPC: NK	1
5. m, 64	p/s	Basal-cell-carcinoma, ID 6/1965, CR	Colon-ca, ID 7/1996, CR	<b>MM, ID 7/2000, PD</b>		nd	2, A
6. m, 55	p/s + SPM	Urothelial (Bladder)- ca, ID 7/1981, CR	<b>MM, ID 10/1985, SD</b>	Colon-ca, ID 5/1999, CR		nd	2, B <sup>#</sup>
7. f, 72	p/s + SPM	Liposarcoma, ID 1/2000, CR	<b>MM, ID 10/2003, SD</b>	t-AML, ID 12/2005, PD		MMPC: NK* t-AML: NK	2 A (PD AML)
8. f, 73	p/s + SPM	Colon (Sigma)-ca, ID 6/2000, CR	<b>MM, ID 6/2006, PD</b>	t-MDS, ID 9/2007, SD		nd	2 A (PD MM: PLC)
9. m, 67	p/s + SPM	MDS (CMML), ID 7/1997, SD	<b>MM, ID 7/2008, SD</b>	Prostate-ca, ID 10/2008, CR		MMPC: NK CMML: 46,XY	1
10. m, 66	SPM	<b>MM, ID 5/1988, SD</b>	Prostate-ca, ID 3/1996, CR	Colon-ca, ID 8/2001, CR	B-CLL, ID 10/2005, PD	nd	2, A
11. m, 77	SPM	<b>MM, ID 1/2006, SD</b>	B-CLL, ID 1/2006, SD	t-AML, ID 6/2007, PD		MMPC: del 13q14 t-AML: 46,XY	2 A (PD AML)
12. f, 67	SPM	<b>MM, ID 2005, PR</b>	t-MDS, ID 2007, SD	Basal-cell-carcinoma, ID 2010, CR		MMPC: NK t-MDS: 47,XX,+8	1
13. m, 83	SPM	<b>MM, ID 5/2005, SD</b> AL-Amyloidosis, ID 5/2005, SD	MCL, ID 8/2006, SD	Basal-cell-carcinoma, ID 9/2008, CR		MMPC: 46,XY MCL: t(11;14)	1

**Abbreviations:** m: male, f: female, ys: age in years, p/s: prior or synchronously to the MM occurring tumor, p/s:prior/synchronous, SPM: second primary malignancy; ca: carcinoma, RCC: renal cell carcinoma, t-MDS/AML: therapy-related MDS/AML, MCL: mantle cell lymphoma, <sup>#</sup>death due to coronary heart disease, PLC: plasma cell leukemia, PD: progressive disease, SD: stable disease, CR: complete remission, PR: partial remission, nd: not done, MMPC: multiple myeloma plasma cells, AML/MDS: cytogenetics of AML/MDS blast cells, NK (FISH): using various probes, e.g. for t(4;14), t(14;16), del17p, del13q14,1p and 1q aberrations, with no cytogenetic abnormalities (CA) found.

**Suppl. Table 2. Cytogenetics in 22 MM patients with p/s hematologic lymphoma or MDS/AML (#1-14) and in those with hematologic SPM (#15-22)\***

<b>m/f, age (ys) at MM diagnosis</b>	<b>Time-line of AMs (p/s vs. SPM)</b>	<b>1<sup>st</sup> tumor, ID</b>	<b>Cytogenetics of 1<sup>st</sup> tumor</b>	<b>2<sup>nd</sup> tumor, ID</b>	<b>Cytogenetics of 2<sup>nd</sup> tumor</b>
1. m, 73	p/s	B-CLL, ID 2003	del 13q14	<b>MM, ID 09/2005</b>	trisomy 11
2. m, 62	p/s	B-CLL, ID 2003	del 11q22	<b>MM, ID 06/2005</b>	nd
3. m, 73	p/s	B-CLL, ID 2003	del 10q24,2-25.2,11q13.1-q24.1,del12p	<b>MM, ID 09/2008</b>	nd
4. m, 63	p/s	B-CLL, ID 09/2005	NK <sup>1</sup>	<b>MM, ID 09/2005</b>	NK <sup>1</sup>
5. f, 66	p/s	B-CLL, ID 09/2008	del 13q14, i(17p), -17	<b>MM, ID 09/2008</b>	del 13q14, i(17p), -17
6. m, 71	p/s	Hodgkin, ID 10/2007	Nd	<b>MM, ID 11/2007</b>	hyperdiploidy: +5, +9, +11, +17, monosomy 16
7. f, 68	p/s	B-NHL (FL), ID 08/2010	Nd	<b>MM, ID 10/2010</b>	nd
8. m, 65	p/s	MCL, ID 2005	Nd	<b>MM, ID 09/2007</b>	nd
9. m, 58	p/s	MCL, ID 2000	Nd	<b>MM, ID 10/2007</b>	nd
10. m, 63	p/s	MDS (CMML), ID 1987	Nd	<b>MM, ID 08/2000</b>	NK*
11. m, 53	p/s	MDS/AML ID 02/2009	45,XY, -7, 48,XY,+8	<b>MM, ID 02/2009</b>	nd
12. m, 67	p/s	AML, ID 07/2008	46,XY	<b>MM, ID 07/2008</b>	NK*
13. m, 72	p/s	MDS/AML, ID 01/2009	47,XY,+13	<b>MM, ID 01/2009</b>	nd
14. m, 73	p/s	AML, ID 07/2008	46,XY	<b>MM, ID 07/2008</b>	nd
15. f, 77	SPM	<b>MM, ID 06/2009</b>	del 13q14, monosomy 16/16q, 7(11;14)	CML, ID 09/2010	Bcr-abl
16. m, 78	SPM	<b>MM, ID 07/2004</b>	NK*	t-MDS, ID 01/2005	46,XY
17. f, 67	SPM	<b>MM, ID 2005</b>	NK*	t-MDS, ID 2007	47,XX, +8
18. f, 50	SPM	<b>MM, ID 11/1997</b>	NK*	t-AML, ID 10/2009	46,XX, der (4)t(4;11) (p14;p11), del5(q14q34), der(8)t(8;11)(p23;q22), der 11 t(4;11)(p14;p11)t(8;11)(p23;q22)**
19. f, 59	SPM	<b>MM, ID 04/1994</b>	NK*	t-AML, ID 04/2003	46,XX, del (5)(q13q33), -21, +2mar
20. m, 49	SPM	<b>MM, ID 01/1992</b>	NK*	t-AML, ID 03/2009	48,XY,der( 5;20) (p10;q10), +19, +22,+22**
21. f, 72	SPM	<b>MM, ID10/2003</b>	NK*	t-AML, ID 12/2005	46,XX
22. m, 77	SPM	<b>MM, ID 01/2006</b>	del 13q14	t-AML, ID 06/2007	46,XY

**Abbreviations:** m: male, f: female, ID: initial diagnosis, p/s: prior or synchronously to the MM occurring tumor, SPM: second primary malignancy, B-CLL: B-chronic lymphocytic leukemia, Hodgkin: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma, MCL: mantle cell lymphoma, t-MDS/AML: therapy-related MDS/AML; nd: not done, NK<sup>1</sup>: no chromosomal aberrations determined by SNP-array, NK\* (FISH): no deletion 13q14 present, mar: marker chromosom, del: deletion, \*\*the final karyotype contains additional cytogenetically-aberrant clones. \*in 9/31 patients, cytogenetics [FISH analysis] were not informative

**Suppl. Table 3A. Characteristics of MM patients with 2<sup>nd</sup> primary malignancies (SPM) compared to those without**

	MM with SPM (n=46; 7%)		MM without SPM (n=626; 93%)	
	n (%)	median (range)	n (%)	median (range)
<b>Host-specific characteristics</b>				
Gender	n=46 (100)		n=626 (100)	
Male / female	31 (67) / 15 (33)		348 (56) / 278 (44)	
Age (years)	n=46 (100)	61 (39-81)	n=626 (100)	61 (27-90)
BMI	n=42 (91)	25 (17-34)	n=537 (85)	25 (15-45)
Smoking	n=30 (65)		n=306 (48)	
Yes / quit / no	11 (37) / 14 (46) / 5 (17)		75 (25) / 167 (55) / 64 (21)	
Alcohol	n=26 (57)		n=253 (40)	
yes <sup>1</sup> / sometimes <sup>1</sup> / no	4 (15) / 12 (46) / 10 (39)		9 (4) / 61 (24) / 183 (72)	
Family risks <sup>2</sup>	n=31 (67)		n=332 (53)	
Yes / no	9 (29) / 22 (71)		118 (36) / 214 (65)	
Infections <sup>3</sup>	n=42 (91)	2 (0-11)	n=596 (95)	1 (0-12)
<b>MM-specific characteristics</b>				
BM-infiltration	n=37 (80)	20 (0-80)	n=465 (74)	30 (0-97)
Type of MM	n=45 (98)		n=595 (95)	
IgG	34 (76)		361 (61)	
IgA	6 (13)		137 (23)	
IgM	1 (2)		5 (1)	
IgD / IgE			1 (0) / 1 (0)	
Light chain only	4 (9)		86 (15)	
Non-secretory	1 (2)		4 (1)	
Light chain type	n=45 (98)		n= 614 (96)	
Kappa	28 (62)		393 (64)	
Lambda	16 (36)		217 (35)	
Extramedullary MM	2 (4)		14 (2)	
Stage (Durie&Salmon)	n=40 (87)		n=612 (98)	
I	13 (33)		183 (30)	
II	6 (15)		78 (13)	
III	21 (52)		351 (57)	
A / B	37 (92) / 3 (8)		510 (83) / 102 (17)	
ISS	n=22 (48)		n=383 (61)	
I	14 (64)		191 (50)	
II	4 (18)		76 (20)	
III	4 (18)		116 (30)	
Cytogenetics (FISH)	n=27 (59)		n=311 (49)	
Favorable risk	5 (19)		116 (37)	
Less favorable risk <sup>4</sup>	3 (11)		53 (17)	
NK	19 (70)		142 (46)	

**Abbreviations:**

BM: bone marrow infiltration, BMI: Body Mass Index, FISH: fluorescent in situ hybridization, ISS: International Staging System, MM: multiple myeloma, NK: Normal karyotype,

<sup>1</sup> yes = >3x/week, sometimes = <3x/week<sup>42</sup>

<sup>2</sup> history of cancer in first-degree relatives

<sup>3</sup> Frequency of infections since diagnosis of MM:<sup>4</sup> recurrent bacterial infection:  $\geq 2$  / year<sup>43</sup>

<sup>4</sup> FISH aberrations defined as less favorable with deletion 13q14, del17p, t(4;14), t(14;16), t(14;20), 1q and/or 1p-abnormalities

**Suppl. Table 3B. Therapy-related risks in patients with SPM compared to those without**

Therapy characteristics	MM with SPM (n= 46)		MM without SPM (n= 626)	
	n (%)	median cycles (range)	n (%)	median cycles (range)
<b>Chemotherapy (CTx)</b>	n=44		n=571	
# of cycles <sup>1</sup>		8 (0-52)		7 (0-97)
# of lines		1 (0-7)		1 (0-11)
Corticosteroids	37 (84)	11 (1-92)	518 (91)	6 (1-123)
Alkylating agents	33 (75)	8 (1-92)	498 (87)	6 (1-66)
Anthracyclines	17 (37)	2 (1-6)	286 (50)	2 (1-15)
Lenalidomide	5 (11)	9 (9-16)	94 (17)	4 (1-46)
Thalidomide	4 (9)	10 (1-28)	150 (26)	5 (1-57)
Bortezomib	3 (7)	4 (4-6)	212 (37)	4 (1-30)
<b>Stem cell transplantation (SCT)</b>				
Single autologous SCT (ASCT)	11 (25)		218 (38)	
Tandem ASCT	4 (9)		79 (14)	
Allogeneic SCT	3 (7)		71 (12)	
Autologous-allogeneic SCT	3 (7)		64 (11)	
<b>Radiotherapy</b>	13 (29)		226 (40)	
Dose (Gray)		60 (10-144)		40 (8-210)
Areas		2 (1-6)		1 (1-8)

**Abbreviations:**

MM: multiple myeloma, <sup>1</sup>corticosteroid therapy alone was not scored within CTx-cycle numbers