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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ABSTRACT

Additional malignancies in multiple myeloma patients after first-line and maintenance treatment have been observed, questioning whether specific risks exist. Second primary malignancies have also gained attention since randomized data showed associations to newer drugs. We have conducted this large registry analysis in 744 consecutive patients and analyzed: 1) frequency and onset of additional malignancies; and 2) second primary malignancy- and myeloma-specific risks. We assessed the frequency of additional malignancies in terms of host-, myeloma- and treatment-specific characteristics. To compare these risks, we estimated cumulative incidence rates for second malignancies and myeloma with Fine and Gray regression models taking into account competing risks. Additional malignancies were found in 118 patients: prior or synchronous malignancies in 63% and subsequent in 37%. Cumulative incidence rates for second malignancies were increased in IgG-myeloma and decreased in bortezomib-treated patients (P<0.05). Cumulative incidence rates for myeloma death were increased with higher stage and age, but decreased in IgG-subtypes and due to anti-myeloma treatment (P<0.05). Cytogenetics in patients acquiring second primary malignancies were predominantly favorable, suggesting that indolent myeloma and long disease latency may allow the manifestation of additional malignancies. An assessment of the Surveillance, Epidemiology, and End Result Program of the National Cancer Institute and our data with long-term follow up of 25 years confirmed a prevalence of second malignancy of 10% at 25 years, whereas death from myeloma decreased from 90% to 83%, respectively. Our important findings widen our knowledge of second malignancies and show that they are of increasing relevance as the prognosis in myeloma improves and mortality rates decrease.

Introduction

Remarkable progress has been made in the biological understanding of multiple myeloma (MM) and biology-based novel drug approaches, resulting in prolonged overall survival (OS) compared to the more dismal prognosis of 10-20 years ago.[1-4]

Current attempts in myeloma focus on further improving survival. Nevertheless, one challenge of this extended survival is that myeloma patients may acquire second malignancies, with an estimated incidence ranging between 2%-10%.[1-5] Living longer with the disease, therefore, involves the risk of long-term sequelae, including both solid tumor and hematologic second malignancies. Previous reports on second malignancies have focused on those developing subsequent to myeloma. Therapy-related risks have been suggested, such as prolonged melphalan exposure and immunomodulatory drugs (IMiDs).[4-7] The risk of IMiDs has been put forward, since there are three randomized trials,[6-8] two in transplant eligible patients and one in transplant ineligible patients, which have not only reported on improved progression-free survival (PFS) and improved OS, but have also shown a higher incidence of second primary malignancies (SPM) after prolonged lenalidomide treatment. SPM included hematologic and solid tumors, and in each trial their risk in the placebo group was 2%-3% *versus* 7%-8% in the lenalidomide group, with the differences being both statistically and clinically significant.[6-9] Some reports have also discussed the possibility that thalidomide may potentiate solid SPM,[5,10,11] suggesting an IMiD class effect associated with melphalan exposure.

Our prior registry study covered almost 600 patients and reported malignancies before the multiple myeloma in 7% and SPM in 3%,[12] in agreement with others.[6-8,10,12] The frequency of solid tumors *versus* hematologic malignancies, both before and after the diagnosis of myeloma, was 78% and 22%, respectively,[12] offering a cautioning note to oncologists that especially solid tumors are a more frequent phenomenon. In our prior registry, we also demonstrated that the prognosis with SPM may be compromised and OS impaired (HR: 2.5, 95%CI: 1.4-4.4).[12] Interestingly, while specific risk factors for SPM have not been clearly determined, some prior studies should be interpreted with caution due to small numbers of patients, inadequate or short-term follow up, retrospective data collection, under-reporting, no control group or other confounding factors, making specific risk factors difficult to identify in what is very likely a multifactorial process.[9,11,12] Moreover, most studies have neither explicitly deciphered the relevant question as to which factors favorably influence the

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occurrence of SPM, nor suggested mechanisms on how to avoid them.

We performed a comprehensive registry analysis going beyond the traditional approach of looking at malignancies after the myeloma, rather than assessing both prior and subsequent malignancies in patients diagnosed with multiple myeloma with long-term follow up of 25 years. The focus of this analysis was to expand the data on SPM- and myeloma-specific risks in a well-characterized cohort, assessing patient-, myeloma-, environmental- and treatment-related risks, cytogenetics and comparing our data with the European cancer registry GEKID.[13] To compare these risks, we estimated cumulative incidence rates for second malignancies and myeloma with Fine and Gray regression models. This provides subdistribution hazard ratios and analyses differences in the percentage of patients experiencing the respective event, taking into account competing risks.

Methods

Patients' characteristics and data source

Consecutive patient data were retrieved from our institution's electronic medical records and an innovative research data warehouse called the University of Freiburg Translational Research Integrated Database Environment (U-RIDE). The latter acquires and stores all patient data contained in the electronic medical records at our hospital and provides immediate advanced text-searching capacity. Through U-RIDE, we could rapidly review data on patients with additional malignancies, both prior and synchronous, and after the diagnosis of myeloma (SPM). Patients' medical histories were reviewed based on their medical records and each case analyzed according to the onset of the first and subsequent malignancy. Depending on the stage and aggressiveness of their disease, patients received follow up on a regular basis, both at our center and by their family doctors. In all deceased patients, follow-up information was meticulously obtained as described.[9,12,14,15]

All 744 patients included in this analysis were treated at our institution between January 1997 and December 2011. The median follow up was 89 months, with long-term follow up of second cancers and death from myeloma being available for 25 years.

Bone marrow examinations were performed at diagnosis and during follow up, along with metaphase karyotyping and interphase FISH for the detection of myeloma, myelodysplasia (MDS) or acute myeloid leukemia (AML), as described.[10,12,14,15] The analysis was carried out in accordance with the Declaration of Helsinki and according to Good Clinical Practice Guidelines. All patients gave their written informed consent for institutional-initiated research studies and analyses of clinical outcome studies, conforming with our institutional review board guidelines.

Disease classification

Myeloma diagnosis was based on bone marrow examination, tumor biopsies (in cases of extramedullary disease), laboratory results and radiological surveys. Clinical stages were classified according to Durie & Salmon and the International Staging System (ISS). Diagnosis of a solid tumor was verified by histology and disease stages were classified according to TNM. Acute leukemia was diagnosed by peripheral blood and marrow examination and classified according to the FAB classification. Malignant lymphomas were diagnosed by lymph node or organ biopsies and staged according to Ann Arbor. MDS was classified according to the WHO classification system. Diagnosis of mature B-cell neoplasms was staged according to the Rai classification.[9,12,14] Primary myeloma was defined as diagnosis of myeloma at least three months prior to diagnosis of another malignancy. Secondary myeloma was defined with an onset longer than three months after diagnosis of a prior malignancy. If multiple myeloma and another malignancy were diagnosed within three months or less, they were classified as synchronous malignancies.

Treatment

Patients underwent standard chemotherapy, autologous stem cell transplantation (ASCT), allogeneic-SCT (allo-SCT) or auto-allo-SCT according to our institutional myeloma pathway. ASCT was recommended for medically fit, symptomatic myeloma patients up to the age of 70 years. Induction consisted of cyclophosphamide, thalidomide and dexamethasone (CTD), bortezomib-based regimens, such as bortezomib, cyclophosphamide, dexamethasone (VCD) or anthracycline-based induction (idarubicin/dexamethasone or VAD) within clinical trial protocols, e.g. Deutsche Studiengruppe Multiples Myelom (DSMM). Mobilization (IEV) and conditioning (melphalan 200 mg/m^2) were performed as described.[1,12,14,15] Patients ineligible for ASCT received either bortezomib, melphalan, prednisone (VMP) or melphalan, prednisone, thalidomide (MPT). Relapse treatment consisted of standard anti-myeloma/novel agent combinations, containing lenalidomide, thalidomide and bortezomib (RD, VRD, VCD). Radiation was performed as supportive treatment for pain control and for localized or extramedullary disease sites for prevention of local progression.

Statistical analysis

Data were analyzed using SAS statistical software v.9.2 (SAS Institute Inc., Cary, NC, USA), and Stata 12.1 (StataCorp, Texas, USA). OS was calculated as time from first diagnosis of myeloma to death from any cause. Patients still alive at the last follow up were treated as censored observations. Death without SPM (myeloma) and SPM were considered to be competing risks, and cumulative incidence rates were calculated using the Aalen-Johanson estimator.[17] This method is acknowledged to be more appropriate than the simple calculation of incidence rates as number of events divided by person-years, because the occurrence of censored observations and competing events has to be taken into account.[18,19] We assessed the frequency of prior/synchronous additional malignancies and SPM in terms of host-, myeloma- and treatment-specific characteristics. To compare these risks, we estimated cumulative incidence rates for SPM and death without SPM (myeloma) with Fine and Gray regression models.[16] This provides subdistribution hazard ratios and analyses differences in the percentages of patients experiencing the respective event within a certain period, taking into account the competing event.[20] In a first step, factors were assessed in univariate models. Finally, we set up a multivariate model with all factors considered to be relevant (i.e. age, sex, Ig-type, stage, anti-myeloma-therapy). As this was a registry-based study, treatment decisions were not determined at random, and since the age and stage distribution changes over the course of time,[21] we considered it important to keep all these factors in the multivariate model. We further investigated 'MM diagnosis before 2004' (as a rough adjustment for changes in the course of time[1-12]) and 'prior/synchronous AM' univariately as potential prognostic factors,[12] but did not keep them in the final multivariate model, as they showed no significant effect on SPM. Moreover, we compared our data with the European GEKID cancer registry to capture the age- and sex-matched German population, with the SEER and prior analyses of other cancer registries.[3,13] Our data were analyzed as of January 1st, 2014.

Results

Occurrence and distribution of different additional malignancies

Table 1 summarizes all 132 additional malignancies which were found in 744 consecutive patients: 31 (23%) were hematologic and 101 (77%) solid tumor malignancies. Interestingly, 105 patients had one additional malignancy, 12 patients with 2, and one patient had 3 additional malignancies, apart from myeloma [118 patients with 132 AMs (105 + 2x12 + 3x1)] (Table 1). Assessing those malignancies that occurred prior/synchronously (n=83) *versus* subsequently (SPM; n=49) to the myeloma, SPM were rarer. Both prior/synchronous and SPM groups showed less hematologic (17% *vs.* 35%) than solid tumor malignancies (83% *vs.* 65%, respectively). Frequent SPM were hematologic tumors, specifically MDS/AML. Most common solid tumor-SPM were colorectal, gynecological/urothelial, lung cancer and basal-cell carcinomas (Figure 1).

Our cumulative incidence of all, hematologic and solid tumor SPM of 6.6%, 2.3% and 4.3%, respectively (Table 2) confirmed prior registry analyses and phase III trial results.[4-8,22] These prospective, retrospective and meta analysis data determined SPM frequencies at 4%-6% (Table 2).[22-34]

Cumulative incidence for developing SPM for disease-, host- and therapy-specific factors

Table 3A and B summarize subdistribution hazard ratios (SHRs), 95% confidence intervals (CI) and *P*-values both for SPM and death without SPM (myeloma) *via* uni- and multivariate analysis.

Table 1. Occurrence and distribution of different additional malignancies (AMs) in multiple myeloma (MM) patients, separating hematologic and solid tumors and the incidence of prior/synchronous *versus* second primary malignancies (SPM).

	N. of all AMs (n=132)[1] n. (%)	N. of prior/ synchronous malignancies (n=83) n. (%)	N. of subsequent malignancies (after the MM=SPM) (n=49) n. (%)
Hematologic	**n=31** (23)	**n=14** (17)	**n=17** (35)
AML/MDS	16 (12)	4 (5)	12 (25)
Lymphoma	14 (11)	10 (12)	4 (8)
CML	1 (0)	0 (0)	1 (2)
Solid tumor	**n=101** (77)	**n=69** (83)	**n=32** (65)
Colorectal cancer	18 (14)	12 (14.5)	6 (12.2)
Prostate cancer	14 (11)	12 (14.5)	2 (4)
Gynecological cancer	11 (8)	8 (10)	3 (6)
Urothelial cancer	11 (8)	8 (10)	3 (6)
Lung cancer	6 (5)	2 (2)	4 (8.2)
Renal cell carcinoma	5 (4)	4 (5)	1 (2)
Oropharynx cancer	3 (2)	1 (1)	2 (4)
CUP	3 (2)	2 (2)	1 (2)
Thyroid cancer	1 (1)	1 (1)	0 (0)
Other cancers	6 (5)	4 (5)	2 (4)
Malignant melanoma	8 (6)	8 (10)	0 (0)
Basal-cell carcinoma	15 (11)	7 (8)	8 (16.3)

AML: acute myeloid leukemia; CUP: carcinoma of unknown primary; CML: chronic myeloid leukemia; MM: multiple myeloma; MDS: myelodysplastic syndrome; SPM: second primary malignancy.[1]105 patients with one AM, 12 patients with 2 AMs, one patient with 3 AMs (=118 patients with 132 AMs [105 + 2x12 + 3x1].

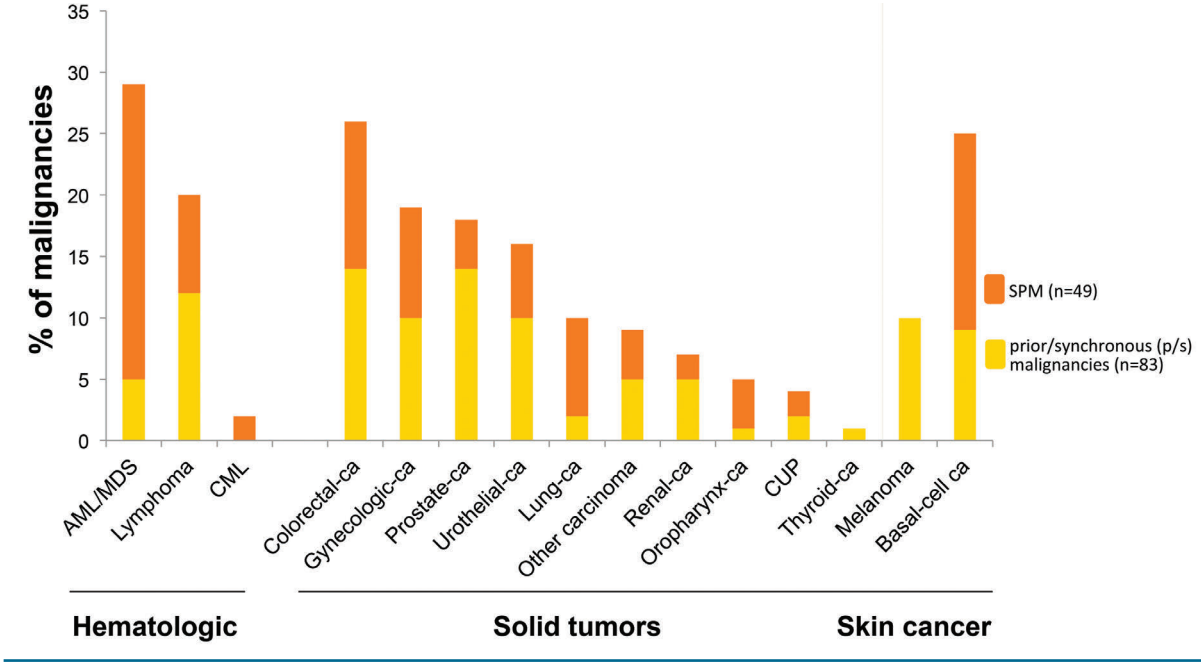

Figure 1. Total of additional malignancies in myeloma patients: overview prior/synchronous (p/s) malignancies *versus* SPM and p/s *versus* SPM frequencies in hematologic-, solid- and skin-tumor entities. Hematologic malignancies occurred more frequently as SPM than p/s malignancies (albeit lymphomas were also frequent as p/s malignancies. Frequent solid tumors were colorectal, gynecological/urothelial and prostate cancer. Except for colorectal cancer, these all occurred more frequently p/s to the myeloma. Skin tumors, such as melanoma and basal-cell carcinomas, also occurred more often p/s to the myeloma, with basal-cell carcinomas appearing as SPM as well.

The cumulative incidence rates are also illustrated in Figure 2 for SMP, and in Figure 3 for death from causes other than SPM. For SPM, cumulative incidence rates were increased in IgG myeloma, males, advanced Durie & Salmon stage, and in lenalidomide-treated patients. Age 65 years or over, anthracyclines, alkylators and radiation did not increase SPM. However, a decrease in SPM was noted with bortezomib and thalidomide, with bortezomib confirming prior retrospective analyses.[10,27,35] Conversely, cumulative incidence rates of death from myeloma showed significant increases for advanced Durie & Salmon stages, patients aged 65 years or over and thalidomide exposure, no increase with regard to alkylators and sex, and decreases for IgG-myelomas and in lenalidomide-, anthracycline-, bortezomib-treated patients or in those after radiation (Figure 3).

Risk analysis of U-RIDE, GEKID and SEER data

The median PFS and OS of all 744 myeloma patients were 33 (95%CI: 30-37) and 61.2 (55-72) months, respectively. Our U-RIDE data and SEER both showed substantially divergent cumulative incidence rates for developing SPM *versus* death from all other causes.[3] SEER data were based on 33,229 patients who received a diagnosis of myeloma between 1973 and 2008 in the United States, showing incidence rates of 8% (SPM) and 90% (death from causes other than SPM) at 25 years (Figure 4A).[3] Our cumulative U-RIDE risks were 11.2% for SPM and 83% for myeloma death at 25 years (Figure 4B). This confirmed the cumulative risk of second cancer of approximately 10% after 25 years and also that the risk of death in myeloma is declining (Figure 4A and B).

Moreover, Figure 4B illustrates cumulative incidence

Table 2. Review of prior studies on second primary malignancies.

Author	Design / study period	N. of pts	N. of any SPM	N. of hematologic SPMs (%)	N. of solid tumors (%)
Randomized phase III trials					
Palumbo A *et al.* (MM-015)[7]	Len. vs. PL after MP +/- Len[c]	455	8% : 6% : 3%	MPR-R: 7/150 (5%) MPR: 5/152 (3.3%) MP: 1/153 (0.7%)	MPR-R: 5/150 (3.3%) MPR: 4/152 (2.6%) MP: 3/153 (2%)
Attal M *et al.* (IFM 2005-02)[8]	Len *vs.* PL after HD-Mel/ASCT[a]	608	8.5% : 3.6%	13/30 (4.2%) : 5/302 (1.7%)	15/306 (5%) : 7/302 (2%)
McCarthy P *et al.* (CALGB 100104)[6]	Len *vs.* PL after HD-Mel/ASCT[b]	460	7.8% : 2.6%	8/231 (3.5%) : 1/229 (0.4%)	10/231 (4.3%) : 5/229 (2.2%)
Palumbo A *et al.*[4]	MPR *vs.* ASCT +/- Len	273	4.3% : 4.3%		
Benboubker L *et al.*[5]	Rd cont. *vs.* Rd18 *vs.* MPT	1623	3% : 6% : 5%	<1% : <1% : 2%	3% : 5% : 3%
Stewart K *et al.* (E1A06)[22] (MPT: n=17 : MPR: n=14)	MPT *vs.* MPR	306	10%		
Palumbo A *et al.*[23]	Len *vs.* non-Len RC-Ph 3	3254	6.9% : 4.8%	3.1% : 1.4%	3.8% : 3.4%
Summary (median)		**6979**	**7.4% : 4.0%***	**3.5% : 1.4%**	**3.8% : 2.2%***
Prospective studies					
Govindarajan R *et al.*[24]	NR	188	3.8%	3.8%	NR
Bergsagel DE *et al.*[25]	1973-1977	364	3.8%	3.8%	NR
Summary (median)		552	3.8%	3.8%	
Registry data					
Barlogie B *et al.*[26]	1989-2007	2418	1.1%	1.1%	NR
Dimopoulos MA *et al.*[27]	2003-2008	3846	1.4%	0.2%	1.1%
Cuzick J *et al.*[28]	1964-1975	648	1.9%	1.9%	NR
Rifkin RM *et al.*[29]	2009-2014	1493	5.1%	1%	4.4%
Dong C *et al.*[30]	1958-1996	8656	5.5%	1.0%	4.5%
Usmani SZ *et al.*[10]	1998-2009	1148	6.4%	3.1%	3.2%
Mailankody S *et al.*[31]	1986-2005	8740	6.6%	0.8%	5.8%
Krishan AY *et al.*[32]	1989-2009	869	8%	1.4%	6.7%
Finnish Leukemia Group[33]	1979-1985	432	9.2%	3.9%	5.3%
Przepiorka D *et al.*[34]	1996-2005	82	12.2%	12.2%	NR
Engelhardt M *et al.*#	**1997-2011**	**744**	**6.6%**	**2.3%**	**4.3%**
Summary (median; range)	**1958-2014**	**29386**	**6.0 (1.1-12.2)**	**1.7% (0.2-12.2)**	**4.5% (1.1-6.7)**

HD-Mel: high-dose melphalan; Len: lenalidomide; MP: melphalan/prednisone; MPR-R: melphalan/prednisone-lenalidomide and lenalidomide maintenance; MPR: melphalan/prednisone-lenalidomide; ms: months; NR: not reported; PL: placebo; pts: patients. [a]Data cut-off as of 1 Oct 2011, NEJM 2012 publication. [b]Data cut-off as of 31 Oct 2011, NEJM 2012 publication. [c]Data cut-off as of 28 Feb 2011, NEJM 2012 publication. RC-Ph 3: randomized controlled phase III clinical trials (metaanalysis). #Prior analysis: Hasskarl J, Ihorst G, De Pasquale D, Schröttner P, Zerweck A, Wäsch R et al. *Association of multiple myeloma with different neoplasms: systematic analysis in consecutive patients with myeloma. Leuk Lymphoma 2011; 52: 247-259. *plus non-melanoma skin cancers from combined data analysis from all 3 randomized trials: 9 (1.1%) vs. 6 (0.9%).*

rates of second cancer at 1, 5, 10 and 20 years which were 0.8%, 4.8%, 6.5% and 11.2%, respectively. Thus, the SMP risk increased primarily between one and 5 years and subsequently remaining at approximately 10%. The cumulative incidence rate after 1, 5, 10 and 20 years accounted for annual incidence rates of 0.77%, 0.99%, 0.67% and 0.59%, respectively, or approximately 0.8%/year. Standard annual incidence rates for cancer within the GEKID database were 452/100,000 for males and 341/100,000 for females,[13] accounting for annual cancer incidence rates of 0.4% per year. This annual incidence rate was therefore approximately 2-fold increased in myeloma patients compared to the GEKID data.[3,12]

As shown in *Online Supplementary Table S1*, 13 patients had 2 or even 3 additional malignancies apart from the myeloma. In these 13 patients, myeloma occurred last, was flanked with both prior and subsequent malignancies or followed by 2 or even 3 additional malignancies in 5, 4 and 4 patients, respectively. The myeloma patient with 3 additional malignancies acquired prostate, colon cancer and B-CLL (Patient #10). Therapy-related MDS/AML (t-MDS/-AML) was observed in 4 of 13 patients, leading to AML- and MM-induced death in 2 and one patient, respectively. Of all multiple malignancy-bearing patients, 4 of 13 are currently alive. Conclusive cytogenetics were available in 7 of 13 patients, and in 5 it was possible to examine both bone marrow plasma cells and additional tumor samples; of note, except in one with del13q14 aberration (Patient #11), all others revealed favorable cytogenetics (*Online Supplementary Table S1*).

Table 3A. Univariate analysis of cumulative incidence rates (regression model according to Fine and Gray).

	SPM			Death without prior SPM		
	SHR	95% CI	*P*	SHR	95% CI	*P*
Patient-specific risks						
Age >65 years	0.99	0.54 - 1.81	*0.979*	2.02	1.66 - 2.46	<0.0001
Alcohol	1.33	0.66 - 2.68	*0.425*	1.04	0.84 - 1.30	0.692
Sex (m)	1.68	0.89 - 3.14	*0.107*	0.99	0.81 - 1.20	0.889
Prior/synchronous AM	0.90	0.32 - 2.51	*0.845*	1.49	1.05 - 2.12	0.027
MM diagnosis 2004 or later	0.85	0.48 - 1.50	*0.567*	1.26	1.03 - 1.55	0.028
MM-specific risks						
IgG	1.86	0.66 - 5.24		0.66	0.50 - 0.88	
IgA	0.89	0.25 - 3.10	*0.269*	0.76	0.54 - 1.05	0.030
IgM	2.36	0.24 - 22.9		0.99	0.48 - 2.06	
IgG (*vs.* others)	1.97	1.02 - 3.79	*0.042*	0.75	0.61 - 0.91	0.003
Durie & Salmon						
Stage II *vs.* I	1.15	0.43 - 3.03	*0.95*	1.80	1.32 - 2.47	<0.0001
Stage III *vs.* I	1.00	0.50 - 2.02		2.00	1.59 - 2.51	
MM-therapy						
Alkylators	0.45	0.23 - 0.89	*0.022*	1.08	0.77 - 1.53	0.643
Anthracyclines	0.68	0.37 - 1.25	*0.213*	0.70	0.57 - 0.86	0.001
Bortezomib	0.17	0.05 - 0.54	*0.003*	0.83	0.67 - 1.03	0.092
Steroids	0.54	0.24 - 1.22	*0.138*	1.41	0.90 - 2.20	0.137
Lenalidomide	0.74	0.29 - 1.85	*0.514*	0.59	0.44 - 0.78	<0.0001
Thalidomide	0.23	0.08 - 0.64	*0.005*	1.21	0.98 - 1.49	0.075
Radiation	0.64	0.34 - 1.22	*0.174*	1.00	0.82 - 1.22	0.989

Table 3B. Multivariate analysis of cumulative incidence rates (regression model according to Fine and Gray).

	SPM			Death without prior SPM		
	SHR	95% CI	*P*	SHR	95% CI	*P*
Patient-specific risks						
Age >65 years	1.18	0.55-2.53	*0.676*	1.81	1.44-2.26	<0.0001
Sex (m)	1.43	0.71-2.86	*0.314*	1.04	0.83-1.29	0.737
MM-specific risks						
IgG (*vs.* others)	2.55	1.17-5.52	*0.018*	0.73	0.59-0.90	0.003
Durie & Salmon						
Stage II *vs.* I	1.49	0.54-4.07	*0.440*	1.71	1.16-2.51	0.007
Stage III *vs.* I	1.11	0.52-2.40	*0.784*	2.10	1.60-2.75	<0.0001
MM-therapy						
Alkylators	0.79	0.34-1.81	*0.573*	1.09	0.73-1.63	0.670
Anthracyclines	1.04	0.47-2.28	*0.926*	0.72	0.57-0.91	0.006
Bortezomib	0.24	0.07-0.81	*0.022*	0.84	0.66-1.06	0.148
Lenalidomide	1.56	0.65-3.73	*0.320*	0.59	0.44-0.80	0.001
Thalidomide	0.37	0.13-1.10	*0.074*	1.33	1.05-1.70	0.020
Radiation	0.91	0.45-1.84	*0.795*	0.90	0.73-1.12	0.350

m: male, prior/synchronous; AM: prior or synchronous additional malignancies; MM: multiple myeloma.

Cytogenetics

Karyotypes were available for 51% of our myeloma cohort. Although cytogenetics were not entirely complete as FISH was not routinely assessed in earlier years, we compared chromosomal aberrations in patients both with and without additional malignancies (*Online Supplementary Table S2*); of note, 'less favorable' FISH abnormalities, defined with del17p, t(4;14), t(14;16), t(14;20), del13q14, 1q and/or 1p abnormalities, were not increased within the group with SPM, suggesting that cytogenetics alone contribute little in unraveling their occurrence. Moreover, we compared FISH aberrations, whenever available on both the primary and second tumor, in patients with prior/ synchronous or SPM hematologic malignancies (*Online Supplementary Table S2*). Cytogenetics in 14 primary lymphoma and MDS/AML cells showed less complex aberrations (Patients #1-14), the same being true for the subsequently occurring myeloma, showing either normal cytogenetics, hyperdiploidy or trisomy 11 in bone marrow plasma cells, while del13q14 and del17p were found in only a single patient (Patient #5). Conversely, 8 patients with subsequent hematologic malignancies after the myeloma (Patients #15-22) showed favorable FISH aberrations in plasma cells, but complex aberrations typically in t-MDS/AML blasts (*Online Supplementary Table S2*). These results confirmed the rather favorable cytogenetics in those 13 myeloma patients with 2 or more additional malignancies, as summarized in *Online Supplementary Table S1*.

Host- and MM-specific characteristics of patients with versus without additional malignancies and in those with versus without SPM

Comparing those 118 myeloma patients with additional malignancies *versus* those with myeloma alone (n=626) showed that myeloma patients with additional malignancies were predominantly male (68% *vs.* 56%), older (median age: 66 *vs.* 61 years) and showed an IgG subtype predominance (71% *vs.* 61%). Other host- or myeloma-specific characteristics were not substantially different (*data not shown*). Moreover, laboratory values (full blood count, total protein, calcium, LDH, β2-MG, albumin, serum creatinine, eGFR, CRP) did not show relevant differences in patients with *versus* without additional malignancies. However, since these laboratory parameters were assessed at the time of the initial myeloma diagnosis, differences between both groups were less likely to be present than if the laboratory values had been compared at the time that the additional malignancy occurred. However, this is of lesser relevance since by that point of time the additional malignancy was already present, whereas our laboratory analysis was performed to decipher whether any easily measureable parameter may suggest the occurrence of an additional malignancy at a later time point.

The comparison of those 46 myeloma patients with SPM, comprising 7% of our cohort, *versus* those without (93%) (*Online Supplementary Table 3A*) showed a predominance of males (67% *vs.* 56%), higher smoking- (37% *vs.* 25%) and alcohol- (15% *vs.* 4%) exposure and a predomi-

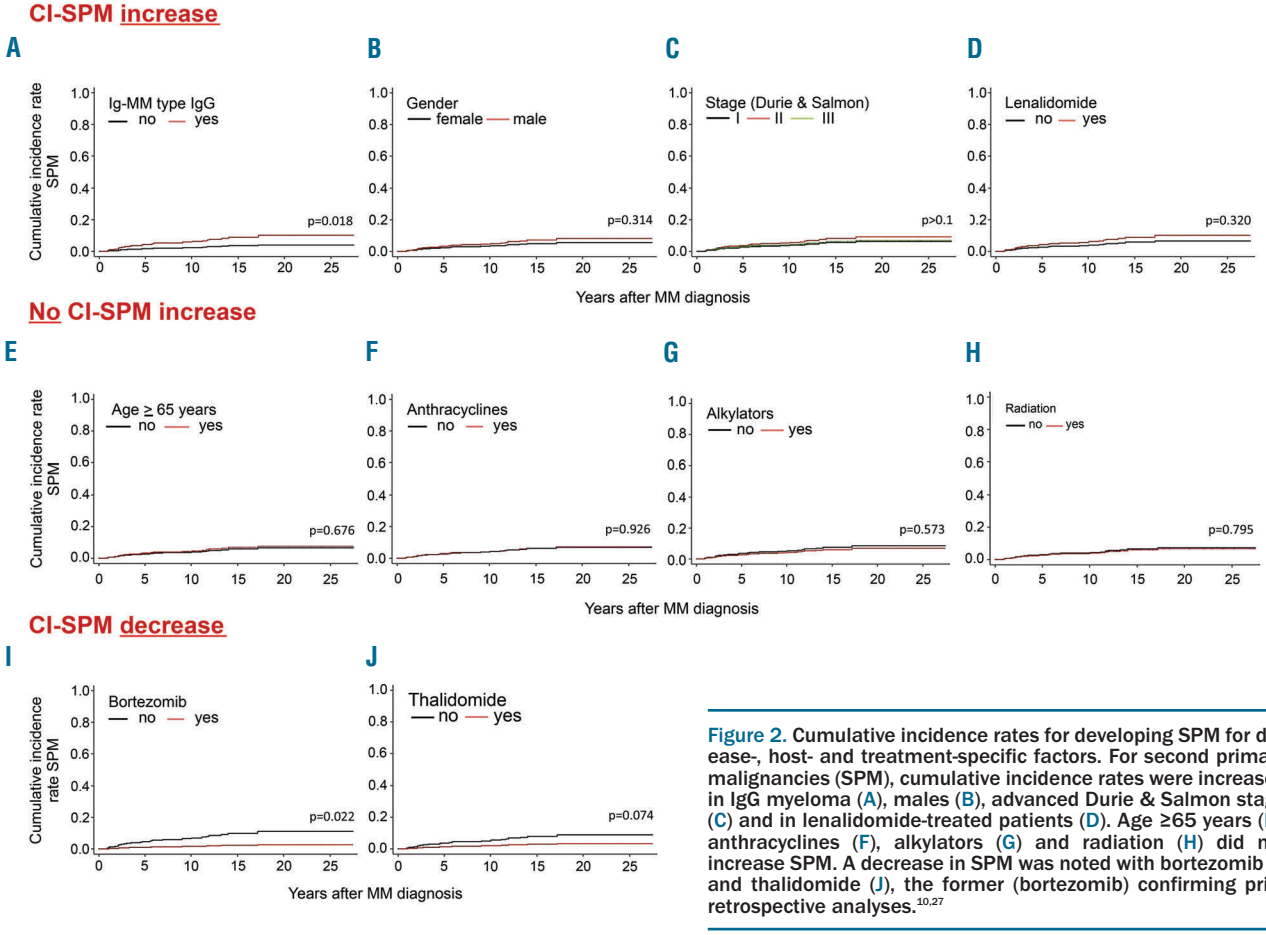

Figure 2. Cumulative incidence rates for developing SPM for disease-, host- and treatment-specific factors. For second primary malignancies (SPM), cumulative incidence rates were increased in IgG myeloma (A), males (B), advanced Durie & Salmon stage (C) and in lenalidomide-treated patients (D). Age ≥65 years (E), anthracyclines (F), alkylators (G) and radiation (H) did not increase SPM. A decrease in SPM was noted with bortezomib (I) and thalidomide (J), the former (bortezomib) confirming prior retrospective analyses.[10,27]

nance of IgG myelomas in the SPM cohort (76% *vs.* 61%). At 61 years, the median age was identical. Other host- or myeloma-specific characteristics were not substantially different. *Online Supplementary Table 3B* summarizes the therapy extent, which was slightly increased in patients with and without SPM, e.g. with a median of 8 *versus* 7 cycles, respectively. Corticosteroid- (median 11 *vs.* 6), alkylator- (8 *vs.* 6), lenalidomide- (9 *vs.* 4) and thalidomide- (10 *vs.* 5, respectively) exposure was increased, whereas anthracycline (both 2) and bortezomib (both 4) cycles were comparable. Single ASCT had been performed to a lesser extent in patients with *versus* without SPM (25% vs. 38%, respectively). The same was true for tandem-SCTs (9% *vs.* 14%), allo-SCTs (7% *vs.* 12%) and auto-allo-SCTs (7% *vs.* 11%, respectively). Radiotherapy, albeit being performed less frequently in patients with *versus* without SPM (29% *vs* .40%) was increased in dose- (60 *vs.* 40 Gy) and field- (2 *vs.* 1) intensity, respectively.

Discussion

In myeloma, second tumors have gained more attention in recent times as people with myeloma live longer.[1-10] A limitation when studying second tumors is the fact that clinical trials are typically not designed to capture such data. Therefore, there can be substantial under-reporting of second tumors (Table 2). An alternative approach is to use large central or well-kept population-based databases with long-term follow up and compare risks to controls from the same database. Such strategies are powerful and provide large sample sizes; however, a limitation with central population-based databases is again under-reporting, because most such resources have their main focus on primary cancers. Using our large population-based U-RIDE dataset matched with detailed clinical and treatment data for individual patients, we have expanded our current knowledge on this topic with long-term follow up of myeloma and SPM for 25 years.[9,12,14,24,34] This U-RIDE dataset was not only suitable for truthful capture of additional malignancies in myeloma, but also more helpful and precise than physician recollection, pooled colleague opinion or clinical trials which were not originally designed to capture prior or subsequent malignancies. Such real-time availability of data to guide decision making and learn from well-kept databanks has already transformed other industries, and the growing prevalence of electronic medical records, along with the development of sophisticated tools for real-time analysis of identified data sets, is advancing the use of data-driven approaches in health care

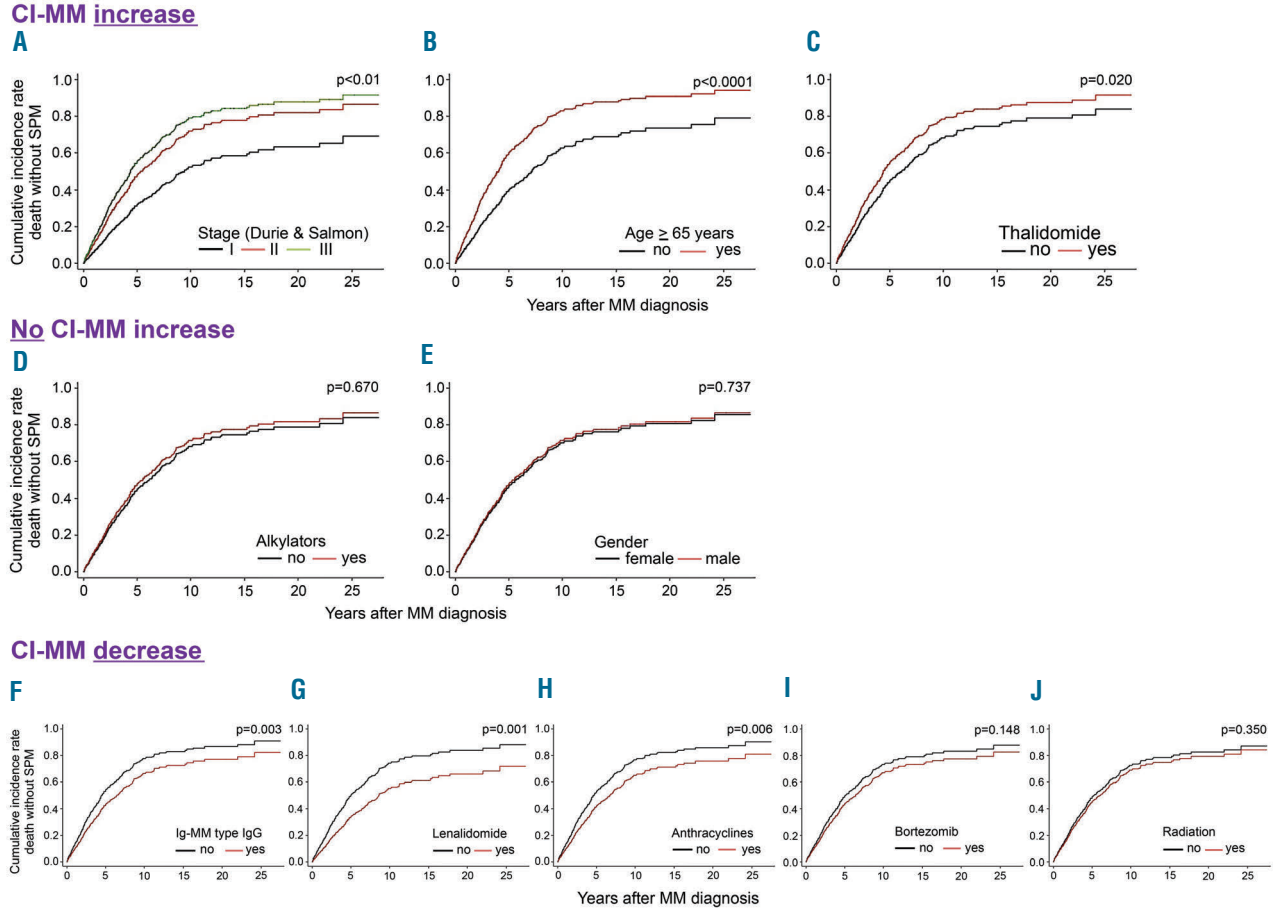

Figure 3. Cumulative incidence rates for death from myeloma for disease-, host- and treatment-specific factors. Conversely, cumulative incidence rates of death from myeloma showed significant increases for advanced Durie&Salmon stages (A), patients ≥65 years (B) and thalidomide exposure (C), no increase with regard to alkylators (D) and sex (E) and decreases for IgG-myelomas (F) and in lenalidomide- (G), anthracycline- (H), bortezomib- (I) and with radiation (J) treated patients.

delivery.[36] Prior analyses have suggested that longer lifespans with myeloma and specific risks may favor SPM. These may include risk factors such as age, sex, prolonged melphalan exposure, IMiDs, myeloablative therapy and radiation.[5-8,10,14]

Studies to elucidate the underlying mechanisms are still ongoing. Moreover, conflicting results exist for both melphalan- and ASCT-risks. In an older study, long-term melphalan in 628 myeloma patients did not contribute to the pathogenesis of second solid tumors,[37] whereas another analysis by the Medical Research Council in 648 patients reported a significant relationship with both the length and amount of melphalan, but no relationship for cyclophosphamide,[28] supporting a recent metaanalysis.[23] In line with this, disparate results on MDS and other SPM after ASCT have been reported, such as a high 5-year cumulative incidence for MDS of 18% in one study,[34] whereas in a larger analysis of ASCT *versus* prolonged conventional chemotherapy that prolonged standard-dose alkylators prior to ASCT, rather than myeloablative treatment, are associated with MDS/AML.[24] In addition, MDS-associated cytogenetic abnormalities have been linked to the development of overt clinical MDS and AML.[26]

Of note, two recent first-line IMiD studies, one with lenalidomide and dexamethasone (Rd/MPR) *versus* ASCT,[4] and the second using Rd in transplant-ineligible patients[5] did not observe excessive SPM risks. The SPM rate in the Rd/MPR *versus* ASCT study was 4.3%, and showed no difference with *versus* without lenalidomide maintenance,[4] while the rate in the non-transplant eligible elderly study was 3% with continuous Rd, 6% with 18 months Rd, and 5% with MPT.[5] This confirms prior studies[6,7] suggesting that the increased risk of SPM among patients treated with IMiDs is related to prior or concurrent melphalan use.[4,5] In line with this, a recent meta analysis revealed an increased risk of developing hematologic SPM in patients with lenalidomide and melphalan, suggesting alternative lenalidomide schedules, such as with cyclophosphamide or alkylator-free combinations.[23] Moreover, myeloma-related factors, such as Ig-type and gene polymorphisms, as well as host genetics that define susceptibility to SPM, seem to be important. Therefore, genome-wide association studies and gene expression microarray analysis of patients with and without SPM are being performed.[9,11,12,14,38]

In our prior registry analysis, we found that the majority of myeloma patients had additional solid tumors rather than hematologic malignancies.[12] These results were confirmed in this even larger U-RIDE-dataset. In solid tumor patients, we confirmed main tumor clusters.[5,8,9,12,39] Most of our solid tumor patients had received combined modality treatment; therefore, therapy-related mechanisms may play a role in the development of myeloma.[12,14] Moreover, familial predisposition of myeloma with different neoplasms, either due to common genetic alterations and/or environmental factors, has been demonstrated, which is supported by genome-wide association studies that have identified single-nucleotide polymorphisms localized to a number of genomic regions that are robustly associated with myeloma risk.[30,40] We have previously described consecutive patients with concomitant CLL and myeloma, in which combined affymetrix SNP mapping array and FISH analyses resolved the clonal relationship with biclonality for both diseases.[14] Moreover, our data showed that age remains a relevant risk factor in myeloma, while IgG subtypes and various anti-myeloma agents (lenalidomide, anthracyclines, bortezomib) decreased the risk of progression, in line with prior data demonstrating a decrease in life expectancy in elderly patients, verifying age as an expectedly important risk factor.[1-3] Conversely, cumulative incidence rates for SPM increased in IgG-myeloma and decreased in bortezomib-treated patients. Even though competing risks have to be interpreted with caution due to confounding factors, these results underline the value of population-based studies, complementing clinical trials and supporting registry data.[1-14] Of interest, our cytogenet-

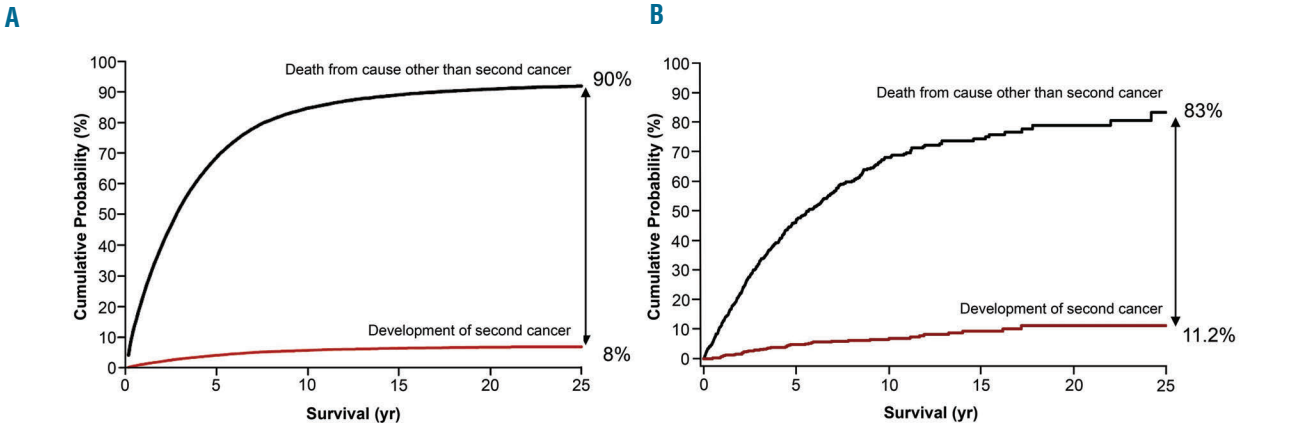

Figure 4. Cumulative incidence rates of developing secondary primary malignancy (SPM) and death from causes other than second cancer. (A) Cumulative incidence rates of developing SPM and of death from all other causes (excluding second cancers): data based on 33,229 patients who received a diagnosis of myeloma, between 1973 and 2008 in the United States were taken from the Surveillance, Epidemiology, and End Result Program of the National Cancer Institute (SEER), showing incidence rates of 8% and 90% at 25 years, respectively.[3] (B) Compared to these SEER data, cumulative incidence rates from our registry analysis involving 744 patients diagnosed with myeloma between 1997 and 2011 was 11.2% for SPM and 83% for death from causes other than second cancer at 25 years. This confirmed the cumulative incidence rate of second cancers after 25 years of approximately 10%, but also revealed that due to substantial advances in myeloma treatment, the risk of death is declining. This demonstrates that the development of second cancer in myeloma remains substantially lower than the risk of death from multiple myeloma, but that both curves detectably converge.

ic analyses revealed that indolent myeloma with favorable cytogenetics, combined with its improved prognosis and long latency, allow the occurrence of additional malignancies to become an important challenge.

Our comparison of incidence rates of SPM among myeloma patients to annual cancer incidence rates obtained from the European cancer registry GEKID[13] showed a 2-fold elevation in SPM rates in myeloma patients. While SEER-data confirmed our cumulative incidence rate of developing SPM after 25 years of 10%, that rates of death from all other causes (myeloma) was 90%,[3] but 83% in our U-RIDE data set. Both SEER and U-RIDE registries involved both overlapping and different treatment periods (U-RIDE 1997-2011; SEER 1973-2008), but verified that the development of SPM remains substantially lower than the risk of death from myeloma.[1-9] Nevertheless, both curves slightly converge, urging us to persistently reassess SPM in the course of the disease.

In line with prior registry analyses, our data can be criticized for the heterogeneous treatment of patients, and because there are confounding and competing risks. However, our U-RIDe data have some strengths. 1) We undertook a very comprehensive look at second malignancies and risks in a well-characterized consecutive myeloma cohort; 2) long-term follow up of second cancers and death from myeloma was available for 25 years; and 3) we compared our data with the European cancer registry GEKID[13] and prior reports (Table 2). For cumulative incidence rates of SPM and myeloma death, we used the Fine and Gray model, which provides subdistribution hazard ratios and analyses differences in the percentages of patients experiencing the respective event within a certain period, taking into account competing events.[16,20] Cumulative incidence rates were both assessed in univariate and multivariate models, within the latter including all relevant factors, such as patient-, myeloma- and treatment-related risks. Since we and others have demonstrated previously that patient characteristics and treatment modalities change over long time periods,[1,9,12,14,15,21] adjustments by means of regression models are necessary, as meticulously performed here. In support of our data, prior analyses have suggested similar cumulative incidence rates for myeloma and SPM as summarized in Table 2.

In conclusion, this large up-dated registry analysis reminds us that, given the remarkable progress in myeloma, second cancers represent long-term complications, which may evolve as a necessary consequence of several factors: 1) life-saving treatment; 2) patients aging with cancer; 3) multi-agent drugs being used; 4) prolonged treatment exposure; 5) better surveillance programs; 6) our greater awareness of SPM; and 7) improved diagnostic measures to detect them.[1,9,12,14,41] The risks for SPM identified by this analysis with long-term follow up of 25 years were disease- and patient- (IgG, males, advanced stage) as well as therapy-related (therapy extent, IMiDs) (Figure 2). SPM may, therefore, emerge as an important after-effect in myeloma, and living longer with the disease. Our large U-RIDE analysis provides clearer answers for cumulative incidence risks for SPM and myeloma, prompting us to discuss treatment risks and benefits with our patients and to stay well informed as further knowledge on prior cancers before and SPM after the myeloma become available.

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Conflict of interest: The authors declare no conflict of interest. Author contribution: ME, RW designed the research; ME, GI, MK, OL, MP, HR, JW, AMM, MS collected data; ME, RW, GI, OL, MS analyzed the data; all authors interpreted the data and made critical contributions to the manuscript. ME wrote the manuscript.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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