



# Identification of patients at high risk of secondary extramedullary multiple myeloma development

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## Summary

Multiple myeloma (MM) is characterized by malignant plasma cell infiltration of the bone marrow. In extramedullary multiple myeloma (EMD), a subclone of these cells migrates out of the bone marrow. Out of 4 985 MM patients diagnosed between 2005 and 2017 in the Czech Republic, we analyzed 234 secondary EMD patients to clarify risk factors of secondary EMD development. We found younger age [ $<65$  years; odds ratio (OR) 4.38, 95% confidence interval (CI): 2.46–7.80,  $P < 0.0001$ ], high lactate dehydrogenase (LDH) levels ( $>5$   $\mu\text{kat/l}$ ; OR 2.07, 95% CI: 1.51–2.84,  $P < 0.0001$ ), extensive osteolytic activity (OR 2.21, 95% CI: 1.54–3.15,  $P < 0.001$ ), and immunoglobulin A (IgA; OR 1.53, 95% CI: 1.11–2.11,  $P = 0.009$ ) or the non-secretory type of MM (OR 2.83; 95% CI: 1.32–6.04,  $P = 0.007$ ) at the time of MM diagnosis to be the main risk factors for secondary EMD development. Newly diagnosed MM (NDMM) patients with subsequent EMD had inferior median progression-free (PFS) and overall (OS) survival when compared to NDMM patients without future EMD [mPFS: 13.8 months (95% CI: 11.4–16.3) vs 18.8 months (95% CI: 17.7–19.9),  $P = 0.006$ ; mOS: 26.7 months (95% CI: 18.1–35.4) vs 58.7 months (95% CI: 54.8–62.6),  $P < 0.001$ ]. We found that NDMM patients with specific risk factors associated with secondary EMD development have a more aggressive disease course before secondary EMD develops.

**Keywords:** multiple myeloma, extramedullary disease, prognostic factors.

## Introduction

Multiple myeloma (MM) is the second most common haematological malignancy. It accounts for 1.7% of all cancers and 10% of all haematological malignancies.<sup>1</sup> Average incidence in Europe is 5/100 000.<sup>2,3</sup> In the last 20 years, novel drugs [proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies, etc.] have significantly prolonged survival of newly diagnosed MM (NDMM) as well as relapsed/refractory MM (RRMM) patients.<sup>1,4</sup>

Better imaging techniques [computed tomography (CT), positron emission tomography (PET), PET-CT or magnetic resonance imaging (MRI)] show higher detection rates of so-called extramedullary myeloma (EMD).<sup>5-9</sup> In EMD, a subclone of plasma cells (PCs) migrates out of the bone marrow (BM) infiltrating soft tissues.<sup>10</sup> Changes in adhesion as well as secondary genetic changes in this subclone have been described, including *TP53* mutations, translocation t(4;14), deletion del(13), etc.<sup>6,11,12</sup> However, causes of EMD have not been clarified.

EMD is classified as primary EMD (found at the time of MM diagnosis) and secondary EMD (at the time of MM relapse); clinical behaviour of primary and secondary EMD is markedly different.<sup>7,11</sup> While prognosis of primary EMD *versus* NDMM without EMD is similar,<sup>13,14</sup> secondary EMD is associated with a poor prognosis.<sup>6</sup> We previously showed that in secondary EMD patients, the worst prognosis was observed in soft-tissue EMD (EMD-S), when PCs completely lose their dependence on the BM microenvironment, infiltrating soft tissues. On the other hand, extramedullary lesions arising from bone (EMD-B) have relatively better prognosis.<sup>7</sup>

According to unsatisfactory treatment outcomes, there is a clinical need to diagnose patients with high risk of secondary EMD development as early as possible. Unfortunately, there is a lack of evidence about clinical features of the patients before secondary EMD develops. Therefore, we analyzed disease course before EMD appearance in a real-life group of secondary EMD patients.

## Methods

### *Clinical characteristics of patients*

This real-life retrospective study was carried out at haematological centres in the Czech Republic between 2005 and 2017. All MM patients' data were recorded in the Registry of Monoclonal Gammopathies (RMG) of the Czech Myeloma Group. All participants provided written informed consent approved by institutional Ethics boards in accordance with the latest Helsinki declaration.

In total, 4 985 MM patients were evaluated; 543 EMD patients (10.9%) were found. Out of this number, 309 primary EMD and 234 secondary EMD patients were identified. As reference, 2 092 MM patients with no EMD involvement during the entire follow-up period were included — we

excluded living patients with shorter follow-up than five years.

Secondary EMD was found in 111 patients at first relapse, in 61 at second and 62 at third or higher relapse. Median follow-up of secondary EMD patients from the time of MM diagnosis was 3.8 years. In secondary EMD patients, 61.1% (143/234) of patients had EMD-B, 30.3% (71/234) had EMD-S, and 8.6% (20/234) of patients were missing data. Only first occurrences of EMD were evaluated.

Before secondary EMD diagnosis, 19.2% of patients were treated with PIs, 22.6% with IMiDs, and 41.5% of patients with both PIs and IMiDs; 16.7% of patients were treated with conventional chemotherapy without novel drugs, and 54.2% of patients underwent autologous stem cell transplant (ASCT). No obligatory diagnostic protocol was used in this study. Diagnostic methods and clinical evaluations at the time of secondary EMD diagnosis were used in a real-life setting corresponding to patients' symptoms and actual clinical availability of diagnostics.

### *Diagnostics of secondary EMD lesions*

In secondary EMD patients, EMD lesions were detected in 119 patients by skeletal survey, in 41 patients by MRI, in 21 patients by CT and in 12 by PET/CT. EMD involvement was also diagnosed by other methods, i.e. scintigraphy, ultrasonography, endoscopy or clinical evaluation. Findings of EMD lesions were confirmed by surgical sampling and histology evaluation, when clinically needed and safe for the patient.

### *Cytogenetics*

Interphase fluorescent *in situ* hybridization (I-FISH) analysis was performed on separated PCs as previously described<sup>12</sup> at the time of MM diagnosis.

### *Statistics*

Data were described by absolute and relative frequencies of categorical variables. Logistic regression analysis was used to assess the association of baseline characteristics at MM diagnosis with EMD occurrence in relapse. Differences in overall (OS) and progression-free (PFS) survival between patients with future EMD and RRMM group not evolving EMD according to line of therapy was computed by the Kaplan–Meier method and statistical significance of differences in survival among subgroups was assessed using the log-rank test. The same methodology was used for identification of secondary EMD as prognostic factor of survival in RRMM patients. Treatment response was assessed according to the current International Myeloma Working Group (IMWG) criteria.<sup>15</sup> Independence of secondary EMD as a prognostic survival factor was verified in a multivariable Cox proportional hazard model in context of other well-known prognostic

factors. All statistical tests were performed at a significance level of  $\alpha = 0.05$  (all tests two-sided). Analysis was performed in the SPSS software (release 2017: IBM SPSS Statistics for Windows, Version 25.0.0.1; IBM Corp. Armonk, NY, USA) and R version 4.0.1. ([www.r-project.org](http://www.r-project.org)).

## Results

### *Clinical features associated with secondary EMD development*

Clinical characteristics at the time of MM diagnosis of both secondary EMD patients as well as reference MM patients are summarized in Table I. We compared these groups and identified associations between clinical, laboratory and cytogenetic features at MM diagnosis and risk for subsequent development of EMD (Fig 1).

In younger NDMM patients (<65 years), there was a significantly higher risk of secondary EMD development [odds ratio (OR) 4.38; 95% confidence interval (CI): 2.46–7.80,  $P < 0.0001$ ]. Moreover, NDMM patients who developed secondary EMD had significantly higher LDH levels ( $>5 \mu\text{kat/l}$ ; OR 2.07, 95% CI: 1.51–2.84,  $P < 0.0001$ ), more than two osteolytic lesions diagnosed by skeletal survey (OR 2.21, 95% CI: 1.54–3.15,  $P < 0.001$ ), hypercalcaemia ( $>2.65 \text{ mmol/l}$ ; OR 1.71, 95% CI: 1.21–2.42,  $P = 0.002$ ) and IgA M-protein type (OR 1.53, 95% CI: 1.11–2.11,  $P = 0.009$ ) or the non-secretory type of MM (OR 2.83, 95% CI: 1.32–6.04,  $P = 0.007$ ).

In NDMM patients who subsequently developed secondary EMD, there were significant differences in the presence of del(13)(q14) (48.3% vs 78.2%,  $P < 0.001$ ) and gain (1q21) (44.2% vs 71.4%,  $P < 0.001$ ). While other aberrations were analyzed, they were not statistically significant. Detailed results of I-FISH analysis are shown in Table SI.

### *Survival of MM patients before secondary EMD development*

We compared survival intervals of MM patients with secondary EMD involvement in the next relapse/progression with patients without any EMD involvement in the future. We analyzed survival from the start of the first line of treatment according to the state of EMD in the second line based on a condition that both groups had to initiate the second line of treatment. Patients who developed EMD in the third or higher lines were not included in this calculation. We proceeded analogously for survival from the second and third lines of therapy (Fig 2).

**NDMM patients.** NDMM patients who subsequently developed EMD had significantly shorter median PFS, when compared to NDMM patients without future EMD involvement (13.8 months, 95% CI: 11.4–16.3 vs 18.8 months, 95% CI: 17.7–19.9;  $P = 0.006$ ). Median OS was significantly shorter in NDMM patients who subsequently developed secondary

EMD when compared to NDMM patients without any future EMD involvement (26.7 months, 95% CI: 18.1–35.4 vs 58.7 months, 95% CI: 54.8–62.6;  $P < 0.001$ ).

**RRMM patients after one previous treatment line.** RRMM patients who developed EMD in the next disease progression and RRMM patients without future EMD involvement had comparable median PFS (10.1 months, 95% CI: 8.1–12.0 vs 12.1 months, 95% CI: 11.3–12.8;  $P = 0.558$ ). Median OS was significantly shorter in RRMM patients who developed EMD when compared to RRMM without any future EMD involvement (28.6 months, 95% CI: 21.1–36.0 vs 41.0 months, 95% CI: 38.0–43.9;  $P = 0.006$ ).

**RRMM patients after two previous treatment lines.** RRMM patients after two previous treatment lines who developed EMD in the next disease progression and RRMM patients without future EMD involvement had comparable median PFS (9.4 months, 95% CI: 6.1–12.8 vs 9.7 months, 95% CI: 8.8–10.5;  $P = 0.510$ ). While there was trend toward worse OS between RRMM patients who developed EMD and RRMM patients who did not (17.8 months, 95% CI: 9.3–26.3 vs 31.1 months, 95% CI: 27.8–34.5;  $P = 0.158$ ), these results were not statistically significant.

### *Survival after the secondary EMD development*

Multivariate analysis showed secondary EMD as an independent risk factor for PFS [hazard ratio (HR) 1.39, 95% CI: 1.06–1.81,  $P = 0.016$ ] and OS (HR 1.61, 95% CI: 1.20–2.15,  $P = 0.001$ ) of RRMM patients. From the time of secondary EMD diagnosis, median PFS was 4.7 months (95% CI: 3.5–5.8) and median OS was 8.6 months (95% CI: 6.3–11.0).

## Discussion

As a result of remarkable progress in the treatment of MM, it is slowly turning into a chronic disease. Due to the widespread use of new drugs, better treatment results are achieved even at MM relapse. In case of relapsed or even refractory MM patients, the disease may become stabilized several times.<sup>1,4,16–19</sup>

At the same time, extramedullary myeloma is still a challenge even in the era of new drugs. Especially, secondary EMD is a hard-to-treat entity associated with poor prognosis.<sup>7,13</sup> Standard widespread treatment protocols for RRMM patients based on bortezomib, lenalidomide or pomalidomide do not significantly improve prognosis of secondary EMD.<sup>20–24</sup> There are only limited data for the second-generation PI carfilzomib in this patient population. Case reports and analyses of small cohorts showed unsatisfactory results, far worse than in non-EMD patients.<sup>25–28</sup> Similarly, ixazomib did not show significant improvement of secondary EMD prognosis in real-life analysis.<sup>29</sup> Anti-CD38 antibodies (daratumumab, isatuximab) have not overcome poor prognosis of secondary EMD, possibly due to low expression of the CD38 surface antigen in EMD PCs.<sup>30,31</sup> A much lower

without EMD ← OR < 1 | OR > 1 → with EMD

Characteristics at diagnosis	Category	MM	secondary EMD	0	1	2	3	4	5	6	7	8	OR (95% CI)	p-value
<b>Sex</b>	Women	1 014	101										reference	
	Men	1078	133		●								1.24 (0.94–1.63)	0.124
<b>Age at diagnosis (years)</b>	> 75	364	13										reference	
	66–75	690	59		●								2.39 (1.30–4.42)	<b>0.005</b>
<b>ECOG</b>	≤ 65	1036	162										4.38 (2.46–7.80)	<b>&lt; 0.001</b>
	0	316	39										reference	
<b>ISS</b>	1	1081	120		●								0.90 (0.61–1.32)	0.587
	2	380	38		●								0.81 (0.51–1.30)	0.381
	3–4	169	12		●								0.58 (0.29–1.13)	0.108
<b>Durie-Salmon stage</b>	Stage 1	613	81										reference	
	Stage 2	597	67		●								0.85 (0.60–1.20)	0.350
	Stage 3	665	57		●								0.65 (0.45–0.93)	<b>0.017</b>
<b>Durie-Salmon substage</b>	I	374	23										reference	
	II	429	45			●							1.71 (1.01–2.87)	<b>0.045</b>
	III	1267	162			●							2.08 (1.32–3.27)	<b>0.001</b>
<b>Beta2 microglobulin (mg/l)</b>	A	1617	196										reference	
	B	467	34		●								0.60 (0.41–0.88)	<b>0.008</b>
<b>Albumin level (g/dl)</b>	< 3.5	750	101										reference	
	3.5–5.5	451	49		●								0.81 (0.56–1.16)	0.243
	> 5.5	634	57		●								0.67 (0.47–0.94)	<b>0.020</b>
<b>LDH (μkat/l)</b>	> 3.5	1227	137										reference	
	≤ 3.5	726	78		●								0.96 (0.72–1.29)	0.797
<b>CRP (mg/l)</b>	≤ 5	1499	137										reference	
	> 5	344	65			●							2.07 (1.51–2.84)	<b>&lt; 0.001</b>
<b>Creatinine level (μmol/l)</b>	≤ 10	1354	133										reference	
	> 10	544	77			●							1.44 (1.07–1.94)	<b>0.016</b>
<b>Calcium total level (mmol/l)</b>	≤ 176	1587	189										reference	
	> 176	411	31		●								0.63 (0.43–0.94)	<b>0.023</b>
<b>Haemoglobin level (g/l)</b>	≤ 2.65	1691	168										reference	
	> 2.65	282	48			●							1.71 (1.21–2.42)	<b>0.002</b>
<b>Thrombocyte count (10E9/l)</b>	≥ 100	1231	150										reference	
	< 100	791	73		●								0.76 (0.57–1.02)	0.064
<b>Serum M-protein level (g/l)</b>	≥ 175	1364	156										reference	
	< 175	638	66		●								0.91 (0.67–1.22)	0.516
<b>M-protein type</b>	≤ 20	723	71										reference	
	> 20	1281	150			●							1.19 (0.89–1.60)	0.245
	IgG	1274	123										reference	
	IgA	439	65			●							1.53 (1.11–2.11)	<b>0.009</b>
	LC only	290	31			●							1.11 (0.73–1.68)	0.630
<b>Light-chain type</b>	Nonsecretory	33	9										2.83 (1.32–6.04)	<b>0.007</b>
	other	50	4			●							0.83 (0.29–2.33)	0.722
	kappa	1283	132										reference	
<b>Osteolytic lesions X-ray</b>	lambda	760	91			●							1.16 (0.88–1.54)	0.291
	negative	655	42										reference	
<b>Bone marrow aspiration cytology (%)</b>	1–2 lesions	228	29			●							1.98 (1.21–3.26)	<b>0.007</b>
	≥ 2 lesions	1054	149			●							2.21 (1.54–3.15)	<b>&lt; 0.001</b>
<b>IGH disruption<sup>1</sup></b>	< 10	421	47										reference	
	10–20	495	51			●							0.92 (0.61–1.40)	0.706
	>20	1008	121			●							1.08 (0.75–1.53)	0.689
<b>t(11;14)<sup>1</sup></b>	negative	186	16										reference	
	positive	384	43			●							1.30 (0.71–2.37)	0.389
<b>t(4;14)<sup>1</sup></b>	negative	285	26										reference	
	positive	53	6			●							1.24 (0.49–3.16)	0.651
<b>del(13)(q14)/monosomy 13<sup>1</sup></b>	negative	349	32										reference	
	positive	85	15			●							1.93 (1.00–3.72)	0.051
<b>gain(1q21)<sup>1</sup></b>	negative	259	12										reference	
	positive	242	43										3.84 (1.98–7.45)	<b>&lt; 0.001</b>
<b>del(17p13)<sup>1</sup></b>	negative	249	14										reference	
	positive	197	35										3.16 (1.65–6.04)	<b>&lt; 0.001</b>
<b>Hyperdiploidy<sup>1</sup></b>	negative	362	39										reference	
	positive	61	3			●							0.46 (0.14–1.52)	0.202
<b>Hyperdiploidy<sup>1</sup></b>	negative	239	29										reference	
	positive	172	12			●							0.58 (0.29–1.16)	0.122

Fig 1. Clinical features measured at diagnosis in multiple myeloma (MM) and secondary extramedullary multiple myeloma (EMD) patients. CI, confidence interval; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group; IGH, immunoglobulin heavy chain; ISS, International Staging System; LDH, lactate dehydrogenase; OR, overall response. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

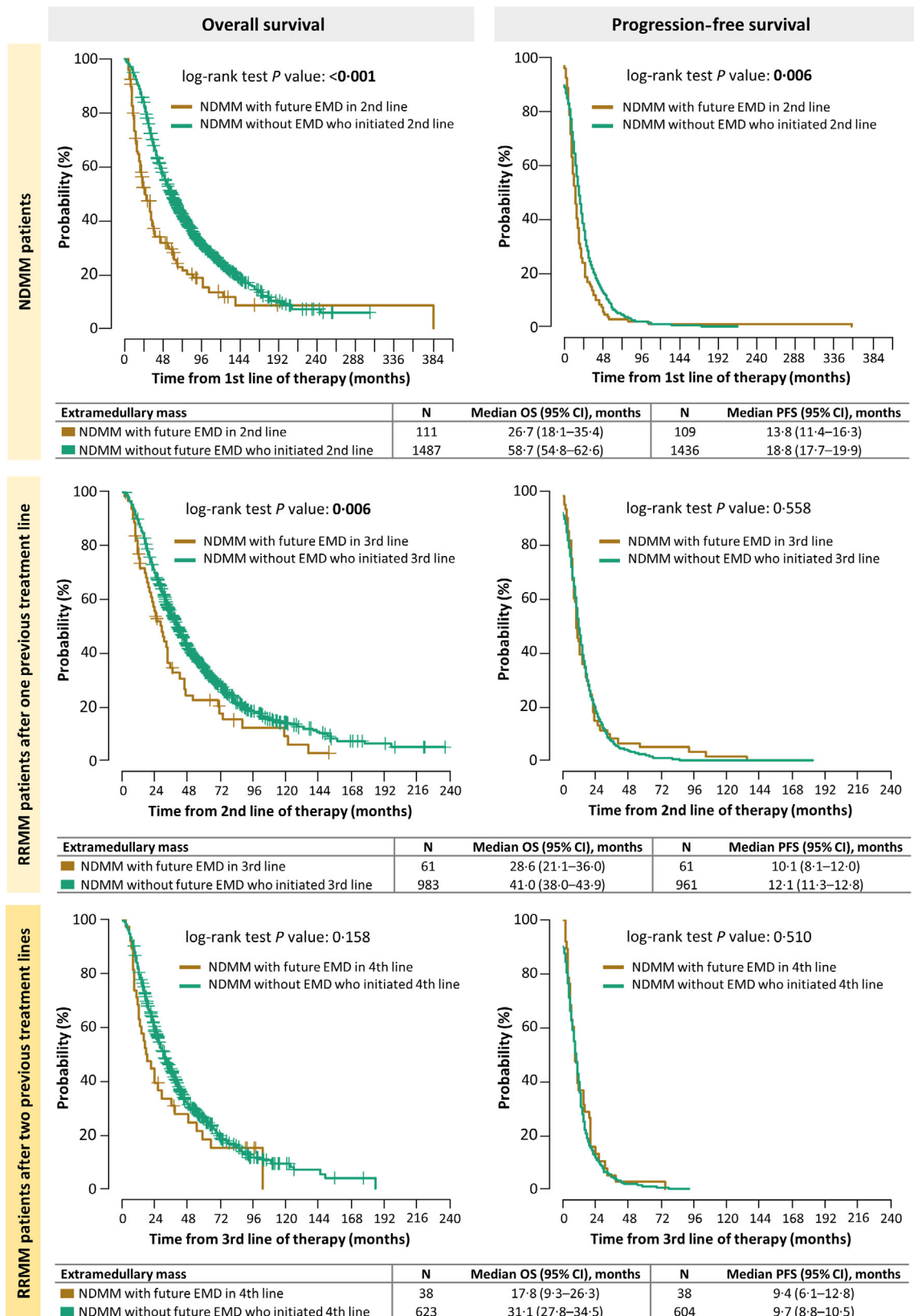


Fig 2. Effect of future secondary extramedullary multiple myeloma (EMD) development on progression-free (PFS) and overall (OS) survival in separate treatment lines. CI, confidence interval; NDMM, newly diagnosed multiple myeloma; RRMM, as relapsed/refractory multiple myeloma. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

response rate was also shown in a subset of EMD patients treated with the anti-BCMA (B cell maturation antigen) drug conjugate belantamab.<sup>32</sup> Preliminary results of the peptide–drug conjugate melphalan flufenamide (melflufen) in a heavily pretreated cohort of secondary EMD patients seem promising, but longer follow-up is necessary.<sup>33</sup> In the current era of immunotherapy, promising results were achieved in several trials of BCMA-targeted CAR-T cells. The CAR-T cells had impressive results even in secondary EMD-S patients, resulting in longer remissions in some trials.<sup>34–36</sup>

Unfortunately, there are no current protocols for secondary EMD treatment.

For better understanding of development of secondary EMD, we identified 234 secondary EMD among almost 5 000 MM patients diagnosed in Czech haematologic centres from 2005 to 2017. To the best of our knowledge, this dataset is the largest in the world so far. With respect to our retrospective cohort and relatively low number of patients pretreated by both IMiDs and PIs, as a recently most frequent induction treatment regimen,<sup>32,37–40</sup> we found similar numbers of EMD patients as in recently published large clinical trials focusing on (PI + IMiDs)-exposed patients.<sup>41,42</sup> These results show PI and IMiDs do not induce EMD; we indirectly confirmed that fact in a much larger cohort of patients.<sup>22</sup> Moreover, similar numbers of EMD patients were found in previous analyses of heavily pretreated patients<sup>21,22</sup> when compared to recent clinical trials, focusing on triple or penta-refractory patients.<sup>43–46</sup> From those findings, we suppose that modern treatment regimens including a new generation of IMiDs, PI and monoclonal antibodies do not induce more EMD. Comparing length of previous treatment in different analyses and incidence of EMD, time of disease duration seems to play an important role in EMD development.<sup>21</sup> Thus, we focused on patient- and disease-related factors as the most important aspects in EMD development.

In our analysis, younger age, extensive bone disease (numerous osteolytic lesions and hypercalcaemia), higher LDH and IgA or a non-secretory type of MM at the time of MM diagnosis were significantly associated with further development of secondary EMD. In similar studies, comparable results for younger age, type of monoclonal immunoglobulin and extensive bone disease were found.<sup>21</sup> In another analysis, hypercalcaemia was also confirmed as a risk factor for secondary EMD development.<sup>22</sup>

We found an increased presence of del(13)/monosomy13 and gain (1q21) at the time of MM diagnosis in patients with future secondary EMD. These results are in concordance with our previous results that showed increased presence of both aberrations at the time of EMD diagnosis both in primary and secondary EMD patients.<sup>47</sup> In other analyses, del (17p) was found to be the most frequent cytogenetic aberration in EMD patients, both in BM and in the extramedullary tumour site.<sup>48–50</sup> We did not observe a higher incidence of del (17p) or other tested aberrations in patients with future EMD development. Possibly, subsequent acquisition of del

(17p) in the disease course, influencing secondary EMD development, occurs.<sup>51,52</sup> However, with respect to the low number of analyzed EMD samples in our study, more robust cytogenetic analyses need to be performed.

In our study, NDMM patients before EMD development had significantly inferior median PFS when compared to NDMM patients who never developed EMD. We presume that NDMM patients who progress to EMD early have a specific and more aggressive disease from the onset of MM. A similar situation was described in NDMM patients with high-risk cytogenetics when the disease course was impaired from the beginning.<sup>53,54</sup> While EMD pathogenesis has not been clarified yet, there may be a hidden molecular mechanism affecting disease course before EMD is revealed. Thus, these patients subsequently manifest with extramedullary involvement, leading to further disease escalation and early death.

Surprisingly, more advanced RRMM patients who developed EMD in the further disease course had comparable treatment outcomes as reference RRMM patients who never developed EMD. However, like in NDMM patients with EMD progression, their prognosis dramatically changed with EMD development.<sup>6</sup>

These clinical observations may be explained by more sudden changes in the MM clone leading to EMD involvement in advanced MM patients.<sup>55</sup> As previously described, treatment-related factors do not seem to be involved in EMD development.<sup>21</sup> Another explanation may be a sudden loss of balance between different subclones leading to expansion of an aggressive clone, independent of the BM environment.<sup>56</sup> Unfortunately, mechanisms leading to these changes in secondary EMD patients remain unknown. Regardless of the time of the secondary EMD development, patients' outcomes remain poor.<sup>6</sup>

A clear limitation of our analysis was the low number of highly sensitivity diagnostic methods such as PET/CT or whole-body MRI. These limitations arise from the retrospective character of this study and time of our data collection during which access to these diagnostic methods dramatically changed.<sup>9,57–59</sup> In our study, the most frequent diagnostic method was X-ray, what clearly could lead to bias from undetected small EMD-B or asymptomatic EMD-S lesions.<sup>9</sup> On the other hand, incidence of secondary EMD in our cohort was comparable to that in the longitudinal real-life study (1971–2007) published by Varettoni *et al.*<sup>6</sup> In a newer study, only 3% of secondary EMD were found threenyears after MM diagnosis.<sup>23</sup> A similar incidence of secondary EMD (3–7%) within five years from the diagnosis was found by the Arkansas group while using PET/CT in diagnostic work-up.<sup>11</sup> Taken together, according to recent recommendations, PET/CT or whole-body MRI clearly reveals more EMD patients due to their well-defined sensitivity.<sup>9,57</sup> In our study, the approach based on combining basic diagnostic methods according to patient's symptoms had acceptable results.

Despite the absence of clearly defined data from clinical trials, an aggressive treatment approach to EMD patients is

generally accepted.<sup>60,61</sup> Using high-sensitive diagnostic methods, describing clinical features of MM patients at high risk of EMD development may lead to closer follow-up. We believe that a future focus on the pre-EMD period may lead to improvement of the poor prognosis of these patients. More clinical and molecular analyses should be performed to identify the optimal treatment approach.

## Conclusion

We found that MM patients with future EMD development show specific features (younger age, extensive bone disease, IgA, or non-secretory type of MM) which are present already at the time of MM diagnosis. In NDMM patients, secondary EMD developed shortly after MM diagnosis, showing the aggressive disease pattern from the beginning. In more pre-treated MM patients, disease course before secondary EMD development was similar to that in other MM patients. After a yet unknown event, EMD occurs probably as a terminal event in MM evolution. Regardless of time, when PCs lose their dependence on the BM microenvironment, there is an absolute turnover of the disease course, leading to early death. We confirmed secondary EMD development as a strong independent negative prognostic factor in MM.

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## Authors contribution

MS, SS and LP designed the study. PK, JR, IS, JS, PP, AJ, TJ, VS, VM and RH performed research. MS, SS, LP and JM co-wrote the paper. LP, LB and JJ analyzed data. All authors critically reviewed and approved the manuscript.

## Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the University Hospital Brno, Czech Republic (2016).

## Informed consent statement

Informed consent was obtained from all subjects involved in the study.

## Conflicts of interest

The authors declare to have no conflicts of interest. The funders had no role in the design of the investigation, in the

collection, analyses or interpretation of data, in the writing of the manuscript or in the decision to publish the results”.

## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table SI.** Cytogenetic aberrations at the time of MM diagnosis (MM *versus* secondary EMD patients).

## References

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