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Second primary malignancy in multiple myeloma: does a prior malignancy matter?

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Data sharing:
The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Patients with multiple myeloma (MM) are living substantially longer due to advances in therapy, creating a growing survivor population at risk of second primary malignancies (SPMs). The cumulative risk of SPM increases with age and exposure to potentially mutagenic treatments and is especially relevant as patients with MM are heavily treated across multiple lines of therapy. In the novel-agent era, the estimated incidence of invasive solid malignancies post autologous stem cell transplantation (ASCT) ranges from 3.3%-10% by 3-10 years post MM diagnosis [1-3]. While prior studies have characterized SPM risk over time in MM, few have examined whether a previous history of malignancy before MM diagnosis confers additional risk particularly in the contemporary era. A prior invasive malignancy may reflect underlying genetic or immunologic susceptibility, cumulative mutagenic exposures, or persistent immune dysregulation that predispose to further malignant transformation. This question is especially relevant amongst MM patients as MM is a cancer of older adults who may already have a history of a previous malignancy and current standards of care for MM treatment increasingly incorporate agents with known or potential carcinogenic effects, such as lenalidomide maintenance, alkylating agents, and T cell–redirecting immunotherapies, earlier in the treatment course [4-6]. Understanding how a history of prior malignancy influences SPM risk could inform personalized treatment decisions, survivorship surveillance, and long-term toxicity counseling. Therefore, the aim of this study was to evaluate whether a history of a prior malignancy is associated with an increased risk of SPM in patients diagnosed with MM and treated in a contemporary treatment era.

The Ontario ICES data repository of administrative healthcare data was used to identify a population-based cohort of adults with incident MM diagnosed between 2007-2023 and treated with anti-myeloma therapy. The Ontario Cancer Registry was used to identify patients with a prior malignancy, defined as any invasive cancer diagnosed before a diagnosis of MM. SPM was any new cancer first identified *after* the MM diagnosis. Non-melanoma skin cancers were excluded in the prior malignancy and SPM definitions. Malignancy types were summarized using ICD-O-3 topography-based groupings. Treatment data was accessed through the Ontario Drug Benefit database and the Cancer Activity Level Reporting database. A competing risk analysis using the Fine-Gray subdistribution hazards model was conducted to assess the time to first SPM post MM diagnosis, accounting for death as a competing risk, and stratifying by prior malignancy status. Given that exposure to lenalidomide occurs after MM diagnosis, a time-dependent analysis was conducted. Supportive analyses were performed using landmark times of 12, 18, 24, and 30 months post diagnosis. The study was approved by the ethics committee of McMaster University and followed data confidentiality and privacy guidelines of ICES.

Overall, 12753 patients with MM diagnosed between January 2007 to August 2023 were included in this study, of whom 2083 (16.3%) had a prior history of invasive malignancy. Overall, 11264 (88%) patients received a novel agent (proteasome inhibitor, immunomodulatory drug, or anti-CD38 monoclonal antibody) during their treatment course, and 4731 (37%) received an ASCT. The baseline and treatment characteristics of patients, stratified by the prior malignancy status, is summarized in **Table 1**. Patients with a prior malignancy tended to be older (median age at MM diagnosis 75 versus 69 years), and had lower rates of exposure to an ASCT (n=395 [19%] versus n=4556 [41%]) or lenalidomide (n=1235 [59%] versus n=7363 [69%]) post MM diagnosis, compared to those without a prior malignancy. The median time to first lenalidomide exposure post MM diagnosis was 11.1 (IQR 4.7-23.8) versus 9.73 (IQR 1.6-21.0) months in patients with versus without a prior malignancy history, respectively. The most common prior malignancies were male reproductive (28%), female reproductive (19%), and gastrointestinal (13%) malignancies, as shown in **Figure 1A**.

Of those with versus without a prior malignancy history, 220 (10.6%) versus 931 (8.7%) were diagnosed with a SPM, respectively. The median time to first SPM diagnosis was versus 2.4 (IQR 0.7-4.9) years versus 3.2 (IQR 1.2-5.7) years among patients with versus without a prior malignancy history,

respectively, and only 0.9% (n=19 and 100 respectively) had ≥2 SPMs. The most common SPM developed were a combination of acute myeloid or lymphoid leukemia or myelodysplastic syndrome (n=267, 23%), followed by gastrointestinal malignancies (n=221, 19%), and female reproductive malignancies (n=114, 10%), see **Figure 1A**. Of the 245 patients with a prior hematologic malignancy requiring chemotherapy (acute leukemia, myelodysplastic syndrome, or lymphoma diagnosis), 12 (4.9%) had a subsequent different hematological SPM.

Among patients with a prior malignancy history, the cumulative incidence of SPM was 4.5% (95% CI 3.7-5.4) at 2 years, 8.9% (95% CI 7.6-10.2) at 5 years, and 12.9% (95% CI 11.3-14.7) at 10 years post MM diagnosis, as shown in **Figure 1B**. In patients without a prior malignancy history, the cumulative incidence of SPM, accounting for death as competing risk, was 3.1% (95% CI 2.8-3.4) at 2 years, 6.7% (95% CI 6.3-7.3) at 5 years, and 10.6% (95% CI 10.0-11.4) at 10 years post MM diagnosis. The hazards ratio was 1.38 (95% CI 1.10 to 1.73, p-value=0.005, see **Table 2**) after adjusting for age at MM diagnosis, sex, diagnosis time-period, ASCT exposure in the previous 36 months, and duration of lenalidomide exposure (categorized as no prior lenalidomide, <6 months, or ≥6 months of lenalidomide exposure at 36 months post MM diagnosis). This indicates that the risk of a SPM amongst patients with a prior malignancy was increased by 38%, and results were similar in landmark analyses at 12, 18, 24, and 30 month timepoints (**Table S1**).

In this large, population-based study of more than 12,000 patients with MM treated with contemporary treatments, we found that a history of prior invasive malignancy was independently associated with a 38% higher risk of developing a SPM following MM diagnosis, after adjusting for age, sex, treatment exposure, and lenalidomide duration and accounting for death as a competing risk. Although the absolute cumulative incidence of SPMs was modest—approximately 9% at 5 years—this absolute excess risk of approximately 1.7% by 5 years among patients with prior malignancy identifies a clinically relevant subgroup that may warrant tailored long-term surveillance. These findings suggest that host-related factors, beyond MM treatment exposure, contribute meaningfully to SPM risk. Potential mechanisms include underlying genomic instability, germline mutations in DNA repair or tumor suppressor genes, and chronic immune dysregulation that predispose to malignant transformation [7,8]. In addition, prior exposure to cytotoxic chemotherapy or radiotherapy may cause latent mutagenic effects that synergize with subsequent myeloma-directed therapies, compounding the risk of secondary neoplasia. Given the increasing use of immunomodulatory drugs and novel immunotherapies, it is possible that the SPM risk may increase with time, beyond what was observed in this report.

Our results add an important dimension to existing literature, which has largely focused on treatment-related SPM risk, with few studies systematically evaluating the impact of pre-existing malignancy history. A prior prospective study of 744 MM patients treated between 1997 and 2011 reported that 11% had a prior non-MM malignancy, including non-invasive skin cancers, at MM diagnosis, while a large Swedish population-based study found that 12.5% of MM patients diagnosed between 1973 and 2010 had a history of prior malignancy [9,10]. The latter study also demonstrated that prior malignancy was associated with an increased risk of SPM (HR 1.42, 95% CI 1.23–1.65, $p < 0.001$); however, it did not provide information on the MM treatment regimens used. Given the older diagnostic eras (median diagnosis year 1999 vs. 1992 for those with and without prior malignancy), most patients would not have been exposed to novel therapeutic agents, further limiting the applicability of those findings to contemporary treatment contexts.

The strengths of our study include its large, population-based design, comprehensive ascertainment of malignancy diagnoses, and adjustment for competing mortality. Limitations include the absence of

cytogenetic, germline, and cumulative dose data, and the potential under-ascertainment of SPMs diagnosed outside hospital settings. Additionally, treatment details for the prior malignancy were unavailable, leaving uncertainty as to whether the increased SPM risk reflects inherent patient biology or the mutagenic effects of prior therapy.

In conclusion, our study provides real-world evidence that prior malignancy independently increases SPM risk in MM survivors. This information should be incorporated into shared decision making, risk stratification, and long-term survivorship follow-up care discussions.

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Table 1. Characteristics of patients with MM stratified by prior malignancy status

	No Prior Malignancy (n=10670)	Prior Malignancy (n=2083)
Median age at MM diagnosis - yrs (IQR)	69 (60-76)	75 (68-81)
Male sex - n(%)	5,940 (56)	1,278 (61)
Time period of MM diagnosis - n(%)		
2007-2010	1,903 (18)	288 (14)
2011-2014	2,389 (22)	474 (23)
2015-2018	2,815 (26)	576 (28)
2019-2022	3,563 (33)	745 (36)
First line treatment within 12 months of MM diagnosis - n(%)		
Cyclophosphamide	5,544 (52)	709 (34)
ASCT	4,096 (38)	366 (18)
Novel agents (PI/IMID/anti-CD38 mAb)	8687 (81)	1549 (74)
Lenalidomide	4,062 (38)	725 (35)
Bortezomib	7,579 (71)	1,229 (59)
Daratumumab	658 (6)	151 (7)
Treatment at any time following MM diagnosis - n(%)		
Cyclophosphamide	6,355 (60)	871 (42)
ASCT	4,336 (41)	395 (19)
Novel agents (PI/IMID/anti-CD38 mAb)	9587 (90)	1677 (81)
Ixazomib	671 (6)	100 (5)
Bortezomib	8,386 (79)	1,359 (65)
Carfilzomib	968 (9)	125 (6)
Lenalidomide	7,363 (69)	1,235 (59)
Thalidomide	83 (1)	13 (1)
Pomalidomide	1,380 (13)	227 (11)
Daratumumab or Isatuximab	2,560 (24)	423 (20)
Number of ASCT post MM diagnosis - n(%)		
0	6,334 (59)	1,688 (81)
1	3,078 (29)	285 (14)
2	1,108 (10)	96 (5)
≥3	150 (1)	14 (1)
Never received lenalidomide or ASCT post MM diagnosis - n(%)	2,527 (24)	770 (37)
Treated with lenalidomide post MM diagnosis (never ASCT) - n(%)	3,807 (36)	918 (44)
Received ASCT at any time (never lenalidomide exposed) - n(%)	780 (7)	78 (4)
Received ASCT and lenalidomide post MM diagnosis - n(%)	3,556 (33)	317 (15)

Abbreviations: multiple myeloma (MM), autologous stem cell transplant (ASCT), proteasome inhibitor (PI), immunomodulatory drug (IMID), monoclonal antibody (mAb)

Table 2. Univariable and multivariable landmark Fine-Gray model at 36 months post MM diagnosis to identify factors associated with SPM, accounting for death as a competing risk (n=7740 patients)

	Univariate Results (sHR, 95% CI)				Multivariate Results (sHR, 95% CI)			
	sHR	Lower	Upper	P-Value	sHR	Lower	Upper	P-Value
Prior malignancy (pre-MM diagnosis)	**1.28**	**1.03**	**1.59**	**0.026**	**1.38**	**1.10**	**1.73**	**0.005**
Age	0.99	0.99	1.00	0.020	1.01	1.00	1.02	0.244
Male sex	1.26	1.07	1.49	0.006	1.24	1.05	1.47	0.011
Diagnosis year 2011-2014	1.07	0.86	1.32	0.555	1.07	0.86	1.32	0.570
Diagnosis year 2015-2018	1.24	1.00	1.53	0.046	1.21	0.96	1.53	0.113
Diagnosis year 2019-2022	1.54	1.09	2.18	0.014	1.49	1.03	2.15	0.033
<6 months of lenalidomide within 36 months post diagnosis	0.67	0.47	0.95	0.024	0.64	0.45	0.92	0.014
6+ months of lenalidomide within 36 months post diagnosis	1.12	0.95	1.32	0.161	1.01	0.84	1.20	0.953
ASCT within 36 months post diagnosis	1.50	1.27	1.77	<.001	1.69	1.34	2.13	<.001

Figure Legend

Figure 1. Characterization of malignancy risk in MM patients. A) Distribution of SPM and prior malignancies among MM patients, **B)** Cumulative incidence of second primary malignancy (SPM), stratified by patients with versus without a prior malignancy history. *Abbreviations: second primary malignancy (SPM), myeloproliferative neoplasm (MPN), myelodysplastic syndrome (MDS), genitourinary (GU), gastrointestinal (GI).*

Figure 1

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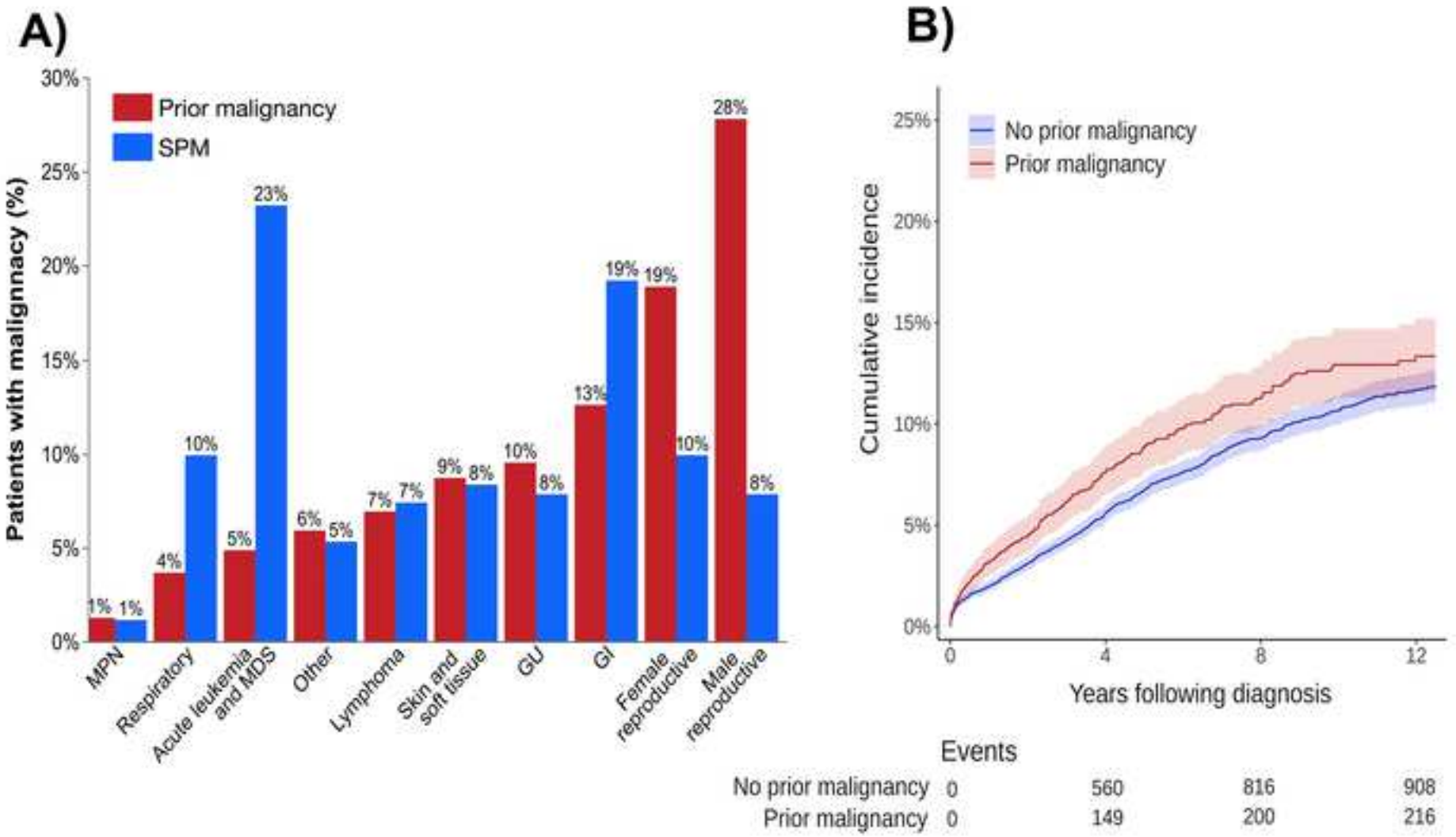

Table S1. Univariate and multivariate landmark model results to identify factors associated with SPM risk with death as a competing risk

Landmark Timeframe	Variable	N	Univariate Results (sHR, 95% CI)				Multivariate Results (sHR, 95% CI)			
			sHR	Lower	Upper	P-Value	sHR	Lower	Upper	P-Value
12 months	**Prior malignancy (pre-MM diagnosis)**	10424	**1.226**	**1.031**	**1.458**	**0.0211**	**1.284**	**1.073**	**1.536**	**0.0062**
	Age		0.995	0.990	1.000	0.0335	1.004	0.997	1.012	0.2620
	Male sex		1.297	1.132	1.486	0.0002	1.278	1.115	1.465	0.0004
	Diagnosis year 2011-2014		1.142	0.950	1.372	0.1579	1.120	0.932	1.347	0.2275
	Diagnosis year 2015-2018		1.247	1.042	1.493	0.0163	1.215	1.002	1.473	0.0475
	Diagnosis year 2019-2022		1.011	0.802	1.274	0.9262	1.021	0.793	1.315	0.8723
	<6 months of lenalidomide within 12 months post diagnosis		1.177	0.995	1.393	0.0576	1.025	0.853	1.231	0.7911
	6+ months of lenalidomide within 12 months post diagnosis		0.806	0.637	1.019	0.0712	0.840	0.652	1.082	0.1774
	ASCT within 12 months post diagnosis		1.353	1.185	1.545	<.0001	1.444	1.195	1.744	0.0001
18 months	**Prior malignancy (pre-MM diagnosis)**	9594	**1.258**	**1.048**	**1.511**	**0.0138**	**1.333**	**1.104**	**1.610**	**0.0029**
	Age		0.994	0.989	1.000	0.0348	1.005	0.996	1.013	0.2727
	Male sex		1.280	1.110	1.476	0.0007	1.256	1.089	1.450	0.0018
	Diagnosis year 2011-2014		1.126	0.931	1.363	0.2212	1.107	0.913	1.342	0.3011
	Diagnosis year 2015-2018		1.240	1.028	1.495	0.0243	1.146	0.930	1.413	0.2014
	Diagnosis year 2019-2022		1.062	0.824	1.369	0.6416	0.963	0.727	1.276	0.7934
	<6 months of lenalidomide within 18 months post diagnosis		1.003	0.795	1.265	0.9813	0.918	0.724	1.165	0.4817
	6+ months of lenalidomide within 18 months post diagnosis		1.240	1.061	1.448	0.0068	1.150	0.961	1.377	0.1275
	ASCT within 18 months post diagnosis		1.372	1.194	1.577	<.0001	1.508	1.230	1.848	<.0001
24 months	**Prior malignancy (pre-MM diagnosis)**	8906	**1.315**	**1.087**	**1.592**	**0.0049**	**1.392**	**1.143**	**1.695**	**0.0010**
	Age		0.993	0.987	0.998	0.0086	1.002	0.994	1.011	0.5758
	Male sex		1.299	1.119	1.507	0.0006	1.270	1.093	1.475	0.0018
	Diagnosis year 2011-2014		1.144	0.939	1.393	0.1820	1.148	0.939	1.402	0.1776
	Diagnosis year 2015-2018		1.256	1.034	1.525	0.0215	1.216	0.979	1.510	0.0767
	Diagnosis year 2019-2022		1.130	0.857	1.492	0.3857	1.090	0.808	1.472	0.5726
	<6 months of lenalidomide within 24 months post diagnosis		0.660	0.490	0.890	0.0065	0.638	0.471	0.865	0.0038
	6+ months of lenalidomide within 24 months post diagnosis		1.177	1.011	1.371	0.0356	1.056	0.889	1.253	0.5371
	ASCT within 24 months post diagnosis		1.398	1.209	1.618	<.0001	1.488	1.204	1.838	0.0002
30 months	**Prior malignancy (pre-MM diagnosis)**	8265	**1.298**	**1.058**	**1.593**	**0.0125**	**1.390**	**1.126**	**1.716**	**0.0022**

	Age		0.993	0.988	0.999	0.0205	1.005	0.996	1.015	0.2433
	Male sex		1.260	1.077	1.474	0.0039	1.233	1.053	1.444	0.0093
	Diagnosis year 2011-2014		1.135	0.923	1.394	0.2298	1.126	0.912	1.390	0.2687
	Diagnosis year 2015-2018		1.275	1.040	1.563	0.0194	1.213	0.968	1.520	0.0935
	Diagnosis year 2019-2022		1.362	1.004	1.847	0.0470	1.286	0.926	1.784	0.1328
	<6 months of lenalidomide within 30 months post diagnosis		0.704	0.515	0.964	0.0284	0.677	0.493	0.931	0.0162
	6+ months of lenalidomide within 30 months post diagnosis		1.186	1.014	1.388	0.0328	1.053	0.885	1.253	0.5576
	ASCT within 30 months post diagnosis		1.461	1.252	1.706	<.0001	1.634	1.309	2.041	<.0001

Table S1. Univariate and multivariate landmark model results to identify factors associated with SPM risk with death as a competing risk

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	Male sex		1.299	1.119	1.507	0.0006	1.270	1.093	1.475	0.0018
	Diagnosis year 2011-2014		1.144	0.939	1.393	0.1820	1.148	0.939	1.402	0.1776
	Diagnosis year 2015-2018		1.256	1.034	1.525	0.0215	1.216	0.979	1.510	0.0767
	Diagnosis year 2019-2022		1.130	0.857	1.492	0.3857	1.090	0.808	1.472	0.5726
	<6 months of lenalidomide within 24 months post diagnosis		0.660	0.490	0.890	0.0065	0.638	0.471	0.865	0.0038
	6+ months of lenalidomide within 24 months post diagnosis		1.177	1.011	1.371	0.0356	1.056	0.889	1.253	0.5371
	ASCT within 24 months post diagnosis		1.398	1.209	1.618	<.0001	1.488	1.204	1.838	0.0002
30 months	**Prior malignancy (pre-MM diagnosis)**	8265	**1.298**	**1.058**	**1.593**	**0.0125**	**1.390**	**1.126**	**1.716**	**0.0022**

	Age		0.993	0.988	0.999	0.0205	1.005	0.996	1.015	0.2433
	Male sex		1.260	1.077	1.474	0.0039	1.233	1.053	1.444	0.0093
	Diagnosis year 2011-2014		1.135	0.923	1.394	0.2298	1.126	0.912	1.390	0.2687
	Diagnosis year 2015-2018		1.275	1.040	1.563	0.0194	1.213	0.968	1.520	0.0935
	Diagnosis year 2019-2022		1.362	1.004	1.847	0.0470	1.286	0.926	1.784	0.1328
	<6 months of lenalidomide within 30 months post diagnosis		0.704	0.515	0.964	0.0284	0.677	0.493	0.931	0.0162
	6+ months of lenalidomide within 30 months post diagnosis		1.186	1.014	1.388	0.0328	1.053	0.885	1.253	0.5576
	ASCT within 30 months post diagnosis		1.461	1.252	1.706	<.0001	1.634	1.309	2.041	<.0001