# Asymptomatic and Treatment-requiring Multiple Myeloma – Data from the Czech Registry of Monoclonal Gammopathies

## Asymptomatický a léčbu vyžadující mnohočetný myelom – data z českého Registru monoklonálních gamapatií

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### Summary

***Background:*** Monoclonal gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma (SMM) are premalignant stages of multiple myeloma (MM). MM is a malignancy of plasma cells, which is associated with a median overall survival of 5 to 7 years. MM accounts for approximately 10% of hematological malignancies. ***Patients and Methods:*** Descriptive analysis of data from 19 Czech centres collected in the Registry of Monoclonal Gammopathies (RMG) was performed. ***Results:*** Over the last 10 years of prospective collection of data, together with retrospectively recorded data on patients diagnosed before the registry establishment, data on 7,467 patients with either asymptomatic or symptomatic form of MM have been gathered. Validation criteria for the analysis were met by 2,506 MGUS patients, 400 SMM patients and 4,738 MM patients. The median duration of follow-up was 4.3 years in MGUS patients and 2.4 years in SMM patients. The overall risk of progression from MGUS to malignancy was 1.7% per year. The risk of progression from SMM to MM was highest in the 1st years after diagnosis: overall, this risk was 16.6% per year. The median duration of follow-up was 2.8 years in MM patients. The median overall survival from the diagnosis was 5.7 years. The median OS from treatment initiation/progression-free survival decreased from 60.5/21.0 months in the 1st line therapy to 34.3/12.4 months in the 2nd line therapy, 22.6/8.9 months in the 3rd line therapy and 13.8/5.8 months in the 4th or higher line therapies. Thanks to the availability of novel drugs for MM treatment in the Czech Republic, treatment strategies have changed dramatically over the last decade. ***Conclusion:*** RMG is a registry designated for the collection of data on diagnosis, treatment, treatment results and survival of patients with monoclonal gammopathies in the long-term follow-up. RMG is a valuable source of data from real clinical practice.

### Key words

registries – monoclonal gammopathy of undetermined significance – smouldering multiple myeloma – multiple myeloma – progression – treatment – survival

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## Souhrn

***Východiska:*** Monoklonální gamapatie nejasného významu (monoclonal gammopathy of undetermined significance – MGUS) a doutnající mnohočetný myelom (smouldering multiple myeloma – SMM) jsou prekancerózními stadii mnohočetného myelomu (MM). MM je malignita plazmatických buněk s mediánem přežití od 5 do 7 let. MM tvoří zhruba 10 % diagnóz v oblasti hematoonkologie. ***Pacienti a metody:*** Na datech z 19 českých center zadaných v Registru monoklonálních gamapatií (Registry of Monoclonal Gammopathies – RMG) byla provedena popisná analýza. ***Výsledky:*** Za posledních 10 let sběru dat, spolu s retrospektivně zadanými daty pacientů diagnostikovaných před založením registru, registr disponuje daty o 7 467 pacientech se asymptomatickou nebo symptomatickou formou MM. Validační kritéria pro analýzu splňovalo 2 506 pacientů s MGUS, 400 pacientů s SMM a 4 378 pacientů s MM. Medián délky sledování pacientů byl 4,3 roku u MGUS a 2,4 roku u SMM. Celkové roční riziko progrese z MGUS do maligního onemocnění bylo 1,7 %. Riziko progrese z SMM do MM bylo nejvyšší první roky po diagnóze; za celou dobu sledování bylo riziko progrese 16,6 % každý rok. Medián délky sledování od diagnózy MM byl 2,8 roku. Medián celkového přežití (overall survival – OS) od diagnózy byl 5,7 roku. Medián OS od zahájení léčby/doby bez progrese klesl z 60,5/21,0 měsíce u 1. linie léčby na 34,3/12,4 měsíce u 2. linie, 22,6/8,9 měsíce u 3. linie a 13,8/5,8 měsíce u 4. nebo vyšší linie léčby. Díky dostupnosti nových léků pro léčbu MM v České republice došlo v posledním desetiletí k dramatickým změnám v léčebných postupech. ***Závěr:*** RMG je registr určený pro sběr klinických dat týkajících se diagnózy, léčby, jejích výsledků a přežití pacientů s monoklonálními gamapatiemi. RMG je cenným zdrojem dat z reálné klinické praxe.



## Klíčová slova

registry – monoklonální gamapatie nejasného významu – doutnající mnohočetný myelom – mnohočetný myelom – progrese – léčba – přežití


## Introduction

Monoclonal gammopathy of undetermined significance (MGUS), smouldering multiple myeloma (SMM; previously called asymptomatic multiple myeloma) and multiple myeloma (MM) are considered to be plasma cell (PC) dyscrasias. Their diagnosis is determined according to the current IMWG (International Myeloma Working Group) criteria [1]. MGUS represents a benign condition characterised by the presence of M-protein (monoclonal protein) in a concentration lower than 30 g/L, by less than 10% of clonal PCs in the bone marrow, and by the absence of myeloma-defining events. The prevalence of MGUS is approximately 3% among the general population aged over 50 [2]. SMM is defined as the presence of M-protein in a concentration of 30 g/L or higher and/or 10–60% bone marrow PC infiltration with no evidence of end-organ damage. MGUS and SMM are considered to be precancerous conditions of MM. MGUS is associated with a 1% risk of progression to MM or related PC disorders per year; patients are at risk of progression even after 25 years of follow-up [3]. IgM (immunoglobulin – Ig) MGUS usually evolves into Waldenström macroglobulinaemia, whereas IgA or IgG variants progress to MM, primary amyloidosis or related PC disorders [4]. On the other hand, MGUS is assumed to precede MM in almost all cases [5]. According to one study, the risk of progression from SMM to MM was 10% per year in the first 5 years, 3% per year in the next 5 years and 1% per year in the last 10 years of a 20-year follow-up [6]. A population-based Scandinavian study revealed that SMM accounts for about 14% of patients with MM [7]. Regular monitoring is the standard of care in MGUS and in SMM. Prognostic models have been proposed to discriminate between patients with a low-risk and a high-risk of progression [8]. An early intervention in high-risk SMM patients has been shown to delay the progression to active MM and to increase the overall survival (OS) [9]. The current IMWG criteria thus reclassified the high-risk SMM patients as patients with MM, which led to the availability of early treatment for these patients [1].

MM is a malignancy of PCs accounting for 1% of all cancers and approximately 10% of all hematological malignancies [10]. MM diagnosis is associated with the presence of clinical symptoms usually described by the acronym CRAB (C – hypercalcaemia in serum, R – renal insufficiency, A – anaemia, B – lytic bone lesions). The median survival is approximately 5 to 7 years, but there are dramatic variations in the survival depending on the patient's characteristics (e.g. age, comorbidities), tumour burden (e.g. stage) and biological characteristics of the disease (e.g. cytogenetic abnormalities) [11]. In 2005, a simple International Staging System (ISS) based on two parameters describing the tumour burden (serum β2 microglubin and serum albumin) was developed [12]. In 2015, the ISS was revised and combined with parameters of disease biology (presence of chromosomal abnormalities and elevation of lactate dehydrogenase) [13]. From the chromosomal abnormalities, deletion on 17p and/or translocation t(4;14) and/or t(14;16) were considered as high-risk factors. Such a stratification systems helps physicians choose the optimal treatment strategy. With the novel drugs, the treatment of MM has advanced dramatically in the last decade [14]. The use of thalidomide, lenalidomide and bortezomib improved the patients' survival rates [15–17]. More recently, pomalidomide, carfilzomib, ixazomib and daratumumab have been used in the treatment of MM in the Czech Republic. The novel drugs are usually combined with chemotherapy and/or corticosteroids. The critical point in the choice of therapy is the patient's eligibility for autologous stem cell transplantation (ASCT); factors such as age, performance status and comorbidities influence the eligibility for ASCT. The upper age limit for ASCT eligibility was increased to 70 years from previous 65 years in the Czech Republic; this is in contrast to the United States, for example, where the age limit is 75 years [14]. After the 1st line therapy, relapse usually occurs and a next-line therapy of the disease is required. The periods between

**Tab. 1. Basic characteristics of MGUS, SMM and MM patients.**

| Characteristics at diagnosis | MGUS (n = 2,506) | SMM (n = 400) | MM (n = 4,738) |
|---|---|---|---|
| **sex** | n = 2,506 | n = 400 | n = 4,738 |
| women | 1,363 (54.4) | 219 (54.8) | 2,281 (48.1) |
| men | 1,143 (45.6) | 181 (45.3) | 2,457 (51.9) |
| **age at diagnosis (years)** | n = 2,506 | n = 400 | n = 4,738 |
| ≤ 50 | 430 (17.2) | 49 (12.3) | 446 (9.4) |
| 51–60 | 606 (24.2) | 100 (25.0) | 1,103 (23.3) |
| 61–70 | 767 (30.6) | 128 (32.0) | 1,642 (34.7) |
| 71–80 | 574 (22.9) | 104 (26.0) | 1,248 (26.3) |
| > 80 | 129 (5.1) | 19 (4.8) | 299 (6.3) |
| median (min.–max.) | 63 (22–93) | 64 (28–88) | 65 (18–92) |
| **ECOG** | n = 2,405 | n = 374 | n = 4,438 |
| 0 | 1,403 (58.3) | 166 (44.4) | 866 (19.5) |
| 1 | 935 (38.9) | 193 (51.6) | 2,395 (54.0) |
| 2 | 59 (2.5) | 13 (3.5) | 792 (17.8) |
| ≥ 3 | 8 (0.3) | 2 (0.5) | 385 (8.7) |
| **ISS** | not available | n = 380 | n = 4,302 |
| stage I | – | 297 (78.2) | 1,563 (36.3) |
| stage II | – | 70 (18.4) | 1,383 (32.1) |
| stage III | – | 13 (3.4) | 1,356 (31.5) |
| **M-protein type** | n = 2,497 | n = 400 | n = 4,702 |
| IgG | 1,740 (69.7) | 276 (69.0) | 2,823 (60.0) |
| IgA | 297 (11.9) | 103 (25.8) | 974 (20.7) |
| LC only | 25 (1.0) | 8 (2.0) | 689 (14.7) |
| IgM | 357 (14.3) | 5 (1.3) | 34 (0.7) |
| biclonal | 74 (3.0) | 5 (1.3) | 57 (1.2) |
| non-secretory | 2 (0.1) | 1 (0.3) | 90 (1.9) |
| other (IgD, triclonal) | 2 (0.1) | 2 (0.6) | 35 (0.7) |
| **Progression status** | n = 2,506 | n = 400 | not available |
| no progression | 2,275 (90.8) | 172 (43.0) | – |
| MM | 173 (6.9) | 228 (57.0) | – |
| WM | 20 (0.8) | – | – |
| lymphoma | 18 (0.7) | – | – |
| other | 20 (0.9) | – | – |
| **Follow-up (years)** | n = 2,506 | n = 400 | n = 4,738 |
| median (min.–max.) | 4.3 (0.0–34.8) | 2.4 (0.3–20.6) | 2.8 (0.0–32.1) |
| **Death** | n = 2,506 | n = 400 | n = 4,738 |
| no | 2,219 (88.5) | 370 (92.5) | 2,517 (53.1) |
| yes | 287 (11.5) | 30 (7.5) | 2,221 (46.9) |

Data are presented as n (%) for categorical variables and as median values (min.–max.) for continuous variables.
MGUS – monoclonal gammopathy of undetermined significance, SMM – smouldering multiple myeloma, MM – multiple myeloma, ECOG – Eastern Cooperative Oncology Group, ISS – international staging system, M-protein – monoclonal protein, Ig – immunoglobulin, WM – Waldenström macroglobulinaemia

relapses and remissions are usually increasingly shorter [6]. If the patient is eligible, ASCT can be repeated at the time of relapse. Treatment history is considered in the choice of therapy in higher-line therapies. Despite improvements in treatment strategies, MM remains to be an incurable disease; nevertheless, there is already a small number of patients who have been in a complete remission for more than 10 years [18,19].

## Patients and methods

Data from Czech and Slovak centres have been collected in the Registry of Monoclonal Gammopathies (RMG) since 2007, the year of establishment of this registry. Only data from Czech centres were used in the analysis. Characteristics of patients with asymptomatic (MGUS, SMM) and symptomatic MM were analysed. Patients with asymptomatic MM have not received any therapy until the progression to a symptomatic disease. The diagnosis, treatment response and time to event endpoints were assessed according to the current IMWG (International Myeloma Working Group) criteria [20,21]. All patients signed the informed consent form, which had been approved by ethical committees of the respective hospitals.

Our analysis had four main objectives: 1. to describe patients' characteristics at the time of MGUS, SMM or MM diagnosis; 2. to evaluate the risk of progression from an asymptomatic MM to a symptomatic MM; 3. to describe the OS from the time of MM diagnosis and 4. to describe treatment of MM and its success in terms of OS and progression-free survival (PFS) in individual lines of therapy. All analyses were descriptive; no hypotheses were tested. Data were described by absolute and relative frequencies for categorical variables and by median values supplemented with range (min.–max.) for continuous variables. Treatment intervals were plotted using the Kaplan-Meier (K-M) methodology. The K-M estimates were completed by the Greenwood confidence interval (CI). Death was censored in the evaluation of time from an asymptomatic MM to disease progression. The annual risk of progression was evaluated as the ratio of the total number of patients with disease progression to the sum of person-years of follow-up in the cohort of MGUS or SMM patients. The analysis was performed using the SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp) and the software R, version 3.3.0 (www.r-project.org).

## Results

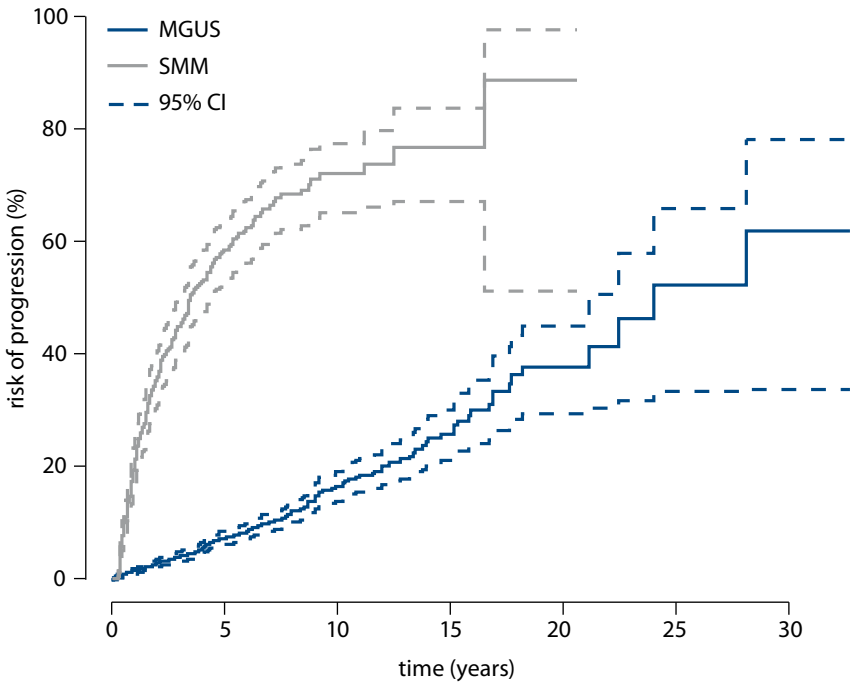
A total of 7,467 patients were diagnosed with monoclonal gammopathies in 19 Czech centres up to March 2017 (prospective collection of data was initiated in 2007). At that time, RMG contained data on 2,759 patients diagnosed with MGUS and 4,888 patients diagnosed with MM; MGUS diagnosis was followed by MM diagnosis in 180 (2.4%) patients. Because RMG does not include any diagnostic form for SMM, SMM patients were selected as a subset of MM patients who met the current IMWG criteria for SMM diagnosis [1]. Moreover, at least a 3-month follow-up without progression was required for SMM patients. From the total number of 4,888 patients diagnosed with MM, SMM criteria were met in 400 (8.2%) patients. Validation criteria for a more detailed analysis were considered and patients who did not meet those criteria were excluded. Validation criteria were defined as the availability of records on the patient's age, follow-up since diagnosis and the progression status (in case of MGUS or SMM). Finally, records on 2,506 MGUS (90.8% from a total of 2,759), 400 SMM (100% from a total of 400) and 4,738 MM (96.9% from a total of 4,888) patients were evaluated in the analysis.

Table 1 shows the basic characteristics of patients diagnosed with MGUS, SMM and MM. Data on patients diagnosed before 2007 (the year of registry establishment) were collected retrospectively. From the total number of patients with a given diagnosis, 600 (23.9%) MGUS, 91 (22.8%) SMM and 777 (16.4%) MM patients were diagnosed before 2007. On average, there were 190, 31 and 393 newly diagnosed patients per year (evaluated since 2007 to 2016) with MGUS, SMM and MM diagnoses, resp. A predominance of women in the group of patients with asymptomatic MM was observed (54.4% in MGUS, 54.8% in SMM) in contrast to MM, which seemed to be slightly more common in men (51.9%). The median age at diagnosis was 63, 64 and 65 years for MGUS, SMM and MM, resp. The diagnosis was established before the age of 50 in 430 (17.2%) MGUS patients and in 46 (12.3%) SMM patients. Although MM is generally considered as a disease associated with old age, 2.1% (99 patients) were diagnosed before the age of 40. Approximately one third of patients were older than 70 years at the time of diagnosis. The majority of MGUS and SMM patients had the ECOG grade (i.e. performance status developed by Eastern Cooperative Oncology Group) ranging between 0 and 1, which corresponds to the range from fully active patients to patients restricted in physically strenuous activities only [22]. ECOG of grade 3 or higher was recorded in 385 (8.7% from 4,438 patients with ECOG available) MM patients; these grades refer to patients with a limited self-care. There were only limited numbers of patients in grade 3 or higher in MGUS and SMM groups. ISS stages were rather uniformly distributed in MM patients (36%, 32% and 32% in stages I, II and III, resp.). The majority of SMM patients (78.2%) had the ISS stage I. Patients with MGUS are usually stratified by the Mayo risk stratification system, which is based on M-protein quantity (high-risk: ≥ 15 g/L), M-protein type (high-risk: non-IgG) and abnormal free light chain ratio (high-risk: < 0.26 or > 1.65) [8]. All three risk factors were recorded in 2,104 (84.0%) patients. MGUS patients were classified into four risk groups with none, one, two and all three risk factors according to the Mayo model; these groups involved 804 (38.2%), 862 (41.0%), 411 (19.5%) and 27 (1.3%) patients, resp. (data not shown). The type of M-protein was available in almost all patients: 2,497 (99.6%) in MGUS, 400 (100%) in SMM and 4,702 (99.2%) in MM. IgG was the most abundant type of M-protein, with a frequency of 70% in MGUS and SMM and 60% in MM. IgM was the second most abundant M-protein in MGUS (n = 357; 14.3%); by contrast, IgM was observed in

less than 2% of patients in SMM and MM groups. IgA M-protein was observed in 11.9%, 25.8% and 20.7% in MGUS, SMM and MM, resp. Light-chain only (LC only) MM or non-secretory MM were more frequently present at the time of MM diagnosis (LC only in 14.7%, non-secretory in 1.9% patients) when compared to MGUS and SMM groups (LC only in ≤ 2%, non--secretory in ≤ 0.3% patients).

The serum level of M-protein was measured repeatedly in the vast majority of MGUS patients (n = 2,438; 97.3%). After 1 year of MGUS diagnosis, the median number of patients' visits to their hematologist was two visits per year. Overall, the median number of check-ups in patients' follow-up was 7, ranging from 1 to 51 (data not shown). Data on progression status and patients' follow-up in MGUS and SMM diagnoses are presented in Tab. 1. The median follow-up was 4.3 years in the cohort of MGUS patients. Progression in MGUS occurred in 231 (9.2%) patients. From the overall number of 231 patients, MGUS developed to MM (n = 173; 74.9%), Waldenström macroglobulinaemia (n = 20; 8.7%), lymphoma (n = 18; 7.8%) or another disorder (n = 20; 8.7%). The overall risk of progression per year was 1.7%. The probability of progression (number of patients at risk) was 7.5% (n = 1,100) at 5 years, 16.7% (n = 329) at 10 years and 25.8% (n = 97) at 15 years (Fig. 1). Only 25 patients were followed for more than 20 years. Death occurred before progression in 287 (11.5%) patients. In SMM patients, only data at the time of diagnosis were collected in RMG. The median duration of follow-up from the SMM diagnosis to the progression to MM or the last date of evaluation was 2.4 years. SMM developed to MM in 228 (57.0%) patients. The overall risk of progression per year was 16.6%. The probability of progression (number of patients at risk) was 20.8% (n = 299) at 1 year, 35.9% (n = 223) at 2 years, 58.3% (n = 96) at 5 years and 71.7% (n = 23) at 10 years (Fig. 1). Only four patients were alive and without progression 15 years after SMM diagnosis. From the cohort of SMM patients, 30 (7.5%) patients died before progression.

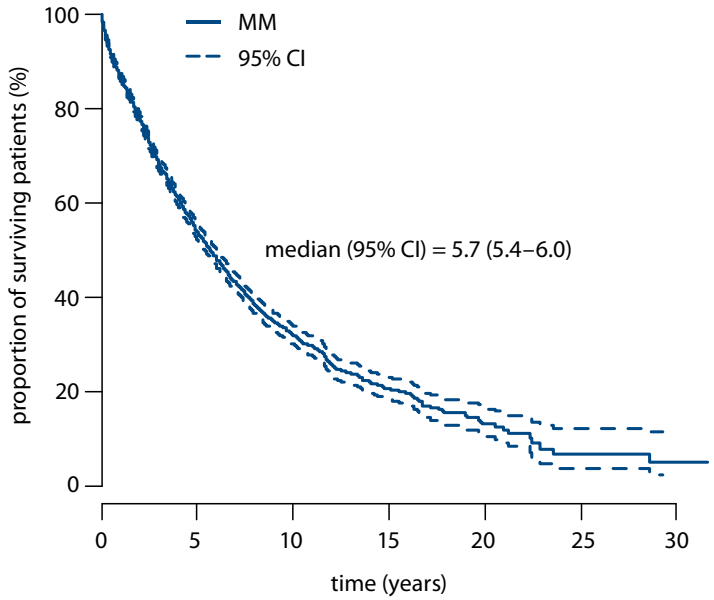
The median follow-up from MM diagnosis to a patient's death or the last date




| | MGUS | SMM |
|---|---|---|
| **total n** | 2,506 | 400 |
| **progression (n)** | 231 | 228 |
| **median (95% CI)** | 24.0 (18.5–29.5) | 3.4 (2.7–4.1) |
| **at risk (years) (n)** | | |
| 1 | 2,137 | 299 |
| 2 | 1,840 | 223 |
| 5 | 1,100 | 96 |
| 10 | 329 | 23 |
| 15 | 97 | 4 |
| 20 | 25 | 1 |
| 25 | 7 | 0 |
| **risk of progression (years)** | **% (95% CI)** | **% (95% CI)** |
| 1 | 1.6 (1.1–2.1) | 20.8 (17.1–25.2) |
| 2 | 3.0 (2.4–3.8) | 35.9 (31.3–41.0) |
| 5 | 7.5 (6.3–8.8) | 58.3 (52.9–63.8) |
| 10 | 16.7 (14.3–19.5) | 71.7 (65.5–77.7) |
| 15 | 25.8 (21.6–30.6) | 76.5 (68.1–84.1) |
| 20 | 37.9 (30.7–46.2) | 88.3 (66.7–98.5) |
| 25 | 52.4 (37.6–68.8) | – |

*Event for MGUS patients defined as progression to MM or related disorders; event for SMM patients defined as progression to MM.
MGUS – monoclonal gammopathy of undetermined signifikance, SMM – smouldering multiple myeloma

**Fig. 1. Time to progression* from MGUS and SMM diagnosis.**




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| at risk (n): | 4,738 | 1,353 | 358 | 103 | 26 | 6 | 1 |
| surviving (%): | 100.0 | 54.0 | 32.0 | 20.6 | 13.0 | 6.7 | 5.0 |

MM – multiple myeloma

**Graph 1. Overall survival from MM diagnosis.**

of evaluation was 2.8 years. Almost half of the cohort of MM patients have already died (n = 2,221; 46.9%). The probability of survival (number of patients at risk) was 54.0% (n = 1,353) at 5 years, 32.0% (n = 358) at 10 years and 20.6% (n = 103) at 15 years (Graph 1). The median OS from the time of diagnosis was 5.7 years (95% CI 5.4–6.0 years).

From the total number of MM patients who met the validation criteria (n = 4,738), 4,375 (92.3%) patients had at least one line of therapy recorded. Only patients with initiated treatment were evaluated in this section. In sum, the total number of lines of therapy for the treated patients was 10,255. In terms of patient numbers, 4,375 (100.0%), 2,452 (56.0%), 1,503 (34.4%) and 872 (19.9%) patients initiated the 1st line, 2nd line, 3rd line and 4th or higher-line therapy, resp. The median of total number of lines of therapy per patient was 2, ranging from 1 to 15. The period between two lines of therapy was generally getting shorter with the increasing number of lines of therapy. The median time to the next line of therapy was 19, 13, 10 and 8 months in the 1st line, 2nd line, 3rd line and 4th line therapy, resp. From the 10,255 lines of therapy, 1,094 (10.7%) therapies were conducted within clinical trials. ASCT was performed in 1,640 (37.5%) patients. If the patient was eligible, ASCT was most frequently performed in the 1st line therapy (n = 1,488; 34.0%). Nevertheless, ASCT was performed in 332 (13.5%), 142 (9.4%) and 145 (16.6%) patients in the 2nd line, 3rd line and 4th or higher-line therapy, resp. ASCT was performed more than once in a patient's follow-up in 394 (9.0%) patients.

The OS from treatment initiation and PFS decreases with higher lines of therapy (Fig. 2). The median OS was 60.5 months (95% CI 57.3–63.7 months) in the 1st line therapy, 34.3 months (95% CI 31.9–36.7 months) in the 2nd line therapy, 22.6 months (95% CI 20.5–24.7 months) in the 3rd line therapy and 13.8 months (95% CI 12.6–14.9 months) in the 4th or higher-line therapy. The median PFS decreased from 21.0 months (95% CI 20.2–21.8 months) in the 1st line therapy to 12.4 months (95% CI 11.8–13.0 months) in the 2nd line therapy, 8.9 months (95% CI 8.4–9.5 months) in the 3rd line therapy and 5.8 months (95% CI 5.3–6.2 months) in the 4th or higher-line therapy. At 10 years after the initiation of the 1st line therapy, 84 patients were alive and without progression.

As regards the evaluation of treatment regimens, only the induction therapy (regardless of switch) was assessed. Treatment strategies up to 2010 and thereafter were compared. After 2010, bortezomib was more frequently administered in the 1st line therapy (60% increase when compared to therapies up to 2010) and less frequently in 2nd or higher-line therapies (15% decrease in the 2nd line therapy). On the other hand, an almost 30% increase was observed for lenalidomide in the 2nd line therapy; for the same drug, there was a 11.4% decrease in the 4th or higher-line therapies; pomalidomide and carfilzomib were more frequently administered in higher-line therapies. Table 2 describes treatment regimens in the 1st line (n = 2,352), 2nd line (n = 939), 3rd line (n = 426) and 4th or higher-line therapies (n = 277) initiated after 2010. As specified in the legend, drugs were classified into four categories: proteasome inhibitor (PI); immunomodulatory drug (IMiD); chemotherapy; or corticosteroids. In about half of the 1st line therapies (n = 1,198; 50.9%), PI was combined with chemotherapy and corticosteroids. From the PIs, bortezomib was the most frequently chosen drug in the 1st line therapy (n = 1,728; 73.5%). Bortezomib was combined with chemotherapy and corticosteroids in 1,168 (49.7%) patients in the 1st line therapy. Moreover, there were 33 (1.4%) 1st line therapies with carfilzomib conducted within clinical trials. From the IMiDs, thalidomide was used in 732 (31.1%) 1st line therapies; thalidomide was combined with chemotherapy and corticosteroids in 402 (17.1%) patients, with bortezomib and corticosteroids in 237 (10.1%) patients in the 1st line therapy. In the 2nd line therapy, 328 (34.9%) patients were treated with IMiD in combination with cortico-

steroids. From the IMiDs, lenalidomide was used in 428 (45.6%) patients in the 2nd line therapy; lenalidomide was combined with corticosteroids in 312 (33.2%) patients, and the same drug was combined with chemotherapy and corticosteroids in 55 (5.9%) patients. Bortezomib was administered to 282 (30.0%) patients in the 2nd line therapy. Bortezomib was combined with corticosteroids and/or chemotherapy in 209 (22.3%) patients. Thalidomide was the third most frequently used drug in the 2nd line therapy (n = 175; 18.6%). Thalidomide was combined with chemotherapy and corticosteroids in 106 (11.3%) patients in the 2nd line therapy. Thalidomide was used in combination with bortezomib in 44 (4.7%) patients in their 2nd line therapy. The majority of ixazomib therapies were administered in the 2nd line therapy (n = 36; 3.8%). A higher proportion of therapies without novel drugs was observed with the increasing number of lines of therapy. Chemotherapy and/or corticosteroids were used in 4.0%, 6.7%, 16.4% and 27.8% cases of 1st line, 2nd line, 3rd line and 4th or higher-line therapy, resp. On the other hand, we observed an increasing trend in the usage of pomalidomide and carfilzomib in higher-line therapies. From the 277 4th or higher-line therapies, 39 (14.1%) therapies included pomalidomide, and 19 (6.9%) therapies included carfilzomib.

## Discussion

RMG contains data on 7,467 patients with either asymptomatic or symptomatic MM. Data for patients with SMM diagnosis are collected within a diagnostic form for MM; subsequent analyses of MM then include patients with SMM. Patients with SMM were selected using new IMWG criteria from 2014; therefore, previously high-risk SMM patients were reclassified as patients with MM [1].

Because MGUS is an asymptomatic disease, it is usually detected during a routine physician examination. Despite the assumption that MGUS precede MM in all cases, a history of MGUS was observed only in 3.7% patients in the MM cohort; rather than reflecting the prevalence, this proportion reflects an early detection of the disease. MGUS is much more common than MM and the majority of MGUS patients will never develop an active MM or a related disorder. The risk of progression from MGUS to MM or a related malignancy is stable in time, in contrast to the risk of progression from

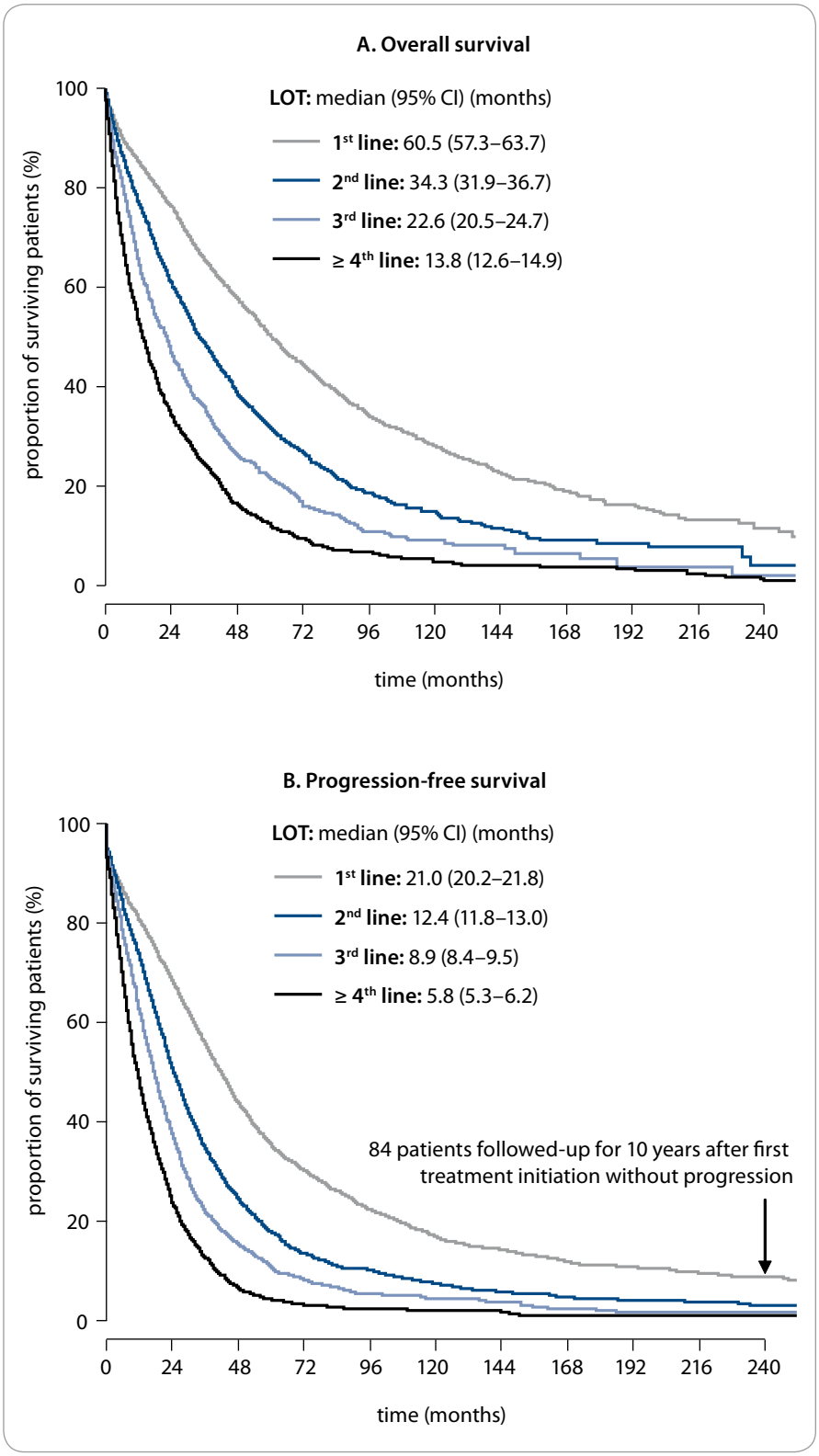



**Fig. 2. Overall survival from treatment initiation (A) and progression-free survival (B) by line of therapy (LOT).**

**Tab. 2. Drugs used in MM therapy after 2010.**

| Treatment regimen[1] | 1st line (n = 2,352), % | 2nd line (n = 939), % | 3rd line (n = 426), % | ≥ 4th line (n = 277), % | Total n |
|---|---|---|---|---|---|
| **Drug combinations** | | | | | |
| PI + chemo + cort. | 50.9 | 12.7 | 6.6 | 3.6 | 1,355 |
| IMiD + chemo + cort. | 17.4 | 17.1 | 13.4 | 12.3 | 661 |
| chemo + cort. | 3.2 | 4.8 | 10.8 | 17.7 | 216 |
| IMiD + cort. | 2.0 | 34.9 | 34.3 | 25.6 | 593 |
| PI + cort. | 7.7 | 10.6 | 10.8 | 12.6 | 361 |
| PI + IMiD + cort. | 10.1 | 7.8 | 8.2 | 7.2 | 366 |
| IMiD | 1.1 | 3.4 | 1.9 | 0.4 | 66 |
| PI | 2.7 | 2.0 | 2.1 | 0.7 | 94 |
| cort. | 0.6 | 1.4 | 4.5 | 6.1 | 64 |
| chemo | 0.1 | 0.5 | 1.2 | 4.0 | 24 |
| PI + IMiD + chemo + cort. | 1.6 | 0.6 | 1.4 | 1.8 | 55 |
| PI + IMiD | 1.2 | 0.6 | 1.2 | 0.4 | 40 |
| other (low N)[2] | 0.8 | 1.2 | 0.5 | 1.8 | 36 |
| other (not specified) | 0.5 | 2.2 | 3.3 | 5.8 | 63 |
| **Drug[3]** | | | | | |
| bortezomib (PI) | 73.5 | 30.0 | 26.3 | 18.8 | 2,174 |
| thalidomide (IMiD) | 31.1 | 18.6 | 22.1 | 18.8 | 1,053 |
| lenalidomide (IMiD) | 2.3 | 45.6 | 33.8 | 15.2 | 669 |
| carfilzomib (PI) | 1.4 | 1.6 | 3.1 | 6.9 | 80 |
| pomalidomide (IMiD) | 0.0 | 0.7 | 4.7 | 14.1 | 66 |
| ixazomib (PI) | 0.2 | 3.8 | 1.2 | 1.4 | 49 |
| daratumumab | 0.4 | 0.7 | 0.2 | 1.4 | 22 |

[1] % based on the number of patients in the respective line of therapy
[2] includes all cases of therapy with daratumumab
[3] drugs can be combined in a single line of therapy
PI (proteasome inhibitor) – bortezomib/carfilzomib/ixazomib
IMiD (immunomodulatory drug) – lenalidomide/thalidomide/pomalidomide
chemo (chemotherapy) – bendamustine/doxorubicin/cyclophosphamide/etoposide/melphalan/vincristine/idarubicin
cort. (corticosteroids) – dexamethasone/prednisone

SMM to MM: in these cases, the highest risk is observed in the first 5 years after the diagnosis and decreases thereafter. The "watch and wait" strategy is the standard of care in MGUS and SMM. Death is a competitive event of progression – death can occur before progression particularly in old patients. Almost 20% of MGUS patients are diagnosed before 50 years of age, which means that they are at a higher risk of progression due to their longer life expectancy. RMG contains data on a high number of patients with MGUS (2,506 patients were involved in the analysis); however, only seven MGUS patients have been followed-up for more than 25 years. The median OS from the time of MM diagnosis was reported in data from RMG, but variation is expected depending on the patients' characteristics (comorbidities) and disease characteristics (chromosomal abnormalities). The combination of novel drugs with chemotherapy and/or corticosteroids and ASCT (if the patient is eligible) is the gold standard of care. Depending on the availability of drugs, therapy of MM varies across different countries. Although MM remains an incurable disease, there is a small group of patients without progression or death 10 years after the diagnosis. Eventually, the power of the registry is expected to grow stronger over time – longer follow-up times will be available to see the complete risk of progression from

precancerous stages and the effects of novel drugs in MM therapy.

## Conclusion

RMG is an international registry collecting clinical data about diagnosis, treatment, treatment results and survival of patients with monoclonal gammopathies in the long-term follow-up. Apart from Czech centres, data from the Slovak Republic are collected in RMG and cooperation with other countries is considered. RMG is one of the main projects of the Czech Myeloma Group [23]. Thanks to the registry, treatment response and other endpoints can be evaluated across all participating centres. The publication policy for data recorded in the registry is based on an online system for the collection of approvals from centres for all analyses. As a source of real-world data, RMG provides real-world evidence about the treatment of monoclonal gammopathies and its results on the population level.

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### Conflicts of interest

I. S. has served as consultant for and received research funding from and holds membership on the board of directors or advisory committee of Celgene, Janssen-Cilag, Amgen, Bristol-Myers Squibb, and Takeda. V. M. consulted for Amgen, Bristol-Myers Squibb, Celgene, Janssen-Cilag and Takeda; received grant support from The Binding Site, honoraria from Amgen, Bristol-Myers Squibb, Celgene and Janssen-Cilag, and has been involved in advisory boards for Amgen, Bristol-Myers Squibb, Celgene, Janssen-Cilag and Takeda. R. H. has a consultant or advisory relationship and received honoraria from Amgen, Bristol-Myers Squibb, Takeda, Celgene and Janssen-Cilag; conducted a clinical research project(s) funded by Takeda, Novartis, Amgen and Janssen-Cilag. Other authors declare they have no conflicts of interest concerning drugs and other medicinal products used in the study.

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